The Affective Brain
Novel insights into the biological mechanisms of motivation and emotion

Het Affectieve Brein: Nieuwe inzichten in de biologische mechanismen van motivatie en emotie

(met een samenvatting in het Nederlands)

Proefschrift

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Abstract

Transcranial magnetic stimulation (TMS) is a method capable of transiently modulating neural excitability. Depending on the stimulation parameters cognitive processing in the brain can be either enhanced or disrupted. This way the contribution of different brain areas involved in mental processes can be studied, allowing a functional decomposition of cognitive behavior both in the temporal and spatial domain, hence providing a functional resolution of brain/mind processes. The aim of the present paper is to argue that TMS with its ability to draw causal inferences on function and its neural representations is a valuable neurophysiological tool for investigating the causal basis of neuronal functions and can provide substantive insight into the modern interdisciplinary and (anti)reductionist neurophilosophical debates concerning the relationships between brain functions and mental abilities. Thus, TMS can serve as a heuristic method for resolving causal issues in an arena where only correlative tools have traditionally been available.

Functional decomposition and localization

The discovery and development of ways to decompose the functional organization of brain-mind processes has proved to be very beneficial for the cognitive sciences (Bechtel, 2002). By building models of cognitive behavior using the functional component principle, that is dividing cognition into discrete information processing units, it becomes feasible to develop sophisticated ways of disentangling the workings of cognitive functions. Bechtel (2002) distinguishes a phenomenological and mechanistic decomposition. The former, Bechtel argues (2002) reflects the attempt of psychology to identify and categorize different cognitive faculties, while the latter seeks to identify how the processes that give rise to cognitive constructs really operate and interact. The differentiation can be best understood in terms of 'what' kind of cognitive construct and components can be identified and 'how' they are generated.
A large difference of opinion between the functionalists and structuralists lies in the mechanistic decomposition approach, that is in the implementation of function within the brain. Whereas the traditional functionalists hold to the idea of 'multiple realizability,' whereby localization of function may be impossible in principle, the structuralists argue that function is predictably related to the operations of specifiable brain systems (Fodor, 1975; Putnam, 1975). 'Multiple realizability' also encompasses the idea that function, and cognition in particular, can be implemented in various physical entities, such as silicon chips and brain matter. The crucial notion however entails the fact that specific types of hardware implementation are independent of functional issues. The hard functionalists state that if cognition can be decomposed and hardwired, in for instance silicon chips, then one has all the information and knowledge regarding the underlying process at hand. In order to understand a given cognitive function one does not need neuroscientific research or to even consider the brain per se. This, of course, is an enormous assumption, and the most telling criticisms is that many different processes can lead to the same end result. This concept can be visualized easily through the metaphor of any mathematical equation, where the results to the

right of the equal sign could be achieved by a vast number of factor structures to the left. From a naturalistic point of view, the critical question is how brains actually achieve the functions that they do, in fact, exhibit. Thus, a complete functional analysis of mind functions simply has to be restrained and guided by neuroscientific facts. Human cognition, no matter how shaped by environmental inputs, is fully dependent on the workings and properties of the brain.

Seemingly paradoxically, the functionalistic approach was initially a reaction to the explanatory shortcomings of behaviorism. However, functionalism is actually a modern version of the latter (at least the black-box variants) in which constructs such as cognition are refined and decomposed on the descriptive level but which remain independent of physical realization, ultimately resembling a new form of dualism (Chalmers, 1996). From the functionalist perspective, the physical implementation can again be treated as a black box. For example, cognitivists interested in artificial intelligence build machines which can actually mimic human cognitive outputs very impressively, but these remain mere simulations of how one thinks a given brain function might work.

The functionalistic approach is fruitful in its own right, however, for a complete explanation of human mentation one has to start thinking how function and its architecture are realized in the brain. The only way to understand function completely is by starting to disentangle the system properties of the brain on which function supervenes. With the advent of various neuroimaging techniques a decade ago, some of the structural correlates of underlying complex human behavior became accessible through *in vivo* investigations of the brain, providing bridging principles between function and structure (Churchland, 1992). The structuralist way of studying behavior has more or less dominated scientific research ever since. While many cognitive scientists still believe that the realization of complex behavior can be studied secondary to structural issues, neuroscientists realize that the intrinsic properties of the structure itself are of the essence in fathoming the way functions work (Schutter, 2001). The whole idea is based on the principles of functional decomposition,

localization of the relevant component functions, and a specification of their interactions.

This type of work is guided by the pragmatic premise that there may exist, at least in a first-pass analysis, a tight relation between the functions and their neural realizations (Bechtel, 2002). In neurophilosophy this assumption is better known as the 'identity' theory, which states that by decomposing cognition one is able to localize the different units as separate neural structures and systems in the brain. Figure I.1 illustrates, based on the 'identity' or 'token' theory, the direct relationship between the processing units of a function and its local neural representations. Although this viewpoint accepts that mind functions may be partly "modular" in the intact adult brain, it does not simply accept that these are evolutionarily derived modules. Many specializations, especially the cortical ones, could as readily be epigenetically derived because higher brain systems resemble random access type memory fields programmed by more genetically dictated patterns of subcortical sensory and emotional circuitries (Panksepp & Panksepp, 2000).

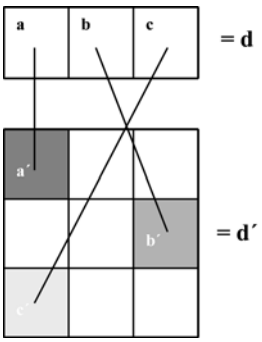

Figure I.1. Function d can be decomposed into a, b, and c and its structural representation d' is localized in a', b' and c' respectively.

In any event, with the advent of modern neuroimaging these different neural representations, whether genetically dictated or epigenetically emergent, can be partly localized in the brain and potentially linked up to the decomposable processing units. The method has been remarkably successful in identifying brain areas that mediate emotions and various

emotional disorders (Damasio, 1999; Drevets, 2001; Mayberg & McGinnis, 2000; Phan, Wager, Taylor, & Liberson, 2002), language functions (Grabowski & Damasio, 2000), as well as a host of other brain functions (Toga & Mazziotta, 2000). This method of localizing is inherent to the relative high spatial resolution of the various neuroimaging techniques and very valuable with respect to studying the different structures of the brain in relation to the expression of cognitive functions *in vivo*. However, important reservations regarding this research method have been recently raised by Uttal (2002) and others (e.g., Logothetis, 2002).

Although Uttal acknowledges the great potential importance and contributions of such approaches to the understanding of the relation between structure and cognitive function, he and others argue that there are major conceptual difficulties using imaging techniques. By coining the term the *new phrenology*, Uttal highlights certain fundamental problems regarding the modern imaging techniques. In other words, the workings of complex cognitive behaviors may not be capable of being unraveled on the basis of decomposition approaches, for the assumption of a one-to-one relation between the function and the localization of its underlying neural representations may be false. Even if it would be possible to provide for a structural solution of cognitive function, it would be impossible to include, for instance, the temporal course of activity and the precise interactions across the different structures involved.

On the other hand, a recent study by Logothetis, Pauls, Augath, Trinath, & Oeltermann (2001) demonstrated that the neurophysiological basis of the blood-oxygen-level-dependent (BOLD) fMRI signal probably rely on a different neural property than electrophysiological activity. More specifically, the BOLD signal is argued to reflect activity at the pre-synaptic level, whereas EEG results from post-synaptic neural activities. At the same time, there is some cross-species data indicating that visually evoked single-unit activities correlate well with fMRI signals from comparable human studies (Rees, Friston, & Koch, 2000). In any event, hemodynamic responses emerge at relatively longer time scales and are

likely to be equally sensitive to synchronous and asynchronous sources of electric activity.

The combined applications of EEG and fMRI can provide for a high temporal and spatial resolution and might constitute part of the solution. However, taking into account that one has to make far fetched mathematical assumptions on how to align fMRI and EEG in time, this endeavor suddenly becomes more complex and difficult than one might have originally anticipated (Horwitz & Poeppel, 2002). Regarding this notion, Uttal (2002) is pessimistic and states that it will not be possible to create a full comprehension of cognition based on such current technologies.

We certainly acknowledge such problems, especially when one recognize since it is obvious that correlative techniques can only give hints concerning causality. However, this does not *a priori* imply that no useful causal knowledge and insight can be obtained from investigating the biological underpinnings of cognition using high-tech neuroimaging, especially new approaches such as *coherence* measures and other cross brain area correlational analyses. In concordance with this notion, Bechtel (2002) argues that neuroimaging can indeed be very useful in our aspiration to find out more about the working mechanisms underlying cognition and function in general. Each technique has limitations, and it is only through the convergence of various methodologies and findings that substantive knowledge can be achieved in this area. Even though brain imaging might not be capable to solve the whole brain-cognition problem, the technique can at the very least be used as a heuristic method of scientific exploration for relevant neural correlates that can guide future causal studies.

Although the 3D visualization methods and the functional activation maps have high face validity with respect to the partial representations of certain functions within the brain, it should not be overestimated what this functional activity actually stands for. For instance, active processing of a function and active inhibition of a function could lead to increased blood flow in areas mediating those functions. Thus, even if a correlation between function and local brain activity can be established, a causal link

remains to be investigated by other methods. For instance, animal brain studies have already provided for an enormous number of causal manipulations. Only a few of them can be applied in humans (Panksepp, 1998). In general, the three major types of causal manipulations are i) contextual and psychological challenges, ii) neurochemical ones (e.g., psychopharmacological manipulations), and iii) direct electrophysiological ones (e.g., brain stimulation). In general, the first two are rather global causal variables that typically effect much of the brain. For the second set of variables, localized brain manipulations cannot be achieved as is routinely done in animal studies where chemical agents are commonly placed directly into specific brain areas. Likewise, electrical brain stimulation in humans has, with few exceptions been achieved secondarily to medically indicated neurosurgical procedures (Heath, 1996). There is presently no way to stimulate deep brain structures of humans non-invasively (although, as will be discussed later, that is a theoretically feasible possibility). Recently however, an approach has emerged for stimulating the human cortical surfaces extracranially, which provides, for the first time, powerful causal ways to manipulate cerebral functions in normal individuals and thereby evaluate the causal roles of many potential structure-functions correlates that have been provided by brain imaging.

Transcranial magnetic stimulation (TMS)

The most robust brain stimulation method presently available which can be utilized to analyze causal relationships between brain structure and function is a technique called transcranial magnetic stimulation (TMS). TMS is based on Faraday's law of electromagnetic induction, which states that, when situated near conductors, a magnetic pulse oriented in the right direction is transformed into an electric current. When the magnitude of this magnetic pulse varies in the order of a few hundred microseconds a secondary current is generated (Pascual-Leone, Walsh, & Rothwell, 2000). Applied over the scalp the electromagnetic induction will result in the depolarization of underlying cortical nerve cells that are

tangential oriented to the magnetic field (Bohning, 2000). The axons excited are oriented in the plane of the induced electric field parallel to the curvature of the heads at the stimulated area. From a neuro-anatomical perspective this technique can influence all cortical areas that face the cranium, even though in practice one has difficulty stimulating many areas such as orbitofrontal and low temporal areas because of the concurrent, and often painful, contraction of major head muscles.

TMS was introduced by Anthony T. Barker in 1985, who demonstrated that in vivo stimulation over the motor cortex induced involuntary hand movements in healthy human subjects (Barker, Jalinous, & Freeston, 1985; Barker, Freeston, Jalinous, & Jarratt, 1987). TMS is a non-invasive method which can, depending on stimulation parameters, transiently inhibit or facilitate on-line information processing. Although, the size of the effective stimulating field and the amount of current spread in the tissue of the head are dependent on intensity and current cortical thresholds, with the use of specially designed stimulation coils, TMS may be capable of mapping cortical functional regions on the scalp with a spatial resolution of about a square centimeter. The cone-shaped field strength directly under the coil can be as large as 2.5 Tesla (T) (Stewart, Ellison, Walsh, & Cowey, 2001). The standardized stimulation parameters consist of frequency, intensity and duration. It seems evident that stimulation frequencies of $\leq$ 1 Hz suppress, whereas frequencies of $\geq$ 5 Hz increase neural excitability (Pascual-Leone, Bartres-Faz, & Keenan, 1999; Pascual-Leone et al., 2000). Since on the cellular level TMS is similar to direct electrical stimulation (George & Belmaker, 2000) the underlying working mechanisms of TMS and its effect are presumably due to transient changes in the intra- and extra-cellular concentrations of sodium (Na^+), potassium (K^+) and chloride (Cl^-) ions.

Based on the neuro-modulatory properties of TMS, one line of research has focused on studying the role of the frontal cortex in relation to psychopathological conditions, such as major depression, in which a relative left hypometabolism has been implicated (for overview see Nahas, Lorberbaum, Kozel, & George, 2003). Several clinical studies have been able to show antidepressant efficacy by applying fast fre-

quency over the left frontal cortex to increase neural excitability (George et al., 1997; Pascual-Leone, Rubio, Pallardo, & Catala, 1996), although negative results have been shown also (see for a review Wassermann & Lisanby, 2001). Furthermore, Klein et al. (1999) reported antidepressant effects by dampening neural excitability after slow frequency TMS over the right FC as well, encouraging them to suggest that in particular the homeostasis in brain activity and interplay between the left and right frontal cortex are disturbed in major depression. There are already a sufficient number of studies, that several meta-analyses have been published demonstrating efficacy across studies and laboratories (Burt, Lisanby, & Sackeim, 2002; Kozel & George, 2002; McNamara, Ray, Arthurs, & Boniface, 2001) and the procedure is now medically approved in Canada, Israel and several other countries.

Although TMS can induce changes in cortical excitability, basically, the neural firing that TMS promotes is random and can best be perceived as neural noise induction (Stewart et al., 2001). In other words, the changes in neural activity have no intrinsic meaning to the system itself and can therefore be utilized as a "virtual lesion" technique, in which the information processing in a targeted part of the brain can be investigated by means of transient disruption (Pascual-Leone et al., 1999; 2000). Using this method, it becomes possible to investigate the specific contribution of an underlying brain area in complex information processing. In this context, it can be noted that for simple responses, such as motor movements, the TMS-induced neural activation can activate the function of a brain area (e.g., a thumb twitch from the motor cortical representation area of the thumb, which can be further facilitated by motor imagery (Fadiga et al., 1999), but in situations where an area has to process complex information, the stimulation effect might invariably be a more functional disruptive one. Thus, wherever one gets a facilitation of a function with high frequency TMS, one can surmise that a generalized arousal state has been promoted, whereas if both low and high frequency parameters have similar effects, one can surmise that detailed information processing was disrupted. In any event this can provide a definitive

causal manipulation to evaluate the functional role of cortical areas in specific types of psychological functions.

Whereas fMRI and EEG for instance have high spatial and temporal resolution respectively, TMS has so-called functional resolution, in which spatial and temporal aspects of activation in brain structures can be combined and causally related to its function. For instance, Amassian et al. (1998) demonstrated the inability for healthy subjects to detect a visually presented stimulus when TMS was applied over the occipital cortex 80-100 ms after stimulus presentation. This work has not only provided causal evidence for the involvement of the occipital cortex in vision, but also provides some information about the conduction velocity from the retina to the occipital cortex.

Wassermann, McShane, Hallett, & Cohen (1992) were among the first who used TMS to non-invasively map the muscle representations in the human motor cortex. Furthermore, it was shown that stimulation over the left inferior frontal cortex (Broca's area) blocks speech output, so-called speech arrest (Epstein, 1998). By topographically mapping the language representations one can readily locate important brain areas which should be spared in patients suffering from epilepsy who are about to receive resection of brain regions in the vicinity of Broca's area. Although it is theoretically feasible and correct to infer that the language area can be mapped, TMS is for instance not capable of inducing speech arrest in every single subject, arguably due to inter-individual variance in brain morphology, which also makes its clinical utility somewhat limited. TMS can easily deal with issues concerning intra-individual variance with respect to functions represented in the superficial layers of the cortex. However, when the critical brain region for speech production in a given individual are buried deep in sulci they are more difficult to reach, since current TMS techniques are not capable of targeting more medial regions of the cortex without focality loss.

Grafman and Wassermann (1999) reviewed the specific contribution of cortical areas in different aspects of learning and attention with the use of TMS and the highlighted idea of functional decomposition. More recently, two TMS studies by D'Alfonso, Van Honk, Hermans, Postma,

& De Haan (2001) and Van Honk, Schutter, D'Alfonso, Kessels, & De Haan (2002) found evidence for the involvement of the left and right prefrontal cortex (PFC) in the modulation of attention to angry and fearful facial expressions respectively. Furthermore, Aleman et al. (2002) demonstrated that the parietal and not the occipital cortex participates in top-down visuospatial mental imagery by showing that TMS over the parietal cortex resulted in the deterioration of task performance, which was not evident after occipital and sham stimulation.

With respect to predictions that can be made on the basis of existing brain imaging data a double dissociation was recently found for cognitively and affectively driven inhibition control in monkeys (Dias, Robbins, & Roberts, 1997). Whereas damage to the lateral prefrontal cortex was accompanied by a loss of inhibitory control in attention selection, a dysfunctional orbitofrontal cortex resulted in the loss of inhibitory control in affective processing. Interestingly, a TMS mapping procedure could be used to investigate whether this double dissociation applies to the human cortex as well, even though the use of TMS in orbitofrontal areas is difficult to use because of pain induced by direct stimulation.

On the basis of decomposing complex cognitive functions into separate units and localization, TMS can determine which brain areas are actively involved in specific functions as well as when they are participating. Since the strength of the induced magnetic field as a function of distance fits a decaying exponential function (Bohning, 2002), the actual depth of penetration is only a few centimeters, thus initially only neocortical tissue is directly affected. However, recent studies have demonstrated that besides the local effects, more remote effects can also be obtained (Fox et al., 1997; Nahas et al., 2001; Schutter, Van Honk, D'Alfonso, Peper, & Panksepp, 2003). The brain consists of functionally interconnected networks, hence stimulating a specific part induces changes in other areas of the network as well. For example, Paus et al. (1997) demonstrated such transsynaptic effects by obtaining distal cerebral blood flow responses in the posterior cerebral regions after stimulating an anterior region of the cortex. It remains possible that these more remote effects, which are filtered through normally operating brain functions, reflect the

promotion rather than simply the disruption of brain functions. This would, of course, substantially complicate the interpretation of findings achieved with TMS.

The above mentioned studies nicely demonstrate the uniqueness of TMS to directly link function and underlying structural representations (isomorphy). Such cortical mappings of function resemble what Uttal (2002) called the *new phrenology*. However, TMS adds a whole new dimension to the discussion that Uttal did not consider. Not only is TMS unique in its ability to establish a causal connection between functions and the underlying neural representations in spatial as well as the temporal domains of information processing, but by combining TMS with brain imaging it can also help map the fuller extent of participating brain systems. This can lead to highly resolved hypotheses about what various brain regions contribute to the whole. Still, a main caveat regarding TMS research is the basic assumption that cognition and structure are directly related in an isomorphic fashion; a linear relationship between function and implementation. For simple cognitive behaviors, such as for instance face recognition which use anatomically restricted functional architectures, this is not problematic. However, complex (meta)cognitive behaviors seem not to be wired up in simple structural clusters in which local computations are performed. Indeed, most higher-order cognitive functions, such as reasoning and problem solving, may emerge from very dynamic, distributed and complex non-linear brain processes. Those types of issues will have to wait further resolution of technological methodologies.

TMS, reductionism and explanatory pluralism

According to the antireductionists, neurobiological models are not suitable in modeling complex cognitive function. McCauley and Bechtel nicely elucidate this notion by writing;

> "…since these antireductionists insist that any of various considerations (such as multiple realizability or intractable complexity or the

> impregnable uniqueness of intentional contents or the elusiveness of subjective consciousness) suffice to block the necessary mapping the classical models of reduction require." (McCauley & Bechtel, 2001; p. 739).

On the other hand, Sober (1999) argues that the essence of reductionism (i.e., relating the higher (functional) and lower (structural) orders of modeling) is the claim that the effect on the appearance of the higher functional attributes are caused by the lower structural properties of the system. Whereas modern neuroimaging can only reveal correlations between the higher and lower orders, TMS is provides access to utilize causal manipulations that may provide bridging principles between the former and the latter. Although most mind-scientists agree on the fact that basis of cognitive function is neural by nature, they largely vary with respect to how the brain actually accomplishes the instantiation of function and more importantly whether it actually tells you something about the intrinsic properties of the function itself McCauley and Bechtel (2001) advocate the idea of explanatory pluralism and the heuristic identity theory (HIT) and state that:

> "Explanatory pluralism holds that a proper interpretation of the consequences of successful inter-theoretic mapping depends (at least) upon the theories' respective levels of explanation in science and their temporal relations." (McCauley & Bechtel, 2001; p. 737).

According to the HIT both the cognitivistic and reductionistic levels of explanations can refer to an independent ontological status. Unique and distinct properties of function can be revealed on both levels and can be used as heuristics in order to promote cross-disciplinary research to link levels in either non-radical reductionist or supervenient relationships. Furthermore, the HIT states that the neural identities are not the end-points of scientific research, but rather constitute the necessary premises in ultimately explaining function. In this respect, the HIT approach provides for an important philosophical ground for the emergence of a

"gentle" reductionism in interdisciplinary research and TMS is one of the main approaches that can currently contribute to the understanding of the physiological underpinnings of functions within the intact human brain.

Most TMS research targets a single cortical site at a given time. However, the use of multiple coils over different locations and specified latency times of stimulation might be able to reveal more dynamic and distributed patterns of neural processes underlying a function both temporally and spatially. For instance, Anand, Olson, & Hotson (1998) and Pascual-Leone and Walsh (2001) stimulated two distinct sites in the visual system at different time points in close proximity in order to investigate signal propagation. The above TMS studies were able to reveal feed-forward and feed-backward projections between the striate and extra-striate cortex, demonstrating a functionally dynamical yet structurally localized approach in investigating the brain-function relationship. A recent study by Harris, Miniussi, Harris, & Diamond (2002) actually demonstrated that the primary sensory cortex served not only as a local conduit for on-line sensory processing, but also forms a temporarily representation for information storage (memory trace) that contributes to working memory.

The maximum magnetic field strengths that current TMS machine can generate lie between 1.5 and 2.5 T. Although presently only cortical areas can be stimulated directly, machines with larger output would be able to penetrate more deeply into the brain, albeit this could make analysis more complex, since more brain areas would be concurrently influenced. Alternatively, in combination with the use of several TMS coils one might eventually employ the so-called non-invasive gamma-knife approach, originally introduced by Lars Leksell in 1967. In this procedure multiple weak sources are used to produce a single strong focus. The gamma knife operates by a process called stereotactic radiosurgery, wherein multiple beams of radiation converge in three dimensions to focus precisely on a small volume or structure with a spatial resolution up to 0.3 mm^3. This way the focality of stimulation can be maximized to target subcortical regions of interest, especially those that have been shown to anatomically converge on specific brain areas. In such endeav-

ors, neuro-navigation using structural MRIs, and potentially fMRIs (see Nahas et al., 2003), can be utilized to further enhance the anatomical precision of stimulation.

Although, the existing tools are not yet able to unveil *all* the mysteries surrounding the spatial and temporal representations of specific psychological functions in the brain, in agreement with Bechtel (2002), we would argue that this type of work is setting the stage for substantive progress. Neuroimaging techniques, despite their many false negatives and some false positives, have been very valuable in providing new insights regarding brain-mind inter-relations, and now these ideas have to be cashed out with causal manipulations such as those that TMS and psychopharmacological interventions provide. Fully in line with the arguments of McCauley and Bechtel (2001), we agree that the identity claims made in a research program presently serve as a heuristic method for guiding progressive thinking and future research in the field. It is premature to assert that either the brain is too complex or that we humans are not sufficiently cognitively sophisticated, to make progress on such issues. At the same time, we agree that assertions that we can solve all brain-mind problems with the current available set of techniques are delusional, but no more so than claims that we are incapable of making remarkable progress.

Considering for how few years we have had such sophisticated approaches to link mind and brain issues, concluding that the body-mind relationship remains forever inscrutable is premature, and potentially counterproductive. There are already striking examples where a problem that was once deemed inscrutable, namely the nature of affective experiences, is now in the realm of the solvable because of advances in neuroscience and evolutionary biology (Damasio, 1999; Panksepp, 1998). The analysis of those systems has been greatly enhanced by the fact that we share various psychobiological functions with other animals, which is now permitting the analysis of human mysteries to be undertaken at a molecular level in carefully chosen animal models (Panksepp, Moskal, Panksepp, & Kroes, 2002). The current rise of this "bottom-up" philosophy of science is also known as *new wave metascience* (Bickle, 2003).

Conclusion

TMS is a valuable tool for a causal evaluation of brain-mind identity theories. It can promote explanatory pluralism with respect to our endeavors to fathom complex cognitive processes and to bridge the gap in our understanding of how localized cortical areas participate in constructing those processes. Although TMS cannot account for the explanatory gap between neurophysiological dynamics and how subjective experiences arise from such functions of the brain, these new and innovative techniques can identify and locate certain psycho-neural entities (or at least key nodes within the greater whole) by means of true causal analyses. With respect to true causal analysis, it might be useful to make a distinction between how causation is conceptualized by brain-scientists on the one hand and mind-scientists on the other. Since neuroscientists are primarily interested in the biological representation of function they consider physiological manipulations, such as TMS to be the premise of causation. Mind-scientists on the other hand envisage environmental/ psychological manipulations to be "causal" as well. Whereas the former allow access biological mechanisms on which function supervenes, the latter only permit access to functional issues with no possibility of deriving information about the neurophysiological causes, imposing a large constraint on studying brain-function relationships.

Regarding the neuroscientific approach, we no longer have to rely simply on mere causal suppositions that can arise in abundance from correlations between structure and function derived from modern brain imaging. When supplemented with additional causal tools, ranging from subtle psychological to neurochemical manipulations, the mind-brain conundrum should yield substantially to the onslaught of the modern affective, behavioral and cognitive neurosciences. We encourage the skeptics to be patient, and to endeavor to evaluate the available technologies directly as opposed to highlighting the all too abundant difficulties merely from the sidelines. It is only by fully entertaining the possibilities of all the new technologies and methodologies that substantive understanding of these very difficult mind-brain issues can emerge.

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1

Introduction: Affective neuroscience

Affective Neuroscience

In experimental psychology, the investigation of processes involving motivation and emotion through rigid scientific practice has long been considered inconceivable and unrealizable. A high degree of subjectivity and inter-individual variance compromised the application of the normative scientific approach in the domain of affective processing. Affective processing has occasionally even been discarded as epiphenomenal or instantiated by our cognitively based information processing apparatus. When the computer metaphor reigned the way scientists looked at human behavior during the 80s and early 90s, affective processing was even almost completely eliminated from the scientific discourse. The main reason for this disinterest was that motivation and emotion could not be captured in a formal digital system comprised of rules, symbols and discrete computations. According to the functionalistic approach, human cognition could be modeled without the necessity of dealing with the hardware (the brain). Lately, rapid advances in technological applications, such as functional neuroimaging methods including positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have caused a revolutionary paradigm shift from a functionally oriented to a neurobiologically oriented approach in studying human behavior. The combination of the traditional neurosciences and psychology resulted in the interdisciplinary emergence of the so-called cognitive neuroscience, which ambitiously set out to build a neural architecture of human cognition. Only a few years ago scientists really started to appreciate the role of emotion and motivation by realizing that the neuroscientific approach was a window for embodying the intangible. This embodiment did not only give rise to a discipline, called affective neuroscience, but also to a more neurobiologically oriented approach in studying emotional disorders, a discipline termed neuropsychiatry.

Although, adversaries of the cognitive and affective neuroscientific account are sometimes accused of reductionism and neo-phrenology, few people will nowadays defy the notion that human behavior is instantiated in the central nervous system (CNS). However, how human behavior is exactly implemented in the CNS is a whole different issue.

havior is exactly implemented in the CNS is a whole different issue. The relation between function and neural representation has been a long-standing issue in both the neurosciences and philosophy. The previous chapter addressed the accusations of reductionism and neo-phrenology by discussing both the potentials as well as the limitations of applying neuroscientific methodology in studying the structure-function relation (Schutter, Van Honk, & Panksepp, 2003). Nevertheless, it has become apparent that comprehension of physical properties of a system is essential in order to be able to get at a more complete understanding of the function the system generates (Schutter, 2001). In other words, by carefully monitoring how the CNS and its peripherals behave during the execution of a function of interest we may attain crucial knowledge regarding the what, where, when and how issues. The remainder of the introductory chapter will focus on neuroscientific studies that have contributed to the current knowledge and understanding of affective processes in the human brain.

Engage- and Retreat-related behavior and the prefrontal cortex

Effectively regulating one's behavior is crucial for adapting to the environment. In simple organisms, adaptive behavior can be established through simple stimulus-response associations in terms of reward and punishment. Reward-punishment contingencies lie at the most basic levels of complex affective experiences and these relative simple reinforcement programs are powerful bioregulatory mechanisms for explaining and predicting behavior.

Although in humans the complexity of affective processing extends beyond simple reward-punishment contingencies, their heuristic value persists. The evolvement of the cerebral cortex was accompanied by increases in functional connectivity between brain regions and paralleled by an expansion of cognitive and affective processing capacity. Davidson (1988, 1998) was among the first to investigate affective processing aspects of human behavior using electrophysiological recordings over the prefrontal cortex (PFC). He discovered that the PFC is part of a

higher order motivational system in which the left and right PFC are involved in approach- and withdrawal-related behavior, respectively. The left PFC subserves an approach system implicated in positive affect, whereas the right PFC subserves the withdrawal system implicated in negative affect (Davidson, 1998). Recent electroencephalogram (EEG) studies (Harmon-Jones & Allen, 1997, 1998; Kalin, Larson, Shelton, & Davidson, 1998) demonstrated a left PFC bias for the emotion anger. Although, these findings defy the positive-negative valence model, they are in accordance with the involvement of the left PFC in approach-related behavior. Anger is an approach related emotion, associated with social dominance and proneness to aggression (Van Honk & De Haan, 2001). Anxiety on the other hand is associated with submission and proneness to avoid threatening social confrontations. When looking at the ecological validity of the fight-flight related dichotomy in affective processing, the emotion anger can be linked to the approach system, whereas the emotion anxiety is involved in the withdrawal system. Although fear and anxiety are often used interchangeably, fear arises in reaction to actual perceived threat, whereas anxiety applies exclusively to humans and includes envisioned representations of danger as well (Marks, 1969).

EEG has a high temporal resolution in the order of milliseconds and is suitable to map out hemispheric differences in neural activity in terms of anterior-posterior and left-right asymmetries. The spatial resolution however is limited, making it hard to draw inferences on specific cortical structures within the PFC. The PFC can be divided in a dorsolateral (DLPFC), ventromedial (VMFC) and orbitofrontal cortex (OFC) part, which all have direct or indirect (via the thalamus) efferent and afferent projections to the phylogenetically older emotion generating structures of the brain, called the limbic system (Fuster, 1997). It has been argued that the DLPFC is more concerned with the cognitive aspect of emotion regulation, while the OFC is involved in integrating the descending DLPFC with the ascending limbic information (Rolls, 2001). This interplay is argued to produce an emotional state which is conveyed into approach- or withdrawal-related behavior. Approach-related behavior is

controlled by the left PFC, whereas withdrawal-related behavior is controlled by the right PFC. On the behavioral level, the state of reward dependency initiates approach-related behavior and is directly linked to the emotion anger, whereas punishment sensitivity directs withdrawal-related behavior and is coupled to the emotion anxiety. The balance between these motivational states is a prerequisite for adaptive goal-directed behavior. In Figure 1.1 this motivational balance model is depicted with the different levels of affective processing as well as the interdependency between these levels. Since the constructs of each axis are highly interdependent and to some extent reflect similar psychological processes, the present thesis axis I is denoted as the Engage system, whereas axis II is termed the Retreat system.

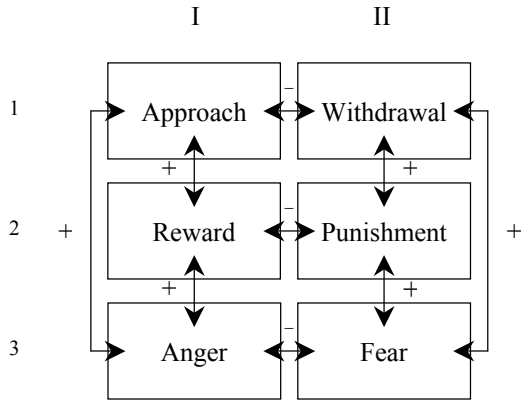

Figure 1.1. Affective processing model comprised of two axes with three levels of representation. Within the "approach-reward-anger" (Engage system) [I] and "withdrawal-punishment-anxiety" (Retreat system) [II] system the different levels, that is [1] emotion, [2] motivation and [3] behavior are positively related. The axes mutually inhibit each other to create an allostasis between the two systems. –; inhibitory: +; excitatory projection.

Prefrontal cortex, steroid hormones and depression

The pursuit of obtaining the neural correlates of affect is not solely intended to gain more insight into its neural architecture, but also to broaden our understanding of psychopathological conditions in which normal brain function is disrupted and has become maladaptive. Several empirical studies have indicated that depression for instance is character-

ized by low approach- and increased withdrawal-related functioning (Kasch, Rottenberg, Arnow, & Gotlib, 2002) or reduced reward dependency and increased punishment sensitivity. In agreement, depression is often accompanied by high levels of the withdrawal-related emotion anxiety. Notably, these findings are conceptually consistent with the neurophysiological evidence of reduced activity in the left PFC (George et al., 1996; Davidson, 1998) and with the more recent proposal that depressives suffer from a relative hypoactivity in the left as compared to the right PFC (Cummings, 1998; Menkes, Bodnar, Ballesteros, & Swenson, 1999). Based on this behavioral and biological based theory of imbalance it is reasonable to conjecture that chronic elevations of anxiety ultimately result in depression or subtypes such as melancholic depression. The elevated state of anxiety reflected by increased punishment sensitivity and lowered reward dependency might compromise the capability to effectively deal with negative events and/ or stressors, thereby potentiating depression. Acute and chronic stress are associated with elevations of the glucocorticoid-hormone cortisol, the end-product of the limbic-hypothalamic-pituitary-adrenal (LHPA)-axis. Chronically elevated cortisol levels have been observed in socially anxious juveniles (Schulkin, Gold, & McEwen, 1998) and depressed individuals (Holsboer, 2000; Gold, Drevets, & Charney**,** 2002). Cortisol facilitates corticotropin releasing hormone (CRH) gene expression in the central and basolateral part of the amygdala thereby enhancing states of fear and anxiety (Schulkin & Rosen, 1999). Therefore, cortisol is considered to be a biochemical marker for anxiety and depression. Interestingly in the present respect is a study of Kalin et al. (1998) which showed that predominantly right-sided PFC activity was associated with higher levels of cortisol. This finding is in accordance with the assumed relationship between cortisol and the withdrawal-related emotion anxiety and depression. Furthermore, Van Honk et al. (1998) demonstrated that increased basal cortisol levels were associated with more avoidant responses to angry facial expressions. The avoidant response to the angry face can evolutionary be linked to submission and intraspecific anxiety-related withdrawal (Van Honk & De Haan, 2001). These avoidant responses

have been characterized as indices of low mood. According to Nesse (2000) low mood can have fitness advantage in terms of conservation withdrawal. However, when low mood reaches a pathological level and looses its advantageous fitness properties, depression lures. In addition, Van Honk, Schutter, Hermans, & Putman (2003) demonstrated that higher basal levels of cortisol is correlated to withdrawal-related affective states of enhanced punishment sensitivity and lowered reward dependency. Although these relations to cortisol were observed in healthy populations, when more extreme this motivational imbalance might predispose for melancholic depression. Kasch, Rottenberg, Arnow, & Gotlib (2002) recently provided evidence for the association between motivational imbalance and depression by showing that depression was positively correlated to punishment sensitivity and inversely to reward dependency. The steroid hormone testosterone, the end-product of the limbic-hypothalamic-pituitary-gonadal (LHPG) axis, is on the other hand associated with well-being (Rabkin, Wagner, & Rabkin, 1999) and anxiolytic properties. In line with these phenomenological properties, testosterone is also associated with a dominating personality style and thus with the approach-related emotion anger (Van Honk et al., 1999). In particular reductions in anxiety promote approach-related behavior, which is reflected in for instance vigilant attentional responses towards threatening angry facial expressions. Van Honk et al. (1999) demonstrated a positive relationship between salivary levels of testosterone and approach-related behavior. Not only did higher levels of testosterone correlate with increased selective attention towards angry faces, testosterone was also related to higher self-reported anger. In line with the fact that testosterone promotes approach-related behavior, increases in the cardiac defense reflex, a rapid acceleration of heart rate reflecting action preparedness, to angry facial expressions have been observed after testosterone administration (Van Honk et al., 2001). Finally, increases in approach-related affective processing characterized by lower punishment sensitivity and enhanced reward dependency have been demonstrated after testosterone administration (Van Honk et al., in press). In sum, testosterone is related to approach-related affective processing and well

being, whereas cortisol is associated with withdrawal-related affective processing and depression.

Dissociated conscious and unconscious affective processing

When emotional facial expressions are displayed in the order of fourteen milliseconds followed by a mask which consists of a scrambled face, individuals are not able to consciously identify the emotional expression. Higher order information processing and emotion regulation in the cerebral cortex is precluded (Ledoux, 1996: Whalen et al., 1998). A primordial limbic route consisting of a thalamic-amygdaloid pathway is nevertheless able to extract crucial emotional features of the masked image display on an unconscious level. Interestingly, the acute central brain effects of testosterone and cortisol on affective processing are primarily established by binding to steroid responsive neural networks. Since the thalamic-amygdaloid pathway of the limbic system is part of a large steroid responsive network (Wood, 1996), testosterone and cortisol levels likely establish their effects on Engage- and Retreat related affective processing by way of the thalamic-amygdaloid pathway. The acute effects of repetitive transcranial magnetic stimulation (rTMS) are, on the other hand, induced primarily at the cortical level. In agreement, the most pronounced effects of testosterone and cortisol on affective processing appear at the unconscious level of affective processing (Van Honk et al., 1998; Van Honk & Schutter, 2000), whereas rTMS predominantly influences conscious affective processing. Further evidence for this dissociation between subcortical-unconscious and cortical-conscious affective processing will be presented in this thesis.

Heuristic neurobiological model

The previous sections have dealt with the neurobiological correlates of affective processing. On the cortical level, it is postulated that the left and right PFC are involved in Engage- and Retreat-related affective processing respectively (e.g., Davidson, 1998). Neurophysiological studies have shown that the left and right PFC exert a mutual inhibitory

influence on activity, which can be linked to the functional workings of the behavioral approach and withdrawal dichotomy. On the limbic-endocrinological level, the LHPG-axis (end-product: testosterone) is associated with approach-related affective processing, whereas the LHPA-axis (end-product cortisol) is related to withdrawal-related affective processing. Interestingly, studies have provided evidence that cortisol suppresses the LHPG axis activity and diminishes the production of testosterone (Keltner, Moffitt, & Stouthamer-Loeber, 1996), whereas testosterone suppresses the LHPA axis activity and diminishes the production of cortisol (Viau, 2002).

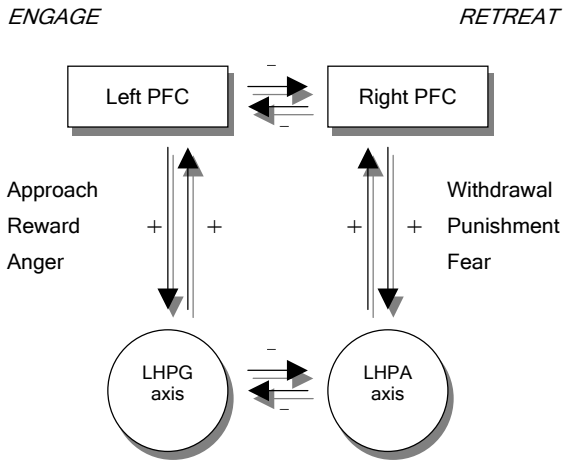

Figure 1.2. Heuristic neurobiological model of Engage- and Retreat-related affective processing. Left PFC; left prefrontal cortex: Right PFC; right prefrontal cortex: LHPA-axis; limbic-hypothalamic-pituitary-adrenal axis: LHPG-axis; limbic-hypothalamic-pituitary-gonadal axis: ⁻; inhibitory: +; excitatory projection.

It is therefore suggested that, comparable to the left-right dichotomy in the PFC, testosterone and cortisol action are mutually inhibitory resulting in opposite effects on Engage- and Retreat-related affective processing, but on a predominantly subcortical level. Figure 1.2 depicts a heuristic neurobiological working model of affective processing. The model incorporates the Engage and a Retreat systems as outlined in Figure 1.1 Whereas the Engage system is coupled to the left PFC and testosterone, the Retreat system is linked to the right PFC and cortisol.

It should however be noted that the model is not intended to present an exhaustive behavioral and physiological architecture of human affective processing, which can be integrated on the basis of isomorphic principles in terms of reducing one functional property to one specific brain region or mechanism (see Schutter et al., 2003).

General outline

Throughout reading this thesis, one should bear in mind, that when the complexity of both brain and function is taken into account it is inevitable that in order to achieve more functional neurophysiological insights into affective processing in the near future, it becomes essential to start investigating more dynamically oriented brain models. These models should focus on functional interactions as well as different levels of neural organization, ranging from information transfer between different regions to the effects of endocrine hormones in these regions. This may not only expand our fundamental knowledge about the physiological instantiation of emotion and motivation, but also provide for more insight into the etiology of mental disorders from a brain-oriented theoretical perspective. The aim of the current thesis is threefold: (1) To further investigate the role of the PFC in the Engage and Retreat systems; (2) To modify our hypothetical model of Engage- and Retreat-related affective processing by incorporating additional brain regions; (3) and to introduce a modified working model of psychopathology by discussing the possible role of alternative rTMS methods in the treatment of major depression. In Chapter 2-4 the psychophysiological, electrocortical correlates of affective processing will be studied by means of deactivating the PFC using slow rTMS. Chapter 5-7 will in particular focus on the psychological and electrophysiological properties of reward and punishment. In Chapter 8-14 the research focus is shifted from the PFC to the parietal cortex, the cerebellum and the functional neuroanatomical connections to the PFC in relation to affective processing. The studies will consist of combined endocrinological, magnetic brain stimulation and electrophysiological studies. Based on the insights ob-

tained and discussed in Chapters 2-14, Chapter 15 will focus on the potential role of magnetic brain stimulation in the treatment of clinical depression. Finally, the outcomes and interpretation of the studies will be recapitulated in Chapter 16, wherein a modified heuristic model of Engage- and Retreat-related affective processing will be presented and future prospects will be discussed.

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2

Effects of slow rTMS at the right dorsolateral prefrontal cortex on EEG asymmetry and mood

Neuroreport 2001, 12, 345-347.

Abstract

In a sham-controlled design (n = 12), slow repetitive transcranial magnetic stimulation (rTMS) was applied to the right dorsolateral prefrontal cortex for 20 min, and the subsequent effects on mood and the EEG spectrum were investigated. Analysis revealed a significant left hemisphere increase in EEG θ activity at 25–35 and 55–65 min after stimulation. In addition, participants reported significant decrease in anxiety immediately after stimulation, as well as 35 and 65 min after rTMS. These findings indicate that reductions in anxiety after slow rTMS at the right dorsolateral prefrontal cortex are associated with a contralateral increase in θ activity.

Introduction

There is now abundant evidence for the involvement of the prefrontal cortex in affective processes. According to the directional model of negative affect, the left anterior sector of the brain is involved in the approach-related emotion anger, whereas the right prefrontal sector is linked to the withdrawal-related emotion anxiety (Fox, 1991; Harmon-Jones & Allen, 1998). Recently, D'Alfonso, Van Honk, Hermans, Postma, & De Haan (2000) applied slow rTMS over the right dorsolateral prefrontal cortex. This method is commonly suggested to decrease neuronal activity in the stimulated area. Enhanced approach and reduced withdrawal-related motivation were found, as indexed by a motivational selective attention task. It was shown that right compared to left prefrontal stimulation induced vigilant attention for angry faces, in agreement with a line of findings in our laboratory in relation to low levels of social anxiety and high levels of anger (Van Honk & De Haan, 2001).
Electrophysiologically, these hemispheric differences are commonly assessed on the α power band (8–13 Hz) in the EEG spectrum, which is inversely related to cortical activity. Decreased activation of the right prefrontal cortex induced by slow rTMS should therefore result in a shift of the cerebral α asymmetry to the right prefrontal area, accompanied by reductions in anxiety and increases in anger. The present study was designed to investigate the latter hypotheses. rTMS was applied over the right dorsolateral prefrontal cortex, and its effects on self-reported mood (i.e., anger and anxiety) and the EEG frequency bands θ (4–7 Hz), α (8–12 Hz) and β (13–30 Hz) were investigated.

Method

Participants
Twelve right-handed volunteers (four females) aged between 19 and 42 years (mean ± SD, 28.4 ± 8.9) participated in this single blind, cross-over, sham-controlled experiment. An informed consent was obtained, and subjects with a history of neurological or psychiatric disorder were excluded. All subjects were naïve of TMS, unaware of the aim of the

study and were paid for participation. The local ethical committee of the Faculty of Social Sciences approved the study.

Apparatus and EEG recordings

A Neopulse transcranial magnetic stimulator (Neotonus, Inc.) was used on separate days either to stimulate the right dorsolateral prefrontal cortex (F4) or to induce sham stimulation, with the coil positioned 90% tangential to the surface of the head. The target of rTMS was based on the international 10/20 system of EEG electrode positions. Subjects were stimulated for 20 min at 130% of the motor threshold (MT) with a frequency of 1 Hz. Stimulation and sham conditions were randomized and counterbalanced across the participants. EEGs were recorded from the homologous F3 and F4 scalp positions, using an Electro-Cap with Ag/AgCl electrodes (Neurosoft, Inc.). EEG signals were referenced to an electrode placed behind the subject's right ear. For the purpose of artifact scoring, vertical (VEOG) and horizontal (HEOG) eye movements were recorded. Ag/AgCl electrode pairs (bipolar) were placed at the supra- and suborbit of the right eye and at the external canthi of each eye. ECI EEG gel was used for both EEG and EOG and all electrode impedances were < 5,000 Ω. An acquisition amplifier (Ampligraph) was used to filter incoming signals (low-pass cut-off frequency 30 Hz; time constant 3 s.). For the EEG recordings NeuroScan software was used. Amplification was set at 20,000 for both the EEG and EOG leads, and the sample rate was 250 Hz. The state anger and anxiety scales of the Spielberger State Trait Anger Scale (STAS) (Spielberger, Jacobs, Russell, Crane, 1983) and State Trait Anxiety Inventory (STAI) (Spielberger, 1998) were used in order to quantify self-reported changes in mood.

Procedure

First, all subjects completed the first of four STAS and STAI scales. Next, the Electro-Cap was positioned, and the subject was instructed to relax, without falling asleep in a dimly lit room. One of two randomly generated sequences of five 1 min blocks of eyes-open relaxation and five 1 min blocks of eyes-closed relaxation measurements were used

during each recording and were counterbalanced within each session. After the first EEG recording, the F3 and F4 electrode sites were marked and the EEG cap was removed in order to start the rTMS procedure. At each first session, the MT was quantified, using the left thumb movement visualization method (D'Alfonso et al., 2000). Afterwards, slow rTMS at 130% MT with a frequency of 1 Hz for 20 min, or sham was applied at the F4 electrode position. A second version of the questionnaires was completed after rTMS. Next, the EEG cap was placed back on the subject's head, ensuring that the F3 and F4 electrodes sites were back on their previous positions and all electrode impedances were < 5,000 Ω.

Ten minutes after rTMS, a second 10 min EEG, 10–20 min post-rTMS was recorded. With a resting period of 5 min a third EEG measurement, 25–35 min post-rTMS was completed followed by a third set of questionnaires. Between 40 and 50 min post-rTMS a fourth EEG was recorded and a last EEG measurement was obtained 55–65 min after rTMS. The session was concluded by a final set of questionnaires.

Analyses

Portions of each 1 min EEG signal containing eye movements, muscle movements, or other sources of artifact were rejected prior to further analysis. The designation of artifact in one of the two leads resulted in the removal of data in both channels to ensure that data preserved in both channels were derived from the identical time periods. After artifact rejection, EEG data were corrected for horizontal and vertical eye movements. Next, 1,024 s. chunks of averaged artifact free EEG were used for spectral analysis. Epochs of artifact-free EEG were extracted through a Hamming window (length 10%) in order to reduce spurious estimates of spectral power. For each chunk, a fast Fourier transform method was used to derive estimates of spectral power (μV^2) in different 1 Hz frequency bins for each electrode site. Spectral power values were then averaged across all epochs within a single baseline. Power values were then converted to power density values ($\mu V^2/Hz$) for the standard

frequency bands. Data were analyzed, using MANOVAs and *post-hoc* paired *t*-tests. Significance level was set at $\alpha < 0.05$ (two-tailed).

Results

Analysis of the EEG spectrum revealed no significant effects of stimulation, on either the expected α band or on the β band. However, a stimulation × hemisphere interaction was found for power [$F(1,11) = 5.40$: $p = 0.04$] and *post-hoc* analysis revealed a significant increase in left prefrontal θ activity between 25 and 35 [$t(11) = 2.28$: $p < 0.04$], and 55–65 min [$t(11) = 2.59$: $p < 0.02$] after rTMS. Figure 2.1 shows the sham corrected differences in θ power densities for the left and right dorsolateral prefrontal regions.

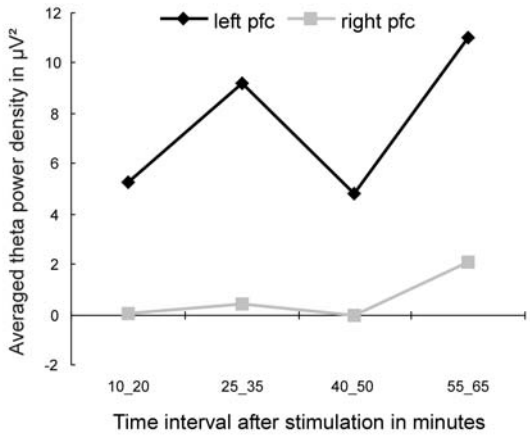

Figure 2.1. Sham corrected difference θ power densities for the left and right prefrontal cortex after slow rTMS.

A MANOVA yielded an overall significant reduction of anxiety in the rTMS condition, compared to the sham condition [$F(1,11) = 10.23$: $p = 0.008$]. Figure 2.2 represents the baseline corrected means for self-reported anxiety. *Post-hoc* analysis revealed that this reduction was significant immediately [$t(11) = 2.93$: $p = 0.01$], following 35 min [$t(11) = 2.22$: $p = 0.04$] and 65 min [$t(11) = 2.32$: $p = 0.04$] after rTMS.

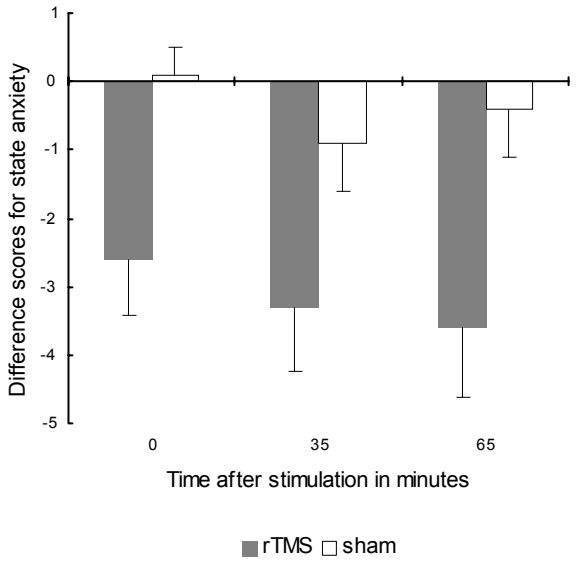

Figure 2.2. Baseline corrected mean scores and SEM for self-reported anxiety after slow rTMS and sham.

Discussion

In accordance with our hypothesis, slow rTMS resulted in a significant reduction in anxiety. Theoretically, inactivation of the right prefrontal area should be accompanied by reduced withdrawal-related negative affect. However, elevations in anger nor the hypothesized reductions in right prefrontal activation on any of the EEG frequency bands were observed. There was a significant contralateral increase in θ activity after slow rTMS. Interestingly, a recent rTMS–fMRI study also provides support for such contralateral effects of slow rTMS when stimulating at high intensities (Nahas et al., 2000). It this interleaved rTMS–fMRI study of Nahas et al. (2000), stimulation site was the left PFC and increases were found in right PFC activity. The authors speculated about the possibility of increased pain at high intensities resulting in activation in right-hemispheric biased pain circuits. The contralateral increases after slow rTMS observed in this study are, however, right-to-left, which refutes such an alternative explanation, and suggests that the findings of

both Nahas et al. (2000) and the present study reflect real rTMS-induced effects on brain activation (Ziad Nahas, personal communication).

There is also substantial evidence for an inverse relationship between the behavioral and physiological effect we observed after rTMS. Elevations in θ power have been linked to reductions in anxiety in several studies (Panksepp, 1998), and the present left-sided bias for θ power has been demonstrated in clinically anxious subjects (Borkovec, Ray, & Stöber, 1998) and in non-clinical subjects, when using anxiety questionnaires (Van Honk, Schutter, D'Alfonso, Postma, & De Haan, 2000) and physiological indications of anxiety (i.e., cortisol levels) (Strelets, Danilova, & Kornilova, 1997). Finally, motivational aspects of attention are suggested to be specifically sensitive to the EEG θ rhythm (Vinogradova, 1995), and in our earlier slow rTMS study (D'Alfonso et al., 2000) we also stimulated over the dorsolateral cortices with comparable stimulation parameters, and found significant changes in motivated attention

This study shows that slow rTMS at suprathreshold intensities over the right dorsolateral prefrontal cortex induces significant reductions in anxiety and instigates contralateral increases in EEG θ power. Increases in left prefrontal θ activity and reductions in anxiety, induced by slow rTMS fit in the anterior asymmetrical models of approach- and withdrawal-related emotion (Fox, 1991; Harmon-Jones & Allen, 1998). The contralateral increases in θ power after slow rTMS add to recent evidence demonstrating that local or distant effects of this technique may depend on the stimulation intensity used (Nahas, et al., 2000). The anxiolytic mechanisms of action of rTMS are largely unknown. The converging evidence from literature for an inverse relationship between EEG θ and anxiety, suggests that the present findings provide a first initial insight in an anxiolytic mechanism of action of rTMS. It should however be noted that the physiological and behavioral changes likely depend on a cascade of effects of a highly complex nature, in which cause–effect relationships elude a detailed understanding as yet.

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3

1Hz rTMS over the right prefrontal cortex reduces vigilant attention to unmasked but not to masked fearful faces

Biological Psychiatry 2002, 52, 312-317.

Abstract

Recent repetitive transcranial magnetic stimulation (rTMS) research in healthy subjects suggests that the emotions anger and anxiety are lateralized in the prefrontal cortex. Low-frequency rTMS over the right prefrontal cortex (PFC) shifts the anterior asymmetry in brain activation to the left hemisphere and *reduces* anxiety. The same rTMS technique results in *enhanced* anger-related emotional processing, observed as elevations in attention for angry faces. The current study used low-frequency rTMS over the right PFC, and indexed selective attention to fearful faces, hypothesizing reduction in attention for fearful faces, i.e. a reversal of the latter effect. In a placebo-controlled design, 1Hz rTMS at 130% of the individual motor threshold (MT) was applied for twenty minutes continuously over the right PFC of eight healthy subjects. Effects on motivated attention were investigated by means of an emotional Stroop task, indexing selective attention to masked and unmasked fearful faces. Vigilant attention for masked and unmasked fearful faces was observed after placebo stimulation. As hypothesized, rTMS reduced the vigilant emotional response to the fearful face, but only in the unmasked task. These data provide further support for the lateralisation of the emotions anger and anxiety in the prefrontal cortex. In addition, the absence of an effect for masked fearful faces suggests that changes in emotional processing after a single session of rTMS predominantly involve the cortical affective pathways.

Introduction

In the human brain, emotion is regulated by a complex compound of cortical and subcortical circuits (Damasio et al., 2000; Panksepp, 1998). Gradually, neuroimaging studies are beginning to unravel the underlying dynamics of these affective processing pathways. In accordance with the approach and withdrawal dimensions of the valence hypothesis (Davidson, 1998), recent electroencephalographic (EEG) studies have found evidence for the lateralisation of the negative emotions anger and anxiety in the prefrontal cortex (PFC). The left PFC is evidently involved in anger proneness and the expression of the *approach-related* emotion anger (Coan, Allen, & Harmon-Jones, 1999; Harmon-Jones & Allen, 1998; Harmon-Jones & Sigelman, 2001), whereas the right PFC is involved in fearful behavior and the expression of the *withdrawal-related* emotion fear (Coan et al., 1999; Kalin, Larson, Shelton, & Davidson, 1998).

The cerebral cortex, however, is not necessarily implicated in the processing of anger and fear. Functional neuroimaging studies have indicated that parallel to cortical routes, a primordial subcortical pathway to the amygdala might act as a neurobiological shortcut for fast activation of the arousal system. When presented briefly and backwardly masked, angry and fearful facial expressions are not consciously recognized, but nevertheless seem to be processed "unseen" by way of the thalamic nuclei (Morris, Öhman, & Dolan, 1999; Rauch et al., 2000). Based on this evidence, a simple model of human approach and withdrawal-related affective information processing has been constructed (Van Honk & De Haan, 2001). In this model, the left and right prefrontal cortices are respectively involved in consciously controlled (and thus more sophisticated forms) of behavioral approach and withdrawal (Davidson, 1998). Furthermore, a subcortical affective shortcut, the thalamic-amygdaloid pathway subserves the more biologically prepared emotional response, not confounded by conscious control (Öhman, 1998; Ledoux, 1996). Conscious control is mediated by orbitofrontal and medial structures of the prefrontal cortex (OMPFC). These OMPFC affective control and relay stations have strong afferent and efferent connections with the

dorsolateral prefrontal cortices and the amygdala (Fuster, 1997). Since responses to masked and unmasked facial threat seem to provide insight in the difference between subcortical and cortical human affective information processing, facial threat might well be used to investigate a so-called attentional bias for threat, which characterizes emotional disorders (McNally, 1995; Rauch et al., 2000).

Recently, we set out to investigate the attentional bias for angry and fearful faces. An emotional Stroop task was used, comparing color-naming latencies of masked and unmasked neutral vs. angry or fearful faces. It is suggested that the angry facial expression plays an important role in regulating social interactions. Vigilant attention to the angry face would indicate an inclination to defend social status, that is face-to-face dominance (Mazur & Booth, 1998; Van Honk & De Haan, 2001). In agreement, subjects with high levels of the emotion anger or the hormone testosterone, both associated with interpersonal dominance, display vigilant attentional responses to angry faces in the Stroop task (Van Honk et al., 1999, 2001). In contrast, the fearful face serves as a danger call, indicating that threat is perceived by a member of the social group, which might readily apply to the observer. Anxiety is accompanied by a preoccupation for danger. Therefore, anxious individuals should display vigilant attention to fearful faces. In concordance, the more vigilant attentional response to the fearful face is related to physiological and self-reported indices of anxiety (Hermans et al., 1999). Notably, in the above line of research with the emotional Stroop task, the observed relations defy and sometimes even depend on backward masking (Hermans et al., 1999; Van Honk, Hermans, Putman, & Tuiten, 2000; Van Honk et al., 1998, 2001), suggesting that the *subcortical* pathway is importantly involved in these motivated aspects of attention (Morris et al., 1999; Rauch et al., 2000).

A technical innovation in neuroscience, repetitive transcranial magnetic stimulation (rTMS), is capable of establishing functional brain-behavior relationships by modulating brain activity in controlled designs (Pascual-Leone, Bartres-Faz, & Keenan, 1999). Moreover, recent studies suggest that rTMS is capable of influencing mood and motivated attention in

ways that can be functionally linked to the approach-withdrawal dimensions of behavior, that is anger and anxiety. Low-frequency rTMS (i.e., stimulation frequency ≤ 1Hz) applied over the right dorsolateral PFC above the motor threshold (MT) for thumb movement (i.e., suprathreshold intensity) reduces anxiety and shifts the anterior asymmetry in brain activation to the left (Schutter et al., 2001). Furthermore, *elevations* in selective attention to unmasked angry faces were found after similar rTMS (D'Alfonso, Van Honk, Hermans, Postma, & De Haan, 2000), which are presumably anger-related and possibly left-prefrontally driven emotional responses (Coan et al., 1999; Harmon-Jones & Allen, 1998; Harmon-Jones & Sigelman, 2001; Van Honk et al., 1999, 2001). Initially, this effect of low-frequency rTMS is induced by a transient neural inhibition of the targeted right PFC (Pascual-Leone et al., 1999). However, distant effects in anatomically interconnected brain areas have also been observed using neuroimaging techniques. For instance, low-frequency rTMS over the left or right PFC at the suprathreshold intensities produces contralateral excitation (Nahas et al., 2001; Schutter, Van Honk, D'Alfonso, Postma, & De Haan, 2001; Speer et al., 2000). This effect is possibly due to a reduction in transcallosal inhibition after the initial unilateral deactivation of the targeted area (Pascual-Leone et al., 1998; Schutter et al., 2001).

In sum, due to unilateral inhibition and/ or contralateral excitation, suprathreshold low-frequency rTMS over the right PFC seems to result in more left PFC dominant processing, reductions in anxiety (Schutter et al., 2001) and enhanced anger-related emotional processing (D'Alfonso et al., 2000). Taken together, these findings corroborate EEG evidence for the lateralisation of the approach-related emotion anger and withdrawal-related emotion anxiety. Moreover, effects on motivated attention were not observed in a lateralized suprathreshold low-frequency rTMS study over the PFC when angry faces were presented backwardly masked in the Stroop task (Van Honk & D'Alfonso, *unpublished data*). This suggests that transient changes in motivated attention induced by single-session rTMS predominantly take place on a cortical level.

The aim of the present rTMS study was to further investigate the anterior lateralisation of the emotion anxiety by using fearful faces in the Stroop task. In addition, it was investigated whether rTMS would again induce a selective effect when using a combined masked-unmasked Stroop paradigm (cf. D'Alfonso et al., 2000; Van Honk & D'Alfonso*, unpublished data*), since this would suggest that rTMS is capable of dissociating between conscious and preconscious affective processing. It was hypothesized that suprathreshold low-frequency rTMS over the right PFC would *reduce* selective attention to fearful faces in the unmasked task exclusively.

Method

Participants

Eight right-handed volunteers (four females) aged between 20 and 26 years participated in this single-blind, cross-over, counterbalanced, sham-controlled experiment. An informed consent was obtained, and subjects with a history of neurological or psychiatric disorder were excluded. All participants were naive of TMS and unaware of the aim of the study. The local ethical committee of the Faculty of Social Sciences approved the study.

Procedure

On separate days, 1Hz or placebo rTMS (Neopulse Magnetic Stimulator; Neotonus Inc., Atlanta) with an intensity of 130% of the MT for thumb movement was applied over the right PFC (position F4 according to the International 10-20 system) (see Figure 3.1a). For placebo stimulation, the coil position was tilted 90º (Schutter et al., 2001). 30 Minutes after stimulation or placebo, selective attention for masked and unmasked fearful faces was assessed using an emotional Stroop task comparing color-naming latencies for neutral and fearful faces. This 30-minute delay was used, because low-frequency rTMS research demonstrated delayed and extended effects in time on several indices of emotional processing (D'Alfonso et al., 1999; Schutter et al., 2001; Van Honk et al., 2001).

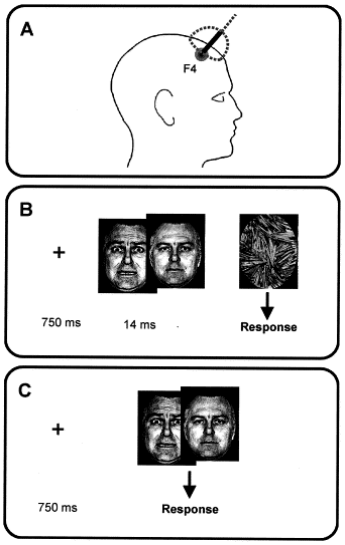

Figure 3.1. (a) Position of stimulation, and sequence of stimulus presentations in (b) masked and (c) unmasked condition.

Emotional Stroop task

Masked and unmasked versions of an emotional Stroop task were employed to measure selective attention to fearful faces. This task requires participants to name as quickly as possible the color of pictures of fearful and neutral facial expressions (red, green, blue and yellow) presented on a 160Hz computer screen at a distance of 60 cm. The dependent measures in the emotional Stroop task are Attentional Bias scores (i.e., the mean individual color-naming latencies of fearful faces minus the individual mean color-naming latencies on neutral faces). Positive Attentional Bias scores, indicating slower color-naming responses to emotional compared to neutral stimuli, are interpreted as a vigilant response, whereas the negative Attentional Bias score, indicating faster color naming responses to emotional compared to neutral stimuli, is interpreted as an avoidant response. The stimuli were taken from Ekman and Friesen's (1976) *Pictures of Facial Affect*. In the masked task, a fixation point was shown for 750 ms, followed by the target stimulus (a neutral or a fearful face) presented for 14 ms, before being replaced by a mask-

ing stimulus. Masking stimuli were randomly cut, reassembled and re-photographed pictures of faces. The presentation of the mask was terminated after vocal response initiation (see Figure 3.1b). In the unmasked task, the fixation point was also shown for 750 ms and followed by the target stimulus (a neutral or a fearful face) and target presentation was terminated after vocal response initiation (see Figure 3.1c). In both tasks, forty neutral and forty fearful faces were presented in random order with the restriction that the same color was never repeated more than twice consecutively. Stimulation and task condition assignments were fully randomized.

Subliminal thresholds were controlled for by both a subjective and an objective awareness check (i.e., a forced-choice emotional-neutral recognition check). Both checks were performed after the second session to ascertain that subjects remained unaware of the variable of interest in the Stroop task, during the course of the experiment. The subjective check was a simple interview asking subjects whether they had recognized the emotional valence of the faces that were displayed before the masks. The objective check was a two-alternative, forced-choice (2AFC) emotional-neutral recognition procedure. In this 2AFC, a random set of 30 masked faces was shown to the subjects. In advance, subjects were explicitly told that the set contained 15 neutral and 15 fearful faces, and were instructed to indicate (or guess), by pushing a button whether the presented picture was a neutral or an emotional expression (see Kemp-Wheeler & Hill (1988) for the rationale behind this instruction).

Results

There was no evidence of recognition of emotional valence during masked presentation, neither by subjective nor by objective checks. Subjects' performance in the objective check did not differ from chance level, that is 15 correct identifications per subject in a two-alternative forced choice recognition check containing 30 stimuli. Of the total number of identifications (=240), 121 were correct (50.4 %). Individual upper limit was set at 19 correct scores. Non-parametric tests for devia-

tion from the expected value (cut-point=15) were not significant (n=8, p=1). Thus, masking was successful. Repeated MANOVAs were performed on the Attentional Bias scores, with Stim (F4 vs. placebo) and Exposure (unmasked vs. masked) as within-subject factors. Analyses showed a significant main effect for both Stim [$F(1,7) = 15.2$: $p < .01$] and Exposure
[$F(1,7) = 16.1$: $p < .01$]. There was, however, also a significant multivariate Stim X Exposure interaction [$F(1,7) = 23.3$: $p < .005$], indicating different effects of stimulation in masked and unmasked exposure conditions. Separate analyses of unmasked and masked data showed no effect of Stim in the masked task [$F(1,7) = 0.3$: n.s.], but a highly significant effect in the unmasked task [$F(1.7) = 19.7$: $p < .004$]. The pattern of results is shown in Figure 3.2.

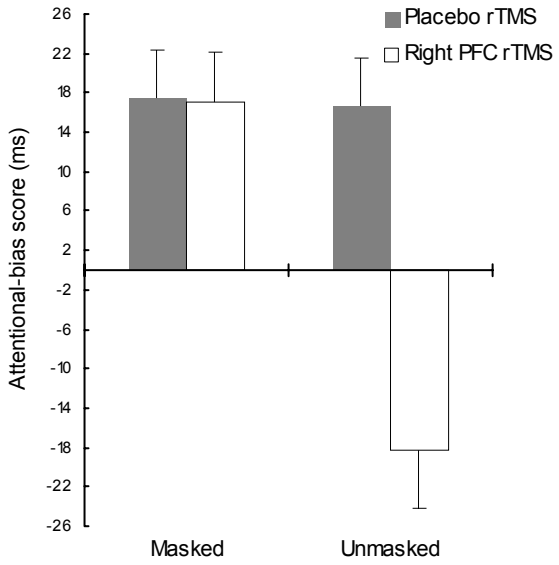

Figure 3.2. Mean attentional bias scores and SEM in milliseconds for the masked and unmasked tasks in placebo and transcranial magnetic stimulation condition.

Additionally, two-tailed paired t-tests were performed to see whether the Attentional Bias scores differed significantly from zero (i.e., indicating no bias). In the placebo condition there was a significant positive Attentional Bias for the masked [$t(7) = 3.5$: $p < .01$] and the unmasked task

[$t(7) = 3.4$: $p < .015$]. In the F4 stimulation condition again, a positive Attentional Bias was observed for the masked task [$t(7) = 3.3$: $p < .015$] but a negative Attentional Bias was found for the unmasked task [$t(7) = -3.1$: $p < .02$].

Discussion

The present study investigated the effects of right PFC rTMS on attentional biases for masked and unmasked fearful faces. Vigilant attention for fearful faces was observed both in the masked and in the unmasked exposure condition after placebo stimulation. As hypothesized, rTMS significantly decreased vigilant attention for fearful faces in the unmasked, but not in the masked task. As previously suggested, this effect could have been induced by a more left-sided dominance in prefrontal processing. As noted, combined rTMS-neuroimaging studies did not only show focal changes in activation of the targeted areas, but also demonstrated distant effects in anatomically interconnected regions. Since these distant changes in activation are supervening on the initial focal effect, these are likely part of functionally connected (affective) networks or neurons in the brain. rTMS-neuroimaging studies might in fact reveal these functionally connected networks of neurons, and provide additional insight in the affective circuits of the human brain (cf. Fox et al., 1997; Paus et al., 1997). Moreover, the present findings in the Stroop task can functionally be linked to left PFC dominant processing as observed by EEG (Coan et al., 1999; Harmon-Jones & Allen, 1998; Harmon-Jones & Sigelman, 2001). Furthermore, evidence from rTMS-EEG and rTMS-fMRI suggest that the present rTMS parameters (when applied over the right PFC) induce a left-sided dominance (Nahas et al., 2001; Schutter et al., 2001). Finally, elevations in attention for *angry faces* were demonstrated after suprathreshold low-frequency rTMS over the right PFC (D'Alfonso et al., 2000), in contrast to the current reductions in biased attention for *fearful faces*. Taken together, these findings seem to further support the involvement of the left PFC in the withdrawal-related emotion anger, and the right PFC in the approach-related emo-

tion fear (Coan et al., 1999; D'Alfonso et al., 2000; Harmon-Jones & Allen, 1998; Harmon-Jones & Sigelman, 2001). In further support of this view, Figure 3.2 shows that biased attention for fearful faces was reversed after rTMS from positive to negative scores in the unmasked task, which indicates that the processing of the fearful faces was strongly inhibited. Disregarding a danger signal is a risky behavioral strategy and can most likely be observed in a low anxious, anger prone individuals, with a presumably left PFC-dominance (Coan et al., 1999; D'Alfonso et al., 2000; Fox, 1991; Hermans et al., 1999).

The current findings also show that the pattern of responding remains unchanged for the masked task after rTMS. This is likely due to the inability of the rTMS technique to directly modulate the emotional response when the emotional stimulus remains unconscious. As noted previously, the left and the right prefrontal cortices are respectively involved in conscious control of behavioral approach and withdrawal, whereas the thalamic-amygdaloid pathway subserves the rudimentary emotional response. The OMPFC contains the brain structures crucially involved in the modulation of emotion (Davidson, Putman, & Larson, 2000; Van Honk et al., 2000), but requires conscious monitoring for acting out its emotional control (Reiman, 1997). In agreement, neuroimaging studies have shown no activation in OMPFC regions when fearful and angry faces are presented masked (Morris et al., 1999; Rauch et al., 2000). Since the OMPFC can only operate when gaining conscious access to emotional value (Davidson et al., 2000; Reiman, 1997), the modulation of the emotional response to the masked fearful face arguably needs subcortical mediation (Van Honk et al., 2000; Van Honk & De Haan, 2001). It seems therefore justifiable to assume that the transient suppression of motivated attention in the present study was observed for the unmasked fearful face only, because the here applied rTMS technique induced functional changes in neural excitability of cortical affective circuits predominantly.

Finally, it may be noted that although rTMS did not induce an effect in the masked task, the present study fulfils all criteria for subliminal activation postulated by Dixon (1981). There was *positive evidence for subliminal*

activation (1) in both the placebo and rTMS condition, that is vigilant attention to masked fearful faces. An objective check of awareness was used, providing *negative evidence of awareness* (2) in the masked task. The crucial *qualitative different effect for masked and unmasked stimuli* (3) was also found, after real rTMS had been applied.

In conclusion, these data corroborate and extend the findings of our earlier reports (D'Alfonso et al., 2000; Schutter et al., 2001) and provide further support for the differential involvement of the PFC in the emotions anger and fear (Coan et al., 1999; Fox, 1991; Harmon-Jones & Allen, 1998; Harmon-Jones & Sigelman, 2001). In addition, the rTMS-induced effect for the unmasked, but not the masked task concurs with data from neuroimaging studies (Morris et al., 1999; Rauch et al., 2000), providing further evidence for a possible dissociation between cortical and subcortical affective circuits in the human brain.

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4

rTMS at the frontopolar cortex reduces skin conductance but not heart rate: Reduced gray matter excitability in orbitofrontal regions

Archives of General Psychiatry 2001, 58, 973-974.

Abstract

Lowered electrodermal, but not cardiovascular activity and reduced prefrontal gray matter have been observed in patients with antisocial personality disorder. The present repetitive transcranial magnetic stimulation study provides evidence for the specific involvement of the orbitofrontal regions in this pattern of autonomic functioning.

Introduction

In the February 2000 issue of the Archives, a methodologically refined study by Raine, Lencz, Bihrle, Lacasse, & Colletti demonstrated reduced prefrontal gray matter accompanied by a reduction in autonomic activity in patients with antisocial personality disorder (APD). An important additional expected observation concerned the dissociative pattern on the indexed indices of autonomic activity: a reduction in prefrontal gray matter was linked to a reduction in electrodermal, but not cardiovascular, activity. Low arousal as indexed by reduced electrodermal activity is argued to indicate insensitivity to punishment or poor fear conditionability. This results in difficulties learning to inhibit antisocial acts (Arnett, 1997; Damasio, 2000). Although it was not possible to be more specific regarding the localization of gray matter reduction within the prefrontal cortex, Raine et al. (2000) and Damasio (2000) in his commentary suggest that the orbitofrontal cortex constitutes the most likely candidate.
A technique suitable for investigating the role of prefrontal brain areas in autonomic activity is repetitive transcranial magnetic stimulation (rTMS). When applied to a specific cortical area, rTMS is able to induce transient gray matter inactivity, a so-called virtual brain lesion (Pascual-Leone, Bartres-Faz, Keenan, 1999), depending on stimulation parameters.

Method

Recently we applied slow rTMS to the frontopolar cortex (FP1), targeting the left orbitofrontal cortex region, to investigate involvement of this area in autonomic arousal (Schutter, Van Honk, D'Alfonso, Postma, & De Haan, 2000). Included as dependent measures were skin conductance and heart rate, as in the study of Raine and colleagues (2000). A within-subject design was used (N = 8) in which stimulation of the left central position of the motor cortex (C3) served as the control condition. Research has shown depression of gray matter excitability after slow rTMS over the motor cortex (Chen et al., 1997).
Subjects were continuously stimulated during 20 minutes at 80% of their motor threshold with a frequency of 1 Hz.

Results

Our findings matched the pattern of autonomic functioning in APD demonstrated by Raine and co-authors (2000). Results showed that rTMS at the Fp1 position compared with rTMS at the C3 position induced a reduction in skin conductance, reaching a significance 20 minutes after stimulation [$p < .01$; 1-way analysis of variance (ANOVA), $F(1,7) = 5.52$], whereas heart rate remained unaffected [$p > .90$; 1-way analysis of variance (ANOVA), $F(1,7) = 0.25$].
Figure 4.1 shows the pattern of these results. Slow rTMS over the dorsolateral prefrontal structures modulates cardiovascular functioning, emphasizing the specificity of the FP1 stimulation (D'Alfonso et al., 1999).

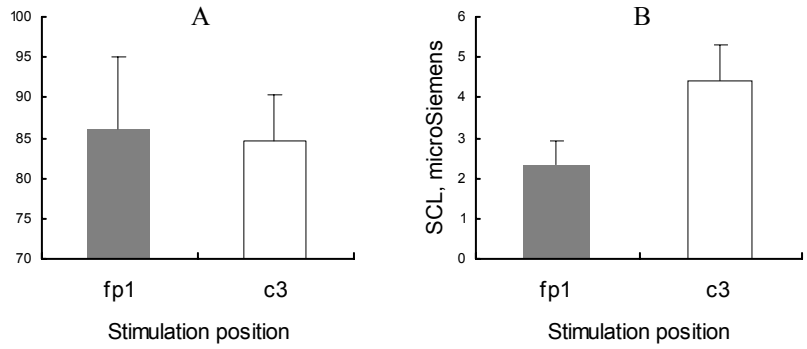

Figure 4.1. Mean and SEM for (A) skin conductance level (SCL) in microSiemens and (B) heart rate in beats per minute (bpm) 20 minutes after repetitive transcranial magnetic stimulation at the frontopolar (FP1) and motor cortex (C3) electrode positions.

Discussion

In conclusion, our pattern of autonomic arousal after slow rTMS targeting orbitofrontal regions is agreement with that of Raine et al. (2000) and thus provides converging evidence for the suggestions that prefrontal gray matter in orbitofrontal regions is reduced in APD.

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5

Defective somatic markers in subclinical psychopathy

Neuroreport 2002, 13, 1025-1027.

Abstract

Damasio's (1994) Somatic Marker Hypothesis (SMH) is argued to be specifically applicable to psychopathy, though evidence is meager until now. The principal evidence for the SMH is based on findings in patients with orbitofrontal lesions, showing absent punishment learning on the Iowa gambling task. Interestingly, neuroimaging studies indicate orbitofrontal dysfunction in psychopathy also. Here we investigated the SMH in subjects selected on low and high psychopathic behavioral characteristics from the outer extreme ranges of a large subject pool (n = 525). The low psychopathic subject group (n=16) showed intact punishment learning, suggesting somatic markers came to guide their decisions in the course of the game. In contrast, such punishment learning was not observed in the high psychopathic subject group (n=16), who mimicked the gambling behavior of orbitofrontal patients. These findings provide further evidence for the hypothesized link between psychopathy and orbitofrontal dysfunction.

Introduction

The psychopath is a fearless remorseless predator whose insensitivity to punishment together with a strong reward dependency results in a tendency to commit violent, anti-social acts. An interesting theoretical framework which may apply to the behavior of the psychopath is Damasio's somatic marker hypothesis (1994). This hypothesis has introduced emotion into the neurocognition of decision making: breaking with longstanding dogmas concerning rationality in decision making, it states that cognition depends on emotion to select appropriate behavior. The somatic marker hypothesis states that emotional learning is established by somatic or bodily feelings unconsciously and consciously marking certain behaviors having unpleasant outcomes. These induce inhibition of these punishment (i.e., fear) contingent behavioral choices. An emotion-governed bio-regulatory system modulates and constrains decision making. A line of reasoning not only defying traditional decision making theory, but also at odds with many theoretical models of psychopathology which tend to (over-)emphasize the destructive value of fear (Chorpita & Barlow, 1998).

The most convincing evidence for the somatic marker hypothesis is based on findings with the Iowa gambling task, a paradigm mimicking real-life uncertainty, reward and punishment (Bechara, Damasio, Damasio, & Anderson, 1994). Unaware of strategy, guided by unconscious markers observable as anticipatory skin conductance responses, normal subjects learn to choose advantageously already in the first half of this game (Tranel, Bechara, & Damasio, 2000). However, patients with orbitofrontal lesions develop neither unconscious nor conscious markers, resulting in impaired decision making. That is, orbitofrontal patients continue choosing from the risky punishing decks throughout the game, even after they have become consciously aware that this is a disadvantageous strategy.

Interestingly, although evidence for the somatic marker hypothesis is almost exclusively based on findings in neurological patients, it is suggested to be specifically applicable to the maladaptive consequences of

fearlessness and impulsive reward craving shown in psychopathy (Bechara, Damasio, & Damasio, 2000; Damasio, 1994; Tranel, 2000). Not only does the personality profile of orbitofrontal patients strikingly resemble that of the psychopath, but there is also evidence from neuroimaging and neuropsychological studies suggesting dysfunctional orbitofrontal circuits in psychopaths (Dinn & Harris, 2000; Raine, Lencz, Bihrle, La Casse, & Colletti, 2000; Van Honk et al., 2001). Thus, the somatic marker hypothesis should also apply to the behavior of the psychopath (Bechara et al., 2000; Tranel et al., 2000).

A first attempt to test the somatic marker hypothesis by assessing the Iowa gambling task in incarcerated psychopaths was not successful (Schmitt, Brinkley, & Newman, 1999). The confounding effects of institutionalization in the tested forensic sample and control group might have resulted in this null finding (Dinn & Harris, 2000). Nevertheless, Blair, Colledge, & Mitchell (2001) recently showed impaired performance on the gambling task in boys with psychopathic tendencies.

Here we started from the premise that a genetic predisposition underlying psychopathy is normally distributed in the population (Mealey, 1995), and assessed Iowa gambling task performance in subjects selected on psychopathic personality characteristics from outer extreme ranges of a large subject pool. If impaired decision making on this task assessing orbitofrontal functioning (Bechara et al., 2000; Tranel et al., 2000) might be demonstrated in such a sub-clinical population, further evidence for the hypothetical link between psychopathy and orbitofrontal function would be obtained.

Method

Participants

525 Students at the Utrecht University completed Carver and White's (1994) orthogonally-dimensioned behavioral inhibition system (BIS) and behavioral activation system (BAS) self-report measures derived from Grays (1987) powerful framework of human personality. Selection of our participants from the large respondent pool was based upon the 2 ex-

treme quadrants along the diagonal in 2-dimensional BIS/BAS space. Medians for BIS and BAS were calculated, respondents scoring within a 3 point range of these parameters were discarded and only participants scoring high BIS/low BAS or low BIS/ high BAS after this restriction were retained for further selection. To obtain a selection of participants with only the strongest punishment-/reward sensitive motivational stances, difference scores BAS minus BIS and BIS minus BAS (range-corrected) were calculated. In this manner, 16 subjects scoring most extremely low on the BIS/high on BAS, and 16 subjects scoring high on BIS/low on BAS were selected for participation (age range = 19-25 years). For both groups female – male ratios were 8 : 8. The BIS is argued to be activated by conditioned signals of punishment, whereas BAS action involves conditioned signals of reward (Avila, 2001). Thus, at an extreme, strong BAS/weak BIS reflects the fearless, reward-craving, punishment insensitive, thus "psychopathic" personality, whereas weak BAS/strong BIS reflects the fearful, punishment sensitive, risk aversive, thus "non-psychopathic" personality (Fowles, 1980; Kring & Bacherowski, 1999). The applicability of the SMH for psychopathy was tested by assessing the computerized version of the Bechara et al. (1994) Iowa gambling task in these subjects in an experimenter- blind design.

Procedure

In the Iowa gambling task players are instructed to try to gain as much money as possible by drawing 100 selections from a choice of four decks, while starting with a fictional loan of 2000 US Dollars. The decisions to choose from the decks should become motivated by reward and punishment schedules inherent in the task. Two of the decks are disadvantageous, producing immediate large rewards but these are (after a pre-punishment phase of about 10-15 cards) accompanied by significant money loss due to extreme punishments. The other two decks are advantageous; reward is modest but more consistent and punishment is low (Bechara et al., 1994).

Results

Performance on the game was divided in 5 periods of 20 card selections (Bechara et al., 1994). A linear ANOVA over these 5 periods of 20 card selections was computed using Group (low vs. high psychopath) and Gender (female vs. male) as between subject factors. There were no significant effects or interactions for Gender [all Fs < 1], therefore Gender was excluded from further analyses. Data showed a highly significant interaction for Group [$F(4,27) = 3.97$: $p = 0.012$].

As can be seen from Figure 5.1, the low psychopaths began to choose advantageously almost immediately after the first punishment trials were delivered, gradually choosing more and more from the advantageous decks. The high psychopaths showed no such learning, they continued to make risky disadvantageous decisions throughout the game, resulting in highly significant group difference in the 5th period [$F(1,30) = 10.21$:, $p = 0.003$]. Finally, some initial gain in the pre-punishment period for the high psychopaths could not prevent significant money loss [$t(15) = 2.93$: $p = 0.01$] by the end of the game. On the other hand, though not a significant amount, some money was gained by the low psychopaths [$t(15) = 1.09$, $p = 0.3$].

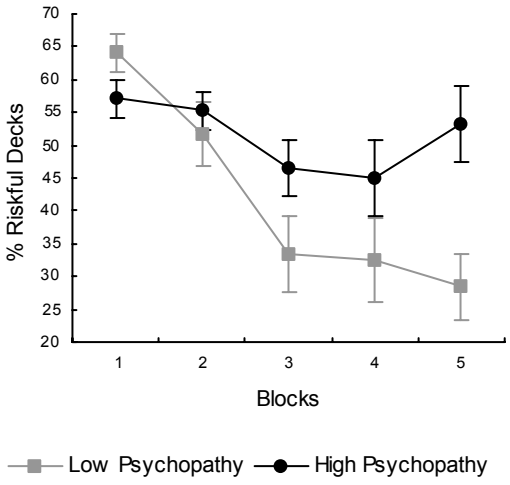

Figure 5.1. Mean scores and SEM for gambling pattern of the subject groups scoring high and low on psychopathy.

Discussion

Here we provide evidence for the applicability of the SMH to psychopathic behavior. As can be seen from Figure 5.1, a significantly different pattern of decision making was observed for the low and the high psychopathic subject-groups. It should furthermore be noted that in earlier research with the gambling task it has been established that the game can be divided in an unconscious and a conscious knowledge stage (Tranel et al., 2000). Until roughly halfway the game (the unconscious stage) patients nor normal control subjects develop any knowledge of the advantageous strategy. From card 50 onwards gradually knowledge about this strategy begins to reach awareness, although the pattern in orbitofrontal patients (approximately 50% reaching full awareness of strategy by the end of the game) differs from normal subjects (approximately 75% reaching full awareness). As might be expected on basis of our subject-selection, post-experimental interview indicated that the latter pattern applied to both our subject groups. This is also in agreement with the fact that performance in the low psychopathic group fairly resembles Iowa gambling of a large group of normal subjects reported by Bechara et al. (2000). Already in the first half of the game, unconscious somatic markers seem to steer decision making towards the advantageous decks, and the proportion of these profitable choices gradually increases during the second half of the game, when the game's strategy becomes conscious to most of the subjects. However, this pattern of learning is not observed in the high psychopathic group, despite a similar pattern of knowledge about strategy, unconscious nor conscious somatic markers seem to affect their behavior.

This observed pattern of decision making in our high psychopathic subject group mimics Iowa gambling performance of patients with orbitofrontal lesions. A disadvantageous pattern of behavior here however unlikely due to orbitofrontal 'damage', but defensibly reflecting a functional difference in affective modulation at the orbitofrontal level, as the Iowa gambling task is a robust marker for orbitofrontal functioning. In sum, already in a sub-clinical manifestation of psychopathy, orbi-

tofrontal patient-alike deficient somatic markers can be observed. Since the Iowa gambling task specifically assesses orbitofrontal functioning, this finding provides further evidence for the hypothetical link between psychopathy and orbitofrontal function.

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6

Anterior asymmetrical alpha activity predicts Iowa gambling performance: Distinctly but reversed

Neuropsychologia 2003, in press.

Abstract

Animal research indicates that the prefrontal cortex (PFC) plays a crucial role in decision making. In concordance, deficits in decision making have been observed in human patients with damage to the PFC. Contemporary accounts of decision making suggest that emotion guides the process of decision making by ways of providing for reward-punishment contingencies. A task capable of assessing the influence of reward and punishment on decision making is the Iowa gambling task. In this task decisions become motivated by inherent punishment and reward schedules. Insensitivity for punishment together with a strong reward dependency results in risk taking, which is in the gambling task the disadvantageous strategy. Interestingly, the processing of punishment and reward is argued to be lateralized over the right and left PFC respectively. Here we investigated whether more relative left compared to right-sided frontal brain activity (left-sided dominance) quantified as reduced alpha (8-12 Hz) activity in the electroencephalogram (EEG) would lead to a more risky, disadvantageous pattern of decision making. Contrary to what was expected, relatively more right compared to left frontal brain activity was strongly associated with the disadvantageous strategy. The results are discussed in terms of recent theoretical accounts which argue that the functional interpretation of baseline frontal alpha activity depends on the mental operation involved and does not necessarily imply inactivity.

Introduction

Decision making is mediated by the individual's motivational stance in which the prefrontal cortex (PFC) plays an important role (Krawczyk, 2002). Electrophysiological studies have provided evidence for the involvement of the PFC in motivation and emotion. The left PFC has been implicated in approach-related emotion, whereas the right PFC is involved in withdrawal-related emotion (Davidson, 1988, 1998; Harmon-Jones & Allen, 1997). Approach- and withdrawal-related emotions are paralleled by the so-called reward and punishment contingencies. Reward serves as a positive reinforcer for action (approach), whereas in punishment a negative reinforcer promotes avoidance (withdrawal). Due to the contralateral inhibition between the hemispheres the lateralized approach and withdrawal or punishment-reward system are mutually inhibitory. Activation of one system will result in the inhibition of the former (Arnett, 1997) and vice versa (Schutter, Van Honk, D'Alfonso, Postma, & De Haan, 2001). The Iowa gambling task (Bechara, Damasio, Damasio, & Anderson, 1994) is argued to be capable of indexing punishment–reward contingencies. In this task decisions become motivated by inherent punishment and reward schedules. Insensitivity for punishment together with a strong reward dependency results in a disadvantageous pattern of decision making. Recently Van Honk, Hermans, Putman, Montagne, & Schutter (2002) demonstrated that punishment insensitive, reward dependent subjects made more risky, disadvantageous choices on the Iowa gambling task. Furthermore, in another study of Van Honk, Schutter, Hermans, & Putman (2003) it was demonstrated that subjects with higher baseline levels of cortisol, a steroid hormone implicated in fear and behavioral inhibition made more choices from the less risky, advantageous decks in the Iowa gambling task. From the above it can be extrapolated that due to the profitable properties of punishment learning in the Iowa gambling task fear ensures for money gain. Interestingly, in nonhuman primates associations between cortisol, behavioral inhibition and lateralized PFC activation patterns have been found by Kalin, Larson, Shelton, & Davidson (1998). Relative left-sided dominance was not

only accompanied by lower levels of cortisol, but also by less extreme fearful defensive responses when provoked. More recently, Buss et al. (2003) showed similar relationships in 6-month-old human infants, again relative right-sided dominance in frontal brain activity was associated with higher levels of cortisol and more fearful responsivity. Finally, evidence for a relative left-sided PFC dominance in reward and a relative right-sided dominance in punishment derived from the approach-withdrawal model was provided by Sobotka, Davidson, & Senulis (1992). Reductions in alpha power in the left frontal brain regions were observed after money gain in the reward trials, whereas punishment trials with decreases of alpha power in the right frontal cortex. The lateralized PFC model of reward and punishment suggests differential contributions of the left and right-sided PFC on decision making strategy in the Iowa gambling. A well known electrophysiological correlate which can be used to investigate the lateralized involvement of the PFC in punishment-reward contingencies is the log transformed brain asymmetry between homologue scalp sites in the 8-12 Hz (alpha) frequency range (Davidson, 1998). Most theorists suggest that alpha activity is a measure for cortical inactivity, and thus informative regarding brain activation state in a reversed manner (Davidson, 1988, 1998; Harmon-Jones & Allen, 1997), but see (Cooper, Croft, Dominey, Burgess, & Gruzelier, 2003). Presently, it was hypothesized that subjects with relatively less left-sided PFC baseline alpha activity (left-sided dominance) would show a disadvantageous pattern of decision making in the Iowa task.

Method

Participants

Eighteen right-handed healthy volunteers (9 males) ranging from 18-26 years participated in the study. The participants were recruited among students at the Utrecht University. Written informed consents was obtained. The study was approved by the medical ethical committee of the Utrecht University in accordance with the declaration of Helsinki. All participants were unaware of the aim of study.

Iowa gambling task

In the Iowa gambling task (Bechara et al., 1994) players are instructed to try to gain as much money as possible by drawing 100 selections from a choice of four decks, while starting with a fictive loan of approximately 2000 US Dollars. The decisions to chose from the decks become motivated by reward and punishment schedules inherent in the task. Two of the decks are more risky and disadvantageous, producing immediate large rewards but these are (after a pre-punishment phase of about 10-15 cards) accompanied by significant money loss due to extreme punishments. The other two decks are advantageous; reward is modest but more consistent and punishment is low. The overall pattern of gambling behavior during the task is argued to be a behavioral correlate for punishment and reward driven motivational stance.

EEG recording

Baseline EEGs were recorded from frontal scalp positions (F3 and F4) according to the International 10/20 System of EEG electrode positions, using an electro-cap with Ag/AgCl electrodes (Neurosoft, Inc.). The reference electrode was placed behind the subject's right ear. Electro-oculogram (EOG) was recorded by placing Ag/AgCl electrodes to the supra- and suborbit of the right eye and on the external canthi of each eye, in order to correct for vertical and horizontal eye movements. ECI EEG gel was used as conducting medium for both EEG and EOG electrodes and all impedances were under 5,000 Ω. An acquisition amplifier (Ampligraph) was used to filter incoming signals (low pass cut-off frequency was 70Hz with a time constant of 3s.). Amplification was set at 20,000 for both the EEG and EOG leads, and the sample rate was 250 Hz.

Procedure

Upon arrival the procedure was explained to the subjects and informed consent was obtained EEG recording was prepared which took on average about 15 minutes. Participants were seated in a comfortable chair in a dimly lit, quiet room, while the experimenter was in an adjacent

control room. To obtain baseline measures of EEG, subjects were asked to relax and to keep head movements to a minimum. One-minute intervals of baseline EEG for a total of four minutes (two with eyes closed and two with eyes open) were recorded. Afterwards, the electro-cap and EOG electrodes were removed and participants performed the Iowa gambling task. The participants were instructed to make as much money they can and were told that the gambling task could be over at any given moment in time.

Analysis

For the Iowa gambling task overall money gain and percentage risky choices were calculated for each participant. Regarding the electrophysiological recording, raw EEG data was offline digitally filtered (Low-pass setting: 30 Hz). EEG signal containing eye and/ or muscle movements, or other forms of artifacts, greater than -50 μV and +50 μV were rejected for further analysis. After artifacts were discarded, data were corrected for horizontal and vertical eye movements. Next, 1024-s chunks of averaged artifact- free EEG were extracted through a Hamming window (length 10%) to reduce spurious estimates of spectral power (Davidson, 1988). For each chunk, a fast Fourier transform method was used to obtain estimates of spectral power (μV^2) in the 1Hz frequency bins for each electrode site. Spectral power values were averaged across all epochs within a single baseline and were then transformed to power density values for the delta (1-3 Hz), theta (4-7 Hz), alpha (8-13 Hz), beta (14-30 Hz) frequency bands. Finally, the frontal brain log-transformed asymmetry for mean power density were calculated. A negative value indicated relative more left-sided activity, and a positive value implied relative right sided activity in a given band.

Results

Bonferroni-corrected non-parametric correlations were performed between percentage risky choices and the different frequency bands. Spearman rank-order correlations revealed a highly significant inverse

relationship between percentage risky choices and the frontal alpha asymmetry [r(18) = - 0.74: p = 0.001]. Figure 6.1 shows the inverse correlation between the frontal alpha asymmetry and percentage risky choices.

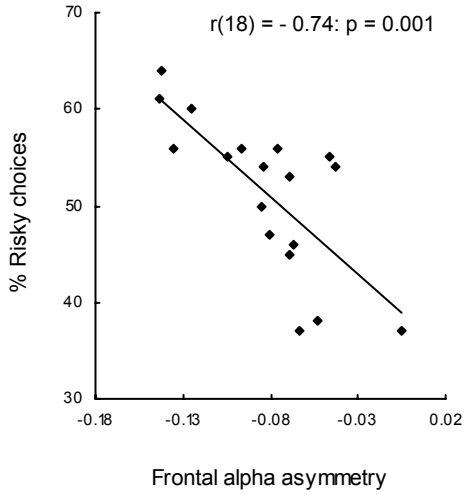

Figure 6.1. Inverse relationship between frontal EEG asymmetry in the alpha frequency range and the percentage risky choices on the Iowa gambling task.

Discussion

The present study investigated the relationship between anterior asymmetrical brain activity and the sensitivity for reward and punishment using the Iowa gambling task. It was hypothesized that reduced left compared to right PFC activity in the alpha frequency range would be associated with a more disadvantageous pattern of decision making, indicating low punishment sensitivity and high reward dependency. Paradoxically, relatively enhanced left compared to right PFC alpha activity was related to the disadvantageous pattern of decision making. This finding seems to be at odds with traditional frontal lateralisation models of emotion and motivation, since these suggest that electrical brain activity in the alpha bandwidth is associated with reduced cortical arousal (Davidson, 1988, 1998; Harmon-Jones & Allen, 1997). In agreement with this notion is the observation that sensory deprived visual

cortex oscillates preferentially in the alpha frequency range. Moreover, a PET study by Sadato et al. (1998) provided evidence for a negative correlation between regional cerebral blood flow (rCBF) in the visual cortex and alpha activity. However, a positive relationship has also been observed between rCBF in the lateral frontal cortex and alpha activity, arguing against the notion of alpha reflecting cortical inactivity. Furthermore, a recent study by Cooper et al. (2003) also challenges the notion of alpha activity and cortical idling. This study demonstrated increases in alpha activity during internal driven mental operations. Since the gambling task incorporates different aspects of cognitive and affective processing in decision making (Bechara, Damasio, & Damasio, 2000), left-sided dominance in the alpha activity might be associated with internal directed attention to reward (Davidson, 1992). On the other hand, it can also be argued that since frontal alpha activity is associated with relaxed wakefulness, the observed tonic activation pattern predicts the reactivity in terms of event-related desynchronisation (ERD) of the system. In crucial defense of the latter notion, Neubauer, Freudenthaler, & Pfurtscheller (1995) showed that subjects with higher baseline levels of alpha power exhibited more pronounced ERD when engaging in information processing. Thus, the frontal alpha power also predicts heightened readiness or susceptibility to engage in information processing. In sum, further research is needed to scrutinize whether relative higher left-sided PFC alpha baseline activity might be predictive for more enhanced alpha ERD in the left PFC during Iowa gambling task. From the above it can be argued that the functional interpretation of alpha activity strongly differs depending on the mental operations at hand and does therefore not necessarily imply cortical inactivity. Furthermore, although various mechanisms may generate similar alpha activity and macroscopic distributions over the scalp (Sadato et al., 1998), the functional interpretations can be quite distinct, making the relation between alpha activity and its functional correlate even more ambiguous.

In conclusion, the present study demonstrates that relative left-sided PFC activity in the alpha frequency range was reversibly associated with a disadvantageous pattern of decision making indicating low punishment

sensitivity and high reward dependency. This finding contradicts the traditional models of emotion and the electrophysiological processing, which suggest that the frontal activity in the alpha frequency range reflects inactivity. It is argued that this interpretation does not take into account the mental operations involved and the differences between action readiness of a system and the operation of the system during the execution of the action itself.

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7

Low fear and reduced feedback-locked brain responses to punishment after high risk gambling

2003, *submitted.*

Abstract

According the low-fear hypothesis of psychopathy, punishment insensitive individuals engage in risky behavior in order to obtain large rewards, thereby neglecting potentially even larger punishments. The present study investigated the early electrocortical brain response to punishment during low and high risk decision-making. Furthermore, it was investigated whether this reactivity could be predicted by self-reports of punishment sensitivity (BIS) and reward dependency (BAS). BIS-BAS scores and event-related potentials (ERP) during a gambling task were obtained from sixteen healthy volunteers. Reductions in feedback-locked P1 and medial frontal negativity (MFN) brain potentials after punishment during high risk gambling were observed. Moreover, punishment insensitivity was significantly related to the lowered P1 amplitudes, whereas reduced MFN amplitudes were associated with increased risk taking. The present findings give further insights into the electrophysiology of fear motivated decision making and may have possible implications for psychopathy.

Introduction

The normative approach of decision-making assumes that a calculation of the benefit-cost ratio governs the individual's behavior. Such purely cognitive based evaluations are however nonexistent, since motivational factors such as punishment and reward sensitivity heavily influence decision making. In the Iowa gambling task, for instance, participants are instructed to gain as much money as possible by choosing from four decks of cards. During the task subjects become gradually aware that two decks of cards are advantageous, while the other two decks are disadvantageous. Decisions to choose advantageously become motivated by an ingenious schema of punishment and reward. Nevertheless, insensitivity for punishment and a strong reward dependency result in choosing disadvantageously. Even though these subjects have explicit knowledge about the strategy which in the long run would turn out advantageously, some continue to choose disadvantageously (Bechara, Damasio, Damasio, & Anderson, 1994; Bechara, Damasio, Tranel, & Damasio, 1997). In concordance, Van Honk, Hermans, Putman, Montagne, & Schutter (2002) demonstrated that low punishment and high reward sensitive subjects made significantly more risky choices in the Iowa gambling task as compared to individuals scoring high on punishment sensitivity and low on reward dependency.

Reward and punishment sensitivity can easily be interpreted within the left and right prefrontal cortex (PFC) implementation of approach- and withdrawal-related emotion respectively (Davidson, 1984; Sobotka, Davidson, & Senulis, 1992). Electrophysiological evidence has factually demonstrated involvement of the left PFC in reward sensitivity and the right PFC in punishment sensitivity (Sobotka et al., 1992). Concurring evidence was recently provided by Schutter, De Haan, & Van Honk (2003) who demonstrated that more left-sided electrocortical brain activity predicted reward dependency and punishment insensitivity in terms of risky, disadvantageous choices in the Iowa gambling task. Above findings provide support for a model of motivational balance with a crucial role for the sensitivity for punishment and reward (Arnett, 1997). The imbalance in this model is seen in for instance psychopathy,

where an insensitivity for punishment potentiates a hypersensitivity for reward (Fowles, 1980). Contrariwise, extreme sensitivity for punishment as observed in pathological anxiety can lead to an absence of reward drive. Besides the fact that the physiological underpinnings of the motivational balance model can be studied in terms of anterior lateralisation processes, its physiology can also be studied by recording the event-related electrocortical responses to punishment and reward. Recently, an event-related potential (ERP) study by Gehring and Willougby (2002) investigated the electrocortical processes of monetary losses and gains. Their findings included a negative-polarity potential peaking over the mid-frontal cortex with an onset latency of approximately 200ms (MFN), which was associated with punishment feedback indicating monetary loss during the performance of a gambling task.

Source localization analyses suggested that this brain potential originated from the medial PFC, which corresponds to the anterior cingulate cortex (ACC), a structure heavily implicated in evaluation and monitoring processes (Posner & Raichle, 1994; Shallice & Burgess, 1991). In particular, punishment seemed to activate this brain structure, presumably due to increased attention for events which can be potentially threatening. Furthermore, prior to the MFN, an early first positive-polarity event-related brain potential (P1) peaking around 100 ms has been argued to reflect an orienting response to relevant stimuli in need for attentional resources. The P1 component is argued to be generated in the thalamus through cholinergic innervations of the reticular activating system (Arai, Tanaka, Pascual-Marqui, & Hirata, 2003). This initial fast detection might be a highly adaptive mechanism for the facilitation of more elaborative evaluation processes reflected by the MFN.

The present study was designed to investigate the possible role of the P1 and MFN brain potentials in low and high risk decision making. It was hypothesized that the feedback-locked P1 amplitude would vary as a function of punishment sensitivity (BIS) and that the MFN amplitude would be more pronounced during the processing of punishment compared to reward (cf. Gehring & Willougby, 2002). Furthermore, as predicted by the motivational balance model outlined above, low punish-

ment sensitivity was hypothesized to result in more risky choices. Finally on a more exploratory level, it was investigated whether the P1 and MFN amplitudes would constitute an electrophysiological complex involved in evaluation processes.

Method

Participants

Sixteen healthy volunteers (mean ± SD age, 21.5 ± 1.6 years) were recruited among students at Utrecht University, Utrecht, The Netherlands. All participants were right-handed as indexed by the Edinburgh Handedness Inventory (Oldfield, 1971) (mean ± SD score, 43.3 ± 3.1) and non-smoking. None of the subjects had a history of psychiatric or neurological conditions and had normal or corrected-to-normal vision. All volunteers were naïve and unaware of the aim of the study. Informed consent was obtained and participants received payment for taking part in the study. The protocol was approved by the medical ethical committee of the University Medical Center in Utrecht, in accordance with the standards set by the Declaration of Helsinki.

Punishment sensitivity

Carver and White's (1994) behavioral inhibition system (BIS) questionnaire was assessed. The questionnaire is derived from Gray's (1987) powerful framework of human personality in which the BIS is associated with punishment sensitivity (Avila, 2001; Van Honk et al., 2002). Note however, that the score on the scales is inversely related to the degree of having the trait characteristics, that is a high BIS score suggests low punishment and *vice versa*.

The gambling task

A task capable of simulating real-life gambling was recently introduced by Gehring and Willougby (2003). A sequence of stimuli, consisting of two squares were horizontally presented to the participants. Both squares contained the numeral 5 or 25, which resulted in six possible stimulus

combinations, namely [5][25], [25][5], [5][5] and [25][25], which were presented in a counter-balanced and random order. The participants were instructed to choose from one of the alternatives by either pressing a left or right button. After their choice, feedback was provided regarding whether they had gained or lost the amount in the square they had decided to pick. Feedback was presented 1.5 seconds after button press by coloring the squares in green or red indicating gain and loss respectively. If the chosen square turned green the amount in the square would be added to their total, whereas the amount would be subtracted from their total amount of gains/ losses when the square turned red. Moreover, the square the subjects did not choose also turned either green or red. As a consequence, they did not only discover whether they had gained or lost money, but also what the result would have been if they had picked the alternative. The task enables the participants to either engage in high or low risk decision-making when presented with [25][5] or [5][25] by choosing the numeral 25 over 5 or *vice versa* respectively. However, in trials containing the stimuli [5][5] or [25][25] the participants are simply forced to make a low or high risk decision. This way, the outcomes and the relations between the "high risk-gain", "high risk-loss", "low risk-loss" and "low risk-loss" conditions can be studied. The order of the trials as well as the outcomes were random, thereby mimicking a real-life game of chance. In the present study half of the participants was assigned green as the gain and red as the loss color, and half was assigned red as the gain color and green as the loss color. The current version of the task consisted of 10 rounds of 32 trials. Each round was interspersed with an update regarding their current total amount of gains minus losses up to that point of the game. The aim of the gambling task was to win as much money as possible. To increase the motivational incentive of the task, the subjects would, if applicable, receive their winnings at the end of the game in real Euro cents next to their standard pay for participating.

EEG recordings

EEGs were recorded from eight electrodes, that is F3, F4, P3, P4, Fz, Cz, Pz and Oz scalp positions, using an Electro-Cap with Ag/AgCl electrodes (Neurosoft, Inc.) and according to the International 10-20 System. EEG signals were referenced to an electrode placed on the subject's right mastoid. For the purpose of artifact scoring, vertical (VEOG) and horizontal (HEOG) eye movements were recorded. Ag/ AgCL electrode pairs (bipolar) were placed at the supra- and suborbit of the right eye and at the external canthi of each eye. ECI EEG Gel was used for both EEG and EOG and all electrode impedances were less than 5,000 Ω. An acquisition amplifier (Ampligraph) was used to filter incoming signals (low-pass cut-off frequency 70 Hz; time constant 3 s.). For the EEG recordings NeuroScan software was used. Amplification was set at 20,000 for both the EEG and EOG leads, and the sample rate was 250 Hz.

Procedure

Upon arrival at the laboratory the procedure of the experiment was briefly explained to the volunteers and informed consent was obtained. Next, right-handedness was assessed using the Edinburgh Handedness Inventory and participants filled out the computerized version of the BIS/ BAS questionnaire. After the EEG preparation, subjects were seated in a comfortable dentist chair placed in a dimly lit room adjacent to the control room. Participants were instructed to relax, stay awake and keep head movements to a minimum during a four-minute baseline EEG recording, in which one minute of eyes open was alternated by one minute of eyes closed. Next, subjects were instructed to remain fixated on the screen and keep head movements to a minimum during the execution of the gambling task. Every trial was initiated with the appearance of two squares containing the numeral 5 or 25. Event-related brain potentials were recorded after visual feedback presentation (t =0), which remained visible for 2 s. followed by the initiation of the next trial. The inter-stimulus interval between feedback offset and the next trial varied randomly across 1400, 1500 and 1600 ms.

The gambling task took on average 30 minutes to complete. Afterwards volunteers were debriefed and paid for participation. The entire experiment took approximately 1.5 hours per subject. In Figure 7.1 a schematic example of the events during a typical trial in the gambling task is displayed.

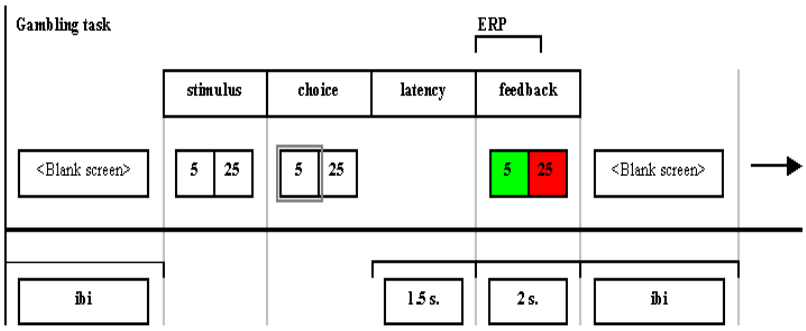

Figure 7.1. Schematic overview of the event sequence during the gambling task.

Data analyses

Punishment sensitivity was quantified as the sum of scores for the BIS scale, in which the sum of scores is inversely related to the trait-like personality characteristic of the BIS scale. With respect to the gambling task individual percentage risky decision-making was calculated.

Regarding the electrophysiological recordings, raw continuous EEG data was offline digitally filtered (30 Hz low-pass setting). EEG signal containing eye and/ or muscle movements, or other forms of artifacts, greater than -50 μV and +50 μV were rejected for further analysis. After artifacts were discarded, data were corrected for horizontal and vertical eye movements. The designation of an artifact in one of the leads resulted in removal of that epoch for all channels in order to ensure that the remaining data were identical for all sites in time. Next, for the baseline EEG recording 1,024-s chunks of averaged artifact- free EEG were extracted through a Hamming window (length 10%) to reduce spurious estimates of spectral power (Davidson, 1988). For each chunk, a fast Fourier transform method was used to obtain estimates of spectral

power (μV^2) in the 1 Hz frequency bins for each electrode site. Spectral power values were averaged across all epochs within a single baseline and were then transformed to power density values for the alpha (8-13 Hz) frequency band. Finally, the frontal brain log-transformed asymmetry for mean power density was calculated from the F3 and F4 scalp positions. A negative value indicated relative more left-sided activity, and a positive value implied relative right sided activity in a given band. Regarding the event-related potentials collected during the gambling task the raw EEG was digitally band-pass filtered in a 4-12 Hz window (Gehring & Willougby, 2002; Luu, Tucker, Derryberry, Reed, & Poulsen, 2003) and the mean P1 and MFN amplitude for each of the four conditions, that is "high risk-gain" and "high risk-loss", "low risk-gain" and "low risk-loss" were calculated by means of the average amplitude between the 100-200 ms and 200-300 ms time intervals respectively.

Results

P1 amplitude

Two three-way within-subjects Greenhouse-Geisser corrected analyses of variance (GG-ANOVAs) were performed on the P1 (mean ± SEM, 1.71 ± 0.84) and MFN amplitude (mean ± SEM, - 2.03 ± 1.50) respectively with Risk (low / high), Outcome (gain / loss) and Electrode Site (Fz, F3, F4, Cz) as factors. The GG-ANOVA for the P1 yielded a significant main Outcome effect [$F(1, 15) = 6.93$: $p = 0.019$], as well as a Risk x Outcome interaction [$F(1, 15) = 12.91$: $p = 0.003$]. Post-hoc Bonferroni corrected paired-samples t-tests showed that P1 amplitude was higher in the "high risk-loss" condition compared to the "high risk-gain" [$t(15) = -3.71$: $p = 0.008$]. Furthermore, P1 amplitude was also higher in the "high risk-loss" condition compared to "low risk-loss" [$t(15) = - 2.87$: $p = 0.048$]. Comparing the "low risk-gain" with the "low risk-loss" condition [$t(15) = 2.09$: n.s.] and the "low risk-gain" with the "high risk-gain" condition [$t(15) = - 0.43$: n.s.] did however not yield significant differences. The present data suggest that in particular the "high risk-loss" condition has the most profound impact on the

early brain physiology. P1 amplitude was significantly higher in the punishment compared to the reward condition. Furthermore, the P1 amplitude for punishment was lower in high risk as compared to low risk gambling.

MFN amplitude

The GG-ANOVA for the MFN showed a statistical significant Risk x Outcome interaction [$F(1,15) = 6.13$: $p = 0.026$]. Post-hoc Bonferroni corrected paired-samples t-testing demonstrated significant MFN amplitude reductions comparing the "high risk-loss" with "low risk-loss" condition [$t(15) = 3.14$: $p = 0.028$]. The "high risk-loss" was not statistically different from the "high-risk gain" [$t(15) = 2.26$: n.s.]. Moreover, no differences between the "low risk-gain" and the "low risk-loss" condition [$t(15) = -0.722$: n.s.] and the "low risk-gain" and "high risk-gain" condition [$t(15) = -0.940$: n.s.] were observed. The findings suggest that the MFN to punishment was in particular modulated by the level of risk taking.

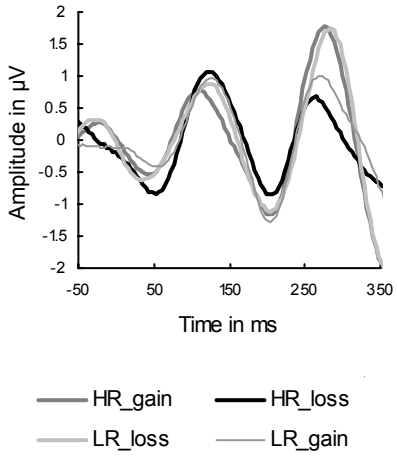

Figure 7.2. Collapsed mean ERP in µV after providing feedback during the gambling task showing a significant main effect for the P1-MFN complex in the "high-risk loss" condition. HR_gain: high risk-gain; HR_loss: high risk-loss; LR_gain: low risk-gain; LR_loss: low risk-loss.

Figure 7.2 displays the collapsed grand averaged ERP for the Fz, F3, F4 and Cz electrode sites in the four conditions after providing visual feedback (t = 0) as outlined in the methods and materials section. Moreover, a parametric Pearson's correlation revealed a functional association between the P1 and MFN [r(16) = - 0.701: p = 0.002], indicating that the components comprise an electrophysiological complex involved in the processing of high risk losses (see also Figure 7.3).

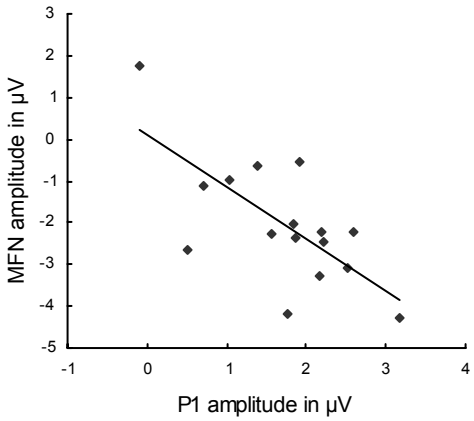

Figure 7.3. The functional association between P1 and MFN in the "high-risk loss" condition, in which larger P1 amplitude are associated with lowered MFN amplitudes.

Phenomenological relationships

To further delineate the hypothesized influence of personality traits and behavior on the electrophysiological chronometry after experiencing loss after high risk decision making, non-parametric Spearman rank-order correlation were performed for the P1 and MFN with punishment sensitivity (BIS) and the actual overall percentage of high risk gambling during the task (mean ± SEM, 57 ± 12.9). Correlation analyses demonstrated a significant association between the P1 amplitude and punishment sensitivity [rho(16) = -0.594: p = 0.015], suggesting a relatively lower P1 amplitude in more punishment *in*sensitive subjects. The relationship is depicted in Figure 7.4. Note the inverse relations between BIS score and punishment sensitivity as mentioned earlier in the Methods section. Furthermore, the MFN amplitude was correlated to the overall

percentage high risk gambling during the task [rho(16) = 0.631: p = 0.009], which is depicted in Figure 7.5 Finally, punishment sensitivity was not associated with overall percentage risk taking [rho (16) = 0.121: p = 0.654], suggesting a dissociation between physiological and behavioral characteristics.

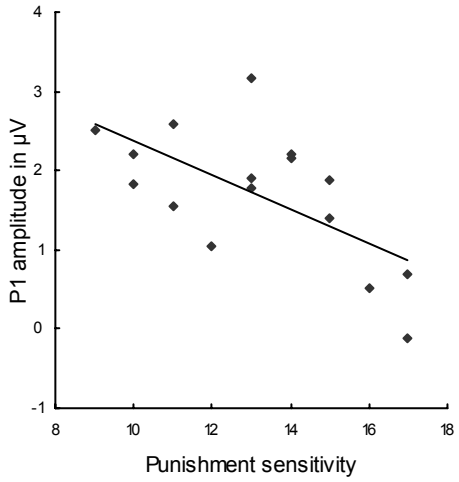

Figure 7.4. Lowered P1 amplitudes after loss in high risk gambling is associated with decreased punishment sensitivity.

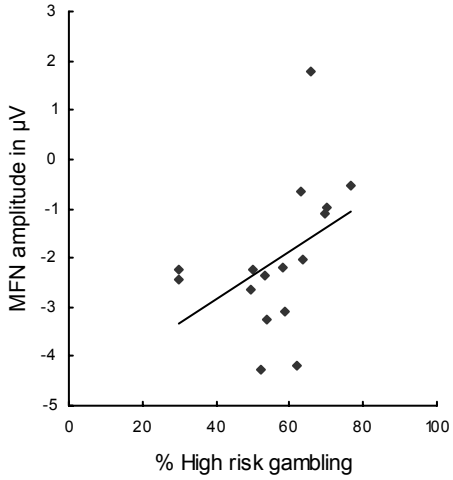

Figure 7.5. Individuals engaging in relative frequent high risk decision making show a reduced MFN amplitude when subsequently confronted with a large monetary loss.

Discussion

The present study investigated the electrophysiological correlates after punishment during low and high risk gambling in healthy volunteers. The results showed differential electrocortical processing after experiencing substantial monetary loss due to high risk decision making. An augmented first positive-polarity brain potential (P1) to punishment was not only observed within 150 ms after high compared to low risk gambling, but P1 amplitude was also higher for punishment as compared to reward. However, the P1 amplitude was inversely associated with higher self-reported punishment sensitivity as reflected by the scores on the BIS questionnaire. Early ERP components are suggested to originate from attentional networks governing orienting-like reactivity to salient stimuli, including punishment feedback. Defensibly, and in accordance with the low fear hypothesis of psychopathy, punishment insensitive subjects experience lower levels of distress when confronted with large monetary losses. The here observed lowered P1 amplitude is arguably due to reduced responsivity of the reticular activating system (Arai et al., 2003) and likely constitutes a physiological index of punishment insensitivity, which is further corroborated by the subject's self-attributed sensitivity for punishment.

Furthermore, an attenuated signal for the high compared to the low risk gambling was observed for the MFN component to punishment. In the study reported by Gehring and Willougby (2002) a negative ERP was greater in amplitude when a subject's choice between two alternatives resulted in a loss compared to a gain. Although a similar paradigm was used in the present study, including the strategy of increasing motivation by enhancing the monetary incentive of the task, we were not able to replicate the MFN effect. Varying task instruction prior to the game might have induced a systematic difference in the execution of the task across the participants, but more importantly, our primary aim was to study the electrophysiological correlates of reward and punishment following high and low risk gambling, instead of studying the relative wins or losses. Interestingly, the present MFN component was specifi-

cally correlated to the overall percentage high risk taking during the game, suggesting that a lowered MFN amplitude to punishment in the high risk gambling condition varies as a function of increased high risk decision making. Although the present study precludes any definite conclusions regarding the neural source underlying the MFN, it may be argued that the ACC plays an important role. The ACC is associated with monitoring and evaluation type attentional processing (Posner & Raichle, 1994; Shallice & Burgess, 1991). The lowered MFN amplitude after punishment related to high risk might therefore reflect differential processing in the ACC, reducing the allocation of attentional resources and hence its impact. Arguably, the P1 component reflects more automatic physiological responses modulated by punishment sensitivity, whereas the MFN component can be interpreted in terms of high risk punishment processing.

A negative relationship between the P1 and MFN amplitude was observed during feedback processing, which is in line with the anatomical efferent fiber projections from the reticular formation of the midbrain via the thalamus to the ACC (Fuster, 1997). Importantly, although the P1 and MFN components were apparently electrophysiologically associated, they nevertheless seem to reflect differential functional processes. Note however that self-attributed punishment sensitivity and overall percentage high risk taking were uncorrelated. Subjects could not actually loose money, even if players were in debit at the end of the game. As already mentioned in the Methods section, volunteers were paid for participation and if they had gained credits at the end of the game, they would receive this amount as a bonus on top of the standard participation fee. The latter information was provided to the subjects prior to the game, which might have reduced the ecological impact of winning and loosing. The statistical relationship between the components nevertheless suggests that the P1 and MFN constitute a distinct ERP complex involved in punishment feedback after high risk decision making. On the functional level, the P1 and MFN both reflect differential, but associated processes in the evaluation process of punishment (i.e., the ERP complex). Relatively indifferent to aversive stimuli and punishment is the

psychopath (Blair, 2001). The psychopath is a fearless individual whose insensitivity to punishment together with a strong reward dependency results in risk taking behavior and antisocial acts (Arnett, 1997; Van Honk, Schutter, Hermans, & Putman, 2003). Based on the present findings it is hypothesized that a similar electrophysiological pattern is present in psychopathy, which might provide additional insight in the biological mechanisms underlying psychopathy. Furthermore, from the current observed physiological and phenomenological dissociation, the ERP complex might prove to be a more sensitive marker for psychopathic tendencies than merely relying on self-reports and observational data, especially given the deceitful nature of psychopaths. In conclusion, the present findings give insight into the electrophysiology of fear motivated decision making and may have possible implications for psychopathy.

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8

Functionally dissociated aspects in anterior and posterior electrocortical processing of facial threat

International Journal of Psychophysiology 2003, in revision.

Abstract

The angry facial expression is an important socially threatening stimulus argued to have evolved to regulate social hierarchies. In the present study, event-related potentials (ERP) were used to investigate the involvement and temporal dynamics of the frontal and parietal regions in the processing of angry facial expressions. Angry, happy and neutral faces were shown to eighteen healthy right-handed volunteers in a passive viewing task. Stimulus-locked ERPs were recorded from the frontal and parietal scalp sites. The P200, N300 and early contingent negativity variation (eCNV) components of the electric brain potentials were investigated. Analyses revealed statistical significant reductions in P200 amplitudes for the angry facial expression on both frontal and parietal electrode sites. Furthermore, apart from being strongly associated with the anterior P200, the N300 showed to be more negative for the angry facial expression in the anterior regions also. Finally, the eCNV was more pronounced over the parietal sites for the angry facial expressions. The present study demonstrated specific electrocortical correlates underlying the processing of angry facial expressions in the anterior and posterior brain sectors. The P200 is argued to indicate valence tagging: a fast and early detection mechanism. The lowered N300 with an anterior distribution for the angry facial expressions indicates more elaborate evaluation of stimulus relevance. The fact that the P200 and the N300 are highly correlated suggests that they reflect different stages of the same anterior evaluation mechanism. The more pronounced posterior eCNV suggests sustained attention to socially threatening information.

Introduction

The selective processing of threatening angry facial expression has been extensively investigated on both the behavioral, functional (e.g., Öhman, Lundqvist, & Esteves, 2001; Tipples, Atkinson, & Young, 2002) and physiological level (e.g., Dimberg & Petterson, 2000; Morris, Öhman, & Dolan, 1998). The threatening facial expression of anger provides an important warning signal in the regulation of social hierarchies (Darwin, 1872; Lorenz, 1966, Van Honk & De Haan, 2001). Recently, Van Honk et al. (2000) and Van Honk, Tuiten, Van den Hout, De Haan, & Stam (2001b) demonstrated attentional biases to angry facial expressions using a modified emotional Stroop task in healthy volunteers. In this task different colored (i.e., blue, green, yellow or red) angry and neutral faces were presented and the subjects had to name the color of the face as fast as possible. The rationale behind this task was that it would take longer for subjects to name the color of the face when they attend towards an emotional compared to neutral facial expression (i.e., interference). Faster color naming on the other hand, would suggest that the perceiver was avoiding the processing of the emotional facial expression (i.e., facilitation). Van Honk et al. (2000, 2001b) showed interference during color naming of angry facial expressions, interpreted in terms of the face capturing attentional resources.

Although electrophysiological studies have demonstrated specific deflections in the ongoing EEG that are related to facial and affective information processing as early as 100 ms post-stimulus (e.g., Orozco & Ehlers, 1998; Pizzagalli, Regard, & Lehmann, 1999), these early brain potentials would appear to reflect processes related to morphological encoding, such as the extraction of physiognomic features of the face (Bruce & Young, 1986). The N170, for instance, is a negative deflection in the EEG that is specifically involved in the structural face encoding, but does not seem directly sensitive for familiarity or the emotional expression of the face (Balconi & Pozzoli, 2003; Eimer & Holmes, 2002; Herrmann et al., 2002). Pizzagalli et al. (2002), however, recently report early brain potentials (~ 160 ms), which were a function of affective

judgment. Notwithstanding, it has been argued that cognitive and affective information processing arises after 200ms.

A brain potential which has proven to be sensitive to emotional visual stimulation is a positivity peaking around 200 ms, designated as the P200 (Carretié, Mercado, Tapia, & Hinojosa, 2001a; Carretié, Martin-Loeches, Hinojosa, & Mercado, 2001b). Horley et al. (2001) for instance demonstrated reduced P200 amplitude following angry, compared to neutral facial expressions. It has been suggested that the relative early P200 reflects a valence specific orienting index for relevant stimuli. Processes that occur later in the ERP chronometry are argued to be related to more complex cognitive and affect-related processes. For example, the N300 has been demonstrated to be a emotion-sensitive potential, which is less affected by cognition (Carretié, Iglesias, & Garcia, 1997). Carretié et al. (1997) argue that the N300 might reflect an arousal dimension of affective characteristics of visual stimuli. Moreover, the N300 in the anterior brain region has been positively associated with arousing negative valenced stimuli, whereas a more posterior N300 distribution was related to arousing positive valenced stimuli. In accordance with a frontal-parietal network of attention put forward by Posner and Raichle (1997), the P200 and N300 might be involved in the detection and evaluation of angry facial expressions, respectively. A vigilance network of attention consisting of the frontal and parietal cortex is argued to maintain a state of alertness when salient stimuli are encountered. Angry facial expression are important socially threatening stimuli (Öhman, 1997), hence the involvement of the vigilance network can be assumed since alertness and action preparation are essential for appropriate responses.

Several studies have reported positive going waveforms after displaying affective pictures (Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000: Keil et al., 2002). Ruchkin, Johnson, Mahaffey, & Sutton (1988) argued that positive going waveforms might particularly be associated with perceptual operations and memory storage, whereas the negative going waveforms are more related to higher order conceptual activity. Cuthbert et al. (2000) suggested that slow waves can be evoked during picture viewing and augmented for emotional laden stimuli, mirroring increases

in resource allocation to motivationally relevant incentives. Enhanced late positive going waveforms have indeed been observed after the display of pleasant and unpleasant pictures from the International Affective Picture System (IAPS) (e.g., Cuthbert et al., 2000: Schupp et al., 2000). However, the neural signature of the positive going waveform remains somewhat elusive. In particular negative going waveforms over posterior regions, including the eCNV are assumed to reflect underlying cortical activation through massive depolarisation of apical dendrites (Weisz, Schandry, Jacobs, Mialet, & Duschek, 2002). Since a slow negative going wave has been found to be indicative of allocation of cortical resources (Altenmüller & Gerloff, 1999) and the CNV in a post-stimulus trace reflects selective attention paid to a highly relevant stimulus (Wilkinson & Ashby, 1974), it is feasible that threatening angry facial expressions will elicit an eCNV rather than a positive going waveform. Thus, albeit the eCNV is typically elicited in S1-S2 paradigms, it may nevertheless be conjectured that the eCNV could be evoked and modulated by angry facial expressions, indexing a rudimentary form of action preparation.

Although, the electrophysiology of face processing has been abundantly investigated, little is known about the processing of angry faces in the fronto-parietal network of attention. The present study was designed to investigate the temporal dynamics of the frontal and parietal EEG displaying angry compared to neutral and happy facial expressions. As noted, the P200 amplitude is argued to indicate valence tagging and amplitude reductions have been observed after displaying angry facial expressions (Horley et al., 2001). Thus, currently reductions in P200 amplitude were hypothesized. Larger N300 amplitude indicating elaborate attentional processing were hypothesized to occur after the angry facial expression. Also, since the eCNV varies as a function of alertness and sustained attention, a more pronounced negativity for the threatening angry facial expression was expected. If indeed the P200, N300 and eCNV amplitude would be modulated by the threatening angry facial expression, it would be worthwhile to investigate possible functional relationships between the components as well.

Method

Participants

Eighteen healthy volunteers (mean ± SD age, 21.6 ± 1.9 years) were recruited among students at Utrecht University, Utrecht, The Netherlands. Participants (11 females) were non-smoking and right-handed as indexed by the Edinburgh Handedness Inventory (Oldfield, 1971) (mean ± SD score, 44.3 ± 3.2). None of the subjects had a history of psychiatric or neurological conditions and had normal or corrected-to-normal vision. All volunteers were unaware of the aim of the study. Informed consent was obtained and participants received payment for taking part in the study. The protocol was approved by the local ethical committee of Faculty of Social Sciences.

Passive viewing task

The stimuli were taken from Ekman and Friesen's (1976) Pictures of Facial Affect and other comparable specially prepared facial stimuli (Van Honk et al., 2000). Pictures of 10 different individuals each displaying angry, neutral and happy facial expression were used. Happy facial expressions were included to control for valence (Van Honk et al., 2001a). The passive viewing task consisted of ninety consecutive non-paced 750 ms presentations of thirty facial expressions of each category. Prior to each sequence of facial picture, a fixation cross appeared at the center of the screen for 750 ms. The inter-stimulus interval between the presentations varied randomly between the 1500 and 2500 ms. All stimuli were projected in the center of the screen in gray-scales on a black background, using a 70Hz computer screen at a distance of 110 cm from the eyes. The image sizes were 14 x 9 cm and the vertical and horizontal visual angles being 3.64° and 2.34° respectively. The stimuli were presented in a random fashion.

Event related potentials

EEGs were recorded from eight electrodes, i.e. F3, F4, P3, P4, Fz, Cz, Pz and Oz scalp positions, using an Electro-Cap with Ag/AgCl elec-

trodes (Neurosoft, Inc.) and according to the International 10-20 System. EEG signals were referenced to an electrode placed on the subject's right mastoid. The choice of the reference has been a longstanding issue in electrophysiological studies (see for instance Nunez et al., 1997; Picton et al., 2000; Reilly, 1999). Various solutions have been proposed in order to minimize the influence of reference, but no agreement on an optimal solution for the reference problem has been reached yet (Hagemann, Naumann, & Thayer, 2001). The mastoid reference is often used to maximize inter-electrode distance and to avoid mixed activity from two different scalp areas. This montage is based on the assumption that unlike, for instance, vertex referencing the mastoid site picks up no or minimal electrical activity. Although, the reference electrode ought to be "silent", this is hard to accomplish. One of the solutions is to use a scalp site with minimal activity (Hagemann, Naumann, Becker, Maier, & Bartussek, 1998). Furthermore, different reference strategies do not necessarily compromise whether and where the ERPs are recorded. For instance, Horley et al. (2001) ran separate analyses with two different reference montages with no unduly effects on the P200 component. Finally, Keil et al. (2002) recently used a high-density electrode (129-sensor) array and an average reference to investigate affective picture processing. Surprisingly, the polarity and topography of the effects were similar to that observed in previous comparable work, which had used smaller montage sizes and linked mastoids.

For the purpose of artifact scoring, vertical (VEOG) and horizontal (HEOG) eye movements were recorded. Ag/AgCL electrode pairs (bipolar) were placed at the supra- and suborbit of the right eye and at the external canthi of each eye. ECI EEG Gel was used for both EEG and EOG and all electrode impedances were less than 5,000 Ω. An acquisition amplifier (Ampligraph) was used to filter incoming signals (low-pass cut-off frequency 70 Hz; time constant 3 seconds). For the EEG recordings NeuroScan software (El Paso, Texas) was used. Amplification was set at 20,000 for both the EEG and EOG leads, and the sample rate was 250 Hz. Raw EEG was digitally low-pass filtered offline with a cut-off frequency of 15 Hz, corrected for eye-movements, using

linear regression, and epoched in a -50 to 1,024 ms stimulus-locked time window. Muscular and other sources of artifacts (-/+ 50 μV) in the stimulus-locked epochs were removed prior to further analysis. The designation of an artifact in one of the leads resulted in removal of that epoch for all channels in order to ensure that the remaining data were identical for all sites in time. The remaining EEG epochs were baseline corrected using the mean amplitude 50 ms prior to stimulus onset and averaged across the different facial expressions, constructing a mean ERP for the angry, neutral and happy facial expressions for the passive viewing task. An averaged waveform from at least 25 artifact-free trials for each emotional facial expression could be obtained.

Procedure

Upon arrival at the psychological laboratory volunteers written informed consent was obtained and the computerized version of the Edinburgh Handedness Inventory was completed. Next, participants were prepared for the EEG recording. After completion, the subjects were seated in a comfortable chair situated in a dimly lit room adjacent to the control chamber. EEG was recorded during passive viewing task, and subjects were instructed to relax, keep head movements to a minimum, and to focus on the screen. The entire experiment took approximately one hour per subject.

Data Analyses

For each individual the average amplitude of the P200 and N300 components for each facial expression category were determined by means of peak-amplitude scoring between 150-250 ms and 250-350 ms time intervals respectively (adapted from Carretié and Iglesias, 1995). The slow wave activity, the eCNV, was defined as the mean amplitude in the 425-525 ms time window. To investigate anterior-posterior and inter-hemispheric differences, separate 3 x 3 MANOVAs for the frontal (F3, F4, Fz) and parietal (P3, P4, Pz) were performed with Electrode and Valence (angry, neutral and happy facial expressions) as within-subject factors and the mean amplitude of the P200, N300 components and the

eCNV as the dependent variables. Potential functional relationship between the brain potentials of interest and emotional face processing were investigated using post-hoc Pearson's correlations. The alpha level of significance (two-tailed) was set at $p \leq 0.05$ throughout.

Results

Separate MANOVAs for the frontal and parietal electrode sites revealed a significant main Valence effect of reduced P200 amplitude for the angry facial expressions compared to both the anterior [$F(2,16) = 3.6$: $p < 0.05$ and posterior regions [$F(2,16) = 5.0$: $p = 0.02$]. Two separate MANOVAs were conducted to test for differences between frontal and parietal distribution of the N300.

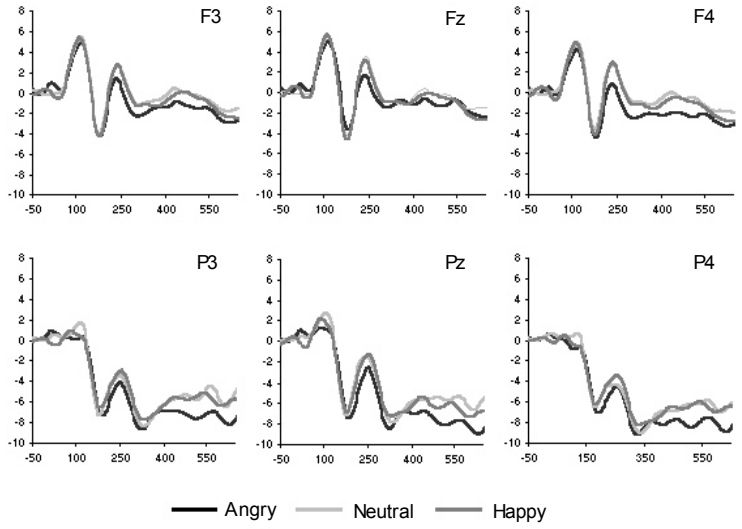

Figure 8.1. Mean scalp-recorded ERPs in μV for the angry, happy and neutral facial expressions.

There was an augmentation of the N300 amplitude over the frontal electrodes [$F(2,16) = 4.4$: $p = 0.03$], but the effect failed to reach significance over the posterior sites [$F(2,16) = 2.2$: $p > 0.15$] for the angry facial expression. Two separate MANOVAs yielded a significance larger

eCNV over the parietal [$F(2,16) = 5.1$: $p < 0.02$], but not the frontal electrode sites for the angry facial expression [$F(2,16) = 1.9$: $p > 0.17$]. The parietal eCNV and its reactivity seem to be in accordance with the typical topographical distribution of the eCNV over the scalp. Figure 8.1 displays the grand-averaged ERPs for the angry, neutral and happy facial expressions over the frontal and parietal electrode sites.

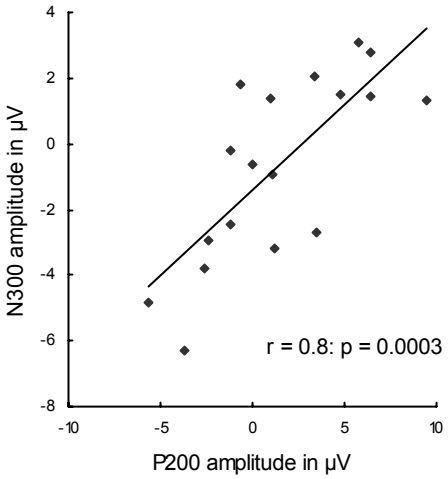

Figure 8.2. The anterior P200-N300 correlation for the angry facial expressions.

Finally, Pearson correlations demonstrated a highly significant relationship between the anterior P200 and N300 amplitude for the angry facial expression [$r(18) = 0.8$: $p = 0.0003$], which is shown in Figure 8.2 An association between P200 and eCNV on the other hand was not found [$r(18) = 0.1$: $p = 0.65$].

Discussion

The present study investigated the electrocortical processes over the anterior and posterior brain regions for angry, neutral and happy facial expressions. Unlike most of the earlier brain potentials the P200 has demonstrated to be valence specific (Carretié et al., 2001a). In accordance with this notion, a recent study by Horley et al. (2001) indeed

showed a relationship between reduced P200 amplitude following the presentation of angry, compared to neutral facial expressions, which is replicated in the present study. Sokolov (1975) suggested that in the case of threatening stimuli the cortical analysers are shut down, in order to preclude higher level cognitive processing to interfere with the need for efficient and quick responses. In other words, Sokolov (1975) argued that the available energetic resources must immediately be re-allocated to (subcortical) brain structures involved in the preparation of fight-flight responses (Ledoux, 2002). In the present respect, it might thus be argued that the reduced P200 component reflects a relative fast and early threat related index of information processing: a global valence tagging or detection system. A similar although reversed pattern was observed for the N300 which showed to be larger for the angry facial expressions. Carretié et al. (1997, 2001a) already emphasized the importance of this negative brain potential in the processing of emotionally salient stimuli. Alternatively, Rockstroh, Elbert, Canavan, Lutzenberger, & Birbaumer (1989) and Schupp, Lutzenberger, Rau, & Birbaumer (1994) have argued that positive and negative brain potentials relate to inhibitory and facilitatory processes. Accordingly, the reduced P200 amplitude would stand for cortical activation and enhanced processing which might explain the physiological relation with the enhanced N300 amplitude. Notably, in the present study the N300 amplitude appeared to be significantly modulated over the anterior brain sectors. This observation is in accordance with the findings of Carretié et al. (1997) who showed that the N300 was most pronounced over the frontal cortex for arousing negative related stimuli. In the present respect, it is argued that the N300 reflects a more in depth evaluation of the relevant stimuli which have passed the initial detection of significance (the P200). It is furthermore interesting to observe that besides from being modulated by the angry facial expression, the P200 was also positively associated with the emergence of the N300. This provides evidence for a relationship between the computations underlying detection and evaluation. This P200-N300 complex is likely part of an anterior network involved in the detection and evaluation of threat. The well-documented executive functions of the frontal

brain areas in cognition and emotion (Fuster, 1997) are in support of this assumption. Parietal enhancements of the eCNV for angry, but not neutral and happy faces were observed in the current study. Cuthbert et al. (2000), Keil et al., (2002) and Schupp et al. (2003) have reported positive going waveforms following emotional pictures. However, in the present study a different set of emotional stimuli was used. The average ERP of their negative IAPS pictures is not exclusively based on emotional facial expressions, since the IAPS also uses rather gruesome negative pictures of, for instance, mutilated bodies (e.g., Cuthbert et al., 2000). This dissimilarity might well evoke a different cascade of electrophysiological effects. The eCNV is assumed to reflect underlying cortical activity through massive depolarisation of apical dendrites (Weisz et al., 2002) and suggested to function as a warning-type signal (Weerts & Lang, 1974). Interestingly as can be read from the Introduction, Wilkinson and Ashby (1974) suggested that the CNV in a post-stimulus time period might index selective attention. The parietal lobules have been implicated in a vigilant attention network (Posner & Raichle, 1997). Adding evidence to this parietal involvement in emotional processing, Schutter, Putman, Hermans, & Van Honk (2002) recently showed that baseline parietal activity was predictive for selective attention to the angry facial expressions. Since no correlation was found between the parietal P200 and the eCNV, it can be argued that the parietal eCNV reflects a separate functional process, instantiated after the completion of the first evaluation stage. Thus, the eCNV might be associated with sustained attention and action preparation. It can nevertheless be argued that the selective processing of the angry facial expression is primarily a consequence of arousal (Cuthbert et al., 2000; Keil et al., 2002; Schupp et al., 2003). At least subjectively, the emotional expressions of anger and happiness do not seem to differ on the arousal dimension. Indeed, Balconi and Pozzoli (2003) recently found that the angry and the happy facial expressions are rated as negative and positive in valence, but both highly arousing. We did not ask the participants to subjectively rate the arousal dimension of the faces nor did we apply autonomic measures. Presently, the angry face did exert selective modulatory effects on the

N300 and the P200 component. Note that the N300 has been linked to negatively arousing events (Carretié et al., 1997), whereas the reduced P200 amplitude has specifically been associated with angry facial expressions (Horley et al., 2001). On basis of above-noted findings (Balconi & Pozzoli, 2003; Horley et al., 2001) and the current differential findings on angry and happy faces, it can be suggested that valence is involved in the ERP of the angry facial expression. A possible limitation of the study is the small number of electrode sites from which EEG was recorded. Larger montage-sizes might provide more detailed information regarding polarity and topographical distribution, albeit the parsimonious use of less dense arrays does not compromise findings with respect to polarity and topographical distribution per se. In defense, Keil et al. (2002) recently used a high-density electrode (129-sensor) array and average referencing and demonstrated that the polarity and topography of ERP components were similar to that observed in previous work with smaller montage sizes and linked mastoids. It should however be noted however that larger electrode arrays do provide better estimates of topographical distribution enabling electrocortical source analysis, but was beyond the scope of our study.

In sum, based on the present data, it is concluded that the frontal brain sector is involved in the detection (P200) and evaluation (N300) of angry facial expressions, whereas the posterior cortices are involved in sustained selective attention and action preparation (eCNV). The frontal P200-N300 complex and parietal eCNV may be part of a functionally dissociated fronto-parietal network of attention in which anterior and posterior sectors are responsible for different aspects of affective processing.

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9

Parietal EEG beta asymmetry and selective attention for angry facial expressions

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Abstract

Research on cerebral affective processing in humans has concentrated on the lateralisation of the prefrontal cortex. However, the parietal cortex also seems to play a role in motivation and emotion. In the present study the lateralized role of the parietal cortex in motivated attention was investigated, using an electrophysiological correlate of brain activity (electroencephalogram (EEG)) and a modified Dot probe task, which indexes selective, i.e. avoidant or vigilant attention for angry faces in a spatial display. Twenty-two participants underwent an EEG baseline recording from the F3, F4, P3 and P4 electrode positions, which was followed by the modified Dot probe task. Spectral power in 1 Hz frequency bins were derived for each electrode site and transformed to power density values in the 8–12 Hz (alpha) and 13–30 Hz (beta) frequency range. Log-transformed prefrontal and parietal asymmetries and bias scores for selective attention to angry and happy faces were calculated. Results showed a highly significant relationship between the asymmetry in parietal EEG beta activity and the attentional response to the angry face. Relative more right-sided parietal EEG activity in the beta frequency domain was predictive of a more avoidant response to angry facial expression. This finding suggests that asymmetrical parietal beta activity might be linked to the behavioral dimensions of approach and withdrawal.

Introduction

The prefrontal cortex is argued to play a crucial role in the perception, processing and regulation of emotion (Davidson, 2000; Harmon-Jones & Allen, 1998). However, there is also support for the involvement of the parietal cortex in emotional processing (Adolphs, Damasio, Tranel, & Damasio, 1996; Davidson, 2000; Davidson & Henriques, 2000; Schutter, Van Honk, Koppeschaar, & Kahn, 2001). For depression evidence often shows a right-sided anterior electroencephalogram (EEG) asymmetry mostly due to left prefrontal hypoactivation, whereas the pattern for posterior asymmetry remains less clear. Data from EEG studies have indicated right-sided increases, as well as right-sided and bilateral decreases in the parietal regions (Davidson & Henriques, 2000). In a recent study with healthy subjects, Van Honk et al. (2000) demonstrated that the active suppression of neural activity in the right parietal cortex, by means of repetitive transcranial magnetic stimulation (rTMS) resulted in decreased self-reported depression, accompanied by increased attention to angry facial expressions (Van Honk et al., 2000). Notably, these behavioral data, i.e. reduced depression and increased attention towards angry faces suggest more approach-related affective behavior (D'Alfonso, Van Honk, Hermans, Postma, & De Haan, 2000; Davidson, 2000; Nesse, 2000; Van Honk & Schutter, 2001). Elevated depression, cf. low mood and avoidant responses to angry faces are assumed to be associated with the withdrawal dimension of affect (Nesse, 2000; Van Honk et al., 1998). Interestingly, low mood is often accompanied by chronically elevated levels of cortisol (Van Honk et al., 1998). A recent study by Schutter et al. (2001) showed an inverse relation between functional connectivity, as indexed by EEG coherence, in the left prefrontal-right parietal circuit and levels of cortisol. Reductions in information transmission between the two cortical regions were associated with higher levels of cortisol, providing additional evidence for the involvement of the right parietal cortex in affective processing.

A valid method for quantifying asymmetries of ongoing cortical activity is electroencephalography (EEG). In the frequency domain of the brain

signals, cortically generated beta (14–30 Hz) synchronization is assumed to reflect underlying neuronal activity, whereas alpha (8–13 Hz) activity is considered to have the opposite relation (Lopes da Silva, 1999; Nunez, 2000). EEG asymmetries for homologue scalp positions are often used to indicate predominant neuronal activity between the two hemispheres (Davidson, 1988). Brain asymmetries are quantified by differences in log-transformed power amplitudes in the EEG spectrum between the two areas of the hemispheres (log Right-side-log Left-side). Positive asymmetries indicate relatively predominant right-sided activity in a given frequency band and vice versa.

Although the parietal cortex seems to be involved in affective processing, its functional aspect is far from clear. The aim of this study was to investigate the relationship between neural asymmetry in the parietal region of the brain and selective attention to angry faces, using a direct neurophysiological correlate of brain activity. In addition the prefrontal asymmetry was also studied, because of its established involvement in emotion and motivation (Davidson, 2000; Davidson & Henriques, 2000; Harmon-Jones & Allen, 1998). A modified Dot probe task was used in which attention towards or away from angry as compared to neutral stimuli was quantified. Happy faces were also included in the modified Dot probe task, in order to scrutinize valence specificity of the attentional bias.

Method

Participants

Twenty-four healthy subjects (12 female), all aged between 20 and 28 years, participated in the experiment. All participants were right-handed and had no history of psychiatric illness. Informed consent was obtained from all subjects and they were paid for participation. Data from two subjects were discarded from the study, because of unreliable EEG data acquisition.

EEG recording and analysis

Baseline EEGs were recorded from the homologous F3, F4, P3 and P4 scalp positions, using an stretchable Electro-Cap with Ag/AgCl electrodes (Neurosoft, Inc.), according to the International 10/20 System. EEG signals were referenced to an electrode placed behind the subject's right ear. For the purpose of artifact scoring, vertical and horizontal eye movements, using an electro-oculogram (EOG) were recorded. Electrode pairs (bipolar) were placed at the supra- and suborbit of the right eye and at the external canthi of each eye. ECI EEG Gel was used for both EEG and EOG and all electrode impedances were less than 5,000 Ω. An acquisition amplifier (Ampligraph) was used to filter incoming signals (low-pass cut-off frequency 30 Hz with a time constant of 3 seconds). For the EEG recordings NeuroScan software was used. Amplification was set at 20,000 for both the EEG and EOG leads, and the sample rate was 250 Hz. After the Electro-cap was positioned, subjects were seated in a dimly lit room and were instructed to relax, but not to fall asleep. A ten-minute baseline EEG recording, consisting of five one-minute blocks of eyes open and five one-minute blocks eyes closed relaxation, was acquired. Raw EEG, data were corrected for horizontal and vertical eye movements and re-filtered (Bandpass: 1-30 Hz) off-line. Portions of each 1-minute EEG signal containing blinks greater than 100 μV, excessive muscular activity or other sources of artifacts were rejected prior to further analysis. Next, 1.024-s chunks of averaged artifact-free EEG was extracted through a Hamming window (length 10%) in order to reduce spurious estimates of spectral power. For each chunk, a fast Fourier transform method was used to derive estimates of spectral power (μV^2) in the 1 Hz frequency bins for each electrode site. Spectral power values were averaged across all epochs within a single baseline and were then transformed to power density values ($\mu V^2/Hz$) for the 8-13 Hz (alpha) and 14-30 Hz (beta) frequency bands respectively. Finally, the prefrontal and parietal brain log-transformed asymmetries for mean power density were calculated.

Dot probe task

After the baseline EEG recording, participants performed the modified Dot probe task, a spatial attention task sensitive to emotional dispositions (Bradley et al., 1997). For this task, a set of uniform, monochrome pictures of six male and six female actors portraying neutral, happy and angry facial expressions was assembled, using a digital video camera and panel-judgments of selected still-frames. The modified Dot probe task was programmed with Testpoint software package and run on a 266 MHz PC. For measurement of reaction times, a Lafayette voice response key connected to a condenser microphone was used. Through a closed circuit video and audio equipment participants' errors and in compliance to instructions were monitored. Before the performance of the task a standard Snellen chart was used to check for visual acuity. The task consisted of 96 trials, each displaying a neutral and emotional face of the same actor on either side (left and right) of a previously displayed central fixation cross which remained visible for 750 ms. The faces were presented for 500 ms. Immediately following the display of the faces, either on the left or right side a probe (the capital character `A' or `O') appeared in the location were previously a neutral or emotional face had been presented. Presentation of the probe was terminated by computer registration of the vocal response of the participant. Inter-trial intervals varied randomly between 1500 and 2500 ms. Emotional valence, its position, target gender, probe type and its position relative to the emotional face were all counterbalanced across the quasi-random task order. Participants were instructed to focus on the fixation cross at the start of each new trial and to identify as fast and accurately as possible the capital character `A' or `O'. In advance, they were given ten practice trials. Bias scores were calculated by subtracting the average latencies to probes replacing an emotional from the probes replacing a neutral face. Negative difference scores indicate more time needed to identify the probes, i.e. avoidance of the emotional faces, whereas positive scores reflect more vigilant attention to emotional faces.

Statistical analyses

The relationships between prefrontal and parietal brain EEG asymmetries and selective attention to angry and happy faces were investigated by means of correlational analyses. The alpha level was set at 0.05, two-tailed throughout.

Results

Bonferroni corrected, non-parametric Spearman correlations (Clark-Carter, 1997) yielded a highly significant relationship between right-sided parietal beta asymmetry and selective attention to angry faces [$r = -0.642$: $p < 0.008$]. Increased right-sided baseline beta activity was associated with a more avoidant response to the angry facial expression. No other significant relationships were found. Figure 9.1 shows the correlation between the bias for angry, as compared to neutral faces in milliseconds (ms) and the EEG asymmetries in the beta frequency range over the parietal cortex.

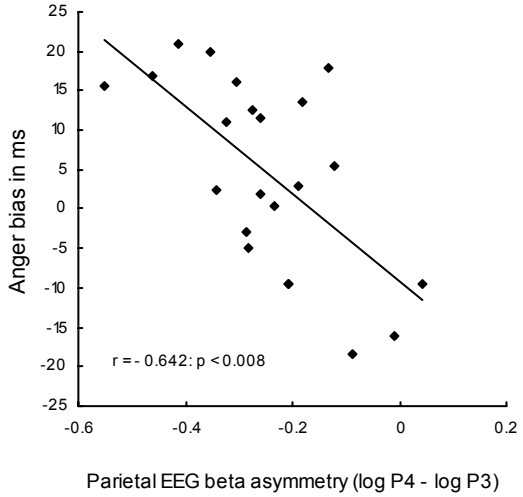

Figure 9.1. Averaged brain asymmetries from the P3 and P4 electrode sites and mean attentional bias for angry facial expressions in milliseconds (ms).

Discussion

The present study shows a relation between parietal brain asymmetry in the beta EEG frequency domain and selective attention towards angry facial expressions.

More specifically, asymmetrical brain activity as measured by EEG favoring the right parietal cortex was related to a more avoidant response to the angry facial expression. This is in line with above noted findings from slow repetitive TMS (a method capable of locally decreasing neuronal activity (Pascual-Leone, Bartres-Faz, & Keenan, 1999) over the right parietal cortex, which was accompanied by the opposite effect, i.e. a more vigilant response towards angry faces and *reduced* depression. Complementary, in earlier studies it was demonstrated that avoidance of angry faces is associated with increased levels of cortisol and *elevated* depression (Van Honk et al., 1999; Van Honk & Schutter 2001), correlates of affective withdrawal. Interestingly, recently Nesse (2000) associated the adaptive value of such an affective withdrawal mode specifically with submissive behavior in threatening interpersonal challenges to figures displaying anger. An avoidant response to the angry facial expression would function as a violence inhibitor preventing aggression and potential harm to the individual (Van Honk et al., 2000). Reduced depression, elevated mood and vigilant attention to angry faces are, on the other hand, linked to the approach dimension of behavior (D'Alfonso et al., 2000; Davidson, 2000). Related to the present findings, a study by Crowne, Richardson, & Dawson (1987) showed that rats with lesions at the right parietal cortex, resulting in contralateral left-dominant processing, exhibit more explorative, approach related behavior (Crowne et al., 1987). Our data indicate that relative hyperactivation of the right parietal cortex is linked to the behavioral dimension of withdrawal or low mood. In sum, the asymmetrical activation of the parietal cortex seems to be associated with the behavioral dimensions of approach and withdrawal.

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10

Reductions in phenomenological, physiological and attentional indices of depression after 2Hz rTMS over the right parietal cortex

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Abstract

Research into emotion and emotional disorders by repetitive transcranial magnetic stimulation (rTMS) has largely been restricted to the prefrontal regions. There is however also evidence for the parietal cortex being implicated in emotional (dys-)functioning. Here we used rTMS to investigate a role of the right parietal cortex in depression. In a placebo-controlled design, 2Hz rTMS at 90% of the individual motor threshold (MT) was applied over the right parietal cortex of eight healthy subjects for 20 minutes continuously. Effects on mood, autonomic activity and motivated attention were investigated. Significant reductions in depressive mood were observed immediately following, and 30 minutes after stimulation. Moreover, these findings were objectified by a concurring pattern of autonomically-mediated changes in the attentional processing of angry facial expressions. These data suggest a role for the right parietal cortex in affective brain circuits regulating phenomenological, physiological and attentional aspects of depressive functioning.

Introduction

Human emotion is regulated by a complex compound of interacting brain circuits (Davidson, 1984). Repetitive transcranial magnetic stimulation (rTMS) may be capable of providing more insights into the workings of these affective circuits by modulating brain activity in controlled designs. Studies in clinically depressed populations show that treatment with high frequency rTMS (≥ 5 Hz) over the *left* prefrontal cortex (PFC) has antidepressant efficacy (Pascual-Leone, Rubio, Pallardo, & Catala, 1996a; George et al., 2000; Szuba et al., 2000; Daskalakis, Christensen, Fitzgerald, & Chen, 2002 for a review). Moreover, the same technique is even capable of improving mood in healthy subjects when applied in a single session (George et al., 1996; Pascual-Leone, Catala, & Pascual-Leone, 1996b). Although null-findings have also been reported (Mosimann, Rihs, Engeler, Fisch, & Schlaepfer, 2000; Jenkins, Shajahan, Lappin, & Ebmeier, 2002). Antidepressant and mood improving effects have been shown when applying low frequency rTMS (< 5Hz) over the *right* PFC (Klein et al., 1999; Schutter, Van Honk, D'Alfonso, Postma, & De Haan, 2001). Originally, it was suggested that the high frequencies produced neural excitation and the low frequencies neural inhibition of the target regions. But, recent research shows that low frequency rTMS at higher intensities produces contralateral excitation (Speer et al., 2000; Nahas et al., 2001; Schutter et al., 2001). Nevertheless, associations between relatively more left prefrontal activity and reduced depression support the valence hypothesis. Approach and withdrawal constitute the dimensions in the valence hypothesis. Imbalance may on the one hand result in anxiety or depression and on the other hand in aggression or psychopathy (Arnett, 1997; Harmon-Jones & Sigelman, 2001).

A methodological drawback in much rTMS-emotion research is the reliance on questionnaires of mood. Although consciously experienced mood constitutes an important output of the emotional system it provides little insight in the other constructs of emotion, physiology and motivational behavior (Buck, 1999). Emotionally generated physiological responses (e.g., heart rate, skin conductance) operate rather independ-

ently of verbal affective reports and provide for the opportunity to track psychological events in real time (Öhman, Hamm, & Kenneth, 2000). Motivational behavior can reliably be measured using motivated attention tasks, such as modified dot probe task or emotional Stroop tasks. These tasks index automatic behavioral tendencies towards or away from emotionally relevant stimuli (Van Honk, Tuiten, De Haan, Van den Hout, & Stam, 2001a). Using an emotional Stroop task, we showed that low-frequency rTMS over the right prefrontal cortex (PFC) induces vigilant attentional responses towards angry facial expressions, whereas left PFC rTMS induces avoidant responses (D'Alfonso, Van Honk, Hermans, Postma, & De Haan, 2000). The vigilant response to the angry face symbolizes the tendency for aggressive approach or social domination (Mazur & Booth, 1998; Van Honk et al., 2001a), while the avoidant response symbolizes submission or withdrawal (Van Honk et al., 1999; Öhman et al., 2000). Since low-frequency rTMS potentiates the contralaterally mediated emotion functions through unilateral inhibition and/or contralateral excitation, the above findings fit the valence hypothesis in terms of approach and withdrawal-related emotion. In further agreement, in the above study, elevations in cardiac sympathetic activity accompanied the vigilant responses after right PFC rTMS, whereas the avoidant responses after left PFC rTMS were accompanied by attenuated physiological responses (Van Honk et al., 2002). The former pattern suggesting preparation for approach-directed action and the latter characterizing conservation withdrawal (Van Honk et al., 1999, 2001a, 2001b; Nesse, 2001).

Research into emotion and emotional disorders by repetitive transcranial magnetic stimulation (rTMS) has largely been restricted to the prefrontal regions. There is however also evidence for the involvement of the parietal cortex in emotional (dys-)functioning (Davidson, 1984; Davidson & Henriques, 2000). Interestingly in this respect we recently showed an inverse relationship between baseline levels of cortisol, an endocrine marker for depression (Holsboer, 2000) and functional connectivity between the left PFC and right parietal cortex (Schutter, Van Honk, Koppeschaar, & Kahn, 2002). For these reasons in this study rTMS was

applied over the right parietal cortex in a placebo-controlled design, using the innovative frequency parameter setting of 2Hz at 90% of the individual motor threshold (MT) for 20 minutes continuously. Dependent measures were self-reported mood, physiology and motivated attention. rTMS was expected to induce reductions in depressive mood and more vigilant responses towards angry facial expressions (D'Alfonso et al., 2000) accompanied by elevations in cardiac activity during the motivated attention task (Van Honk et al., 2002).

Method

Participants

Eight right-handed volunteers (female-male ratio 4:4) aged between 20 and 28 years participated in this single blind, counterbalanced, cross-over, placebo-controlled design. An informed consent was obtained, and subjects with a history of neurological or psychiatric disorder were excluded. All subjects were naïve of TMS, unaware of the aim of the study and were paid for participation. The local ethical committee of the Faculty of Social Sciences approved the study.

Mood, physiological measures and motivated attention

Mood was established by the Profile of Mood States (POMS) using the subscales depression, anger and anxiety (Shacham, 1983). The subscales of the POMS seem to reveal changes in mood associated with changes in physiological functioning (Abplanalp, Donnelly, & Rose, 1979). Since slight but pertinent changes in mood in normal subjects are unlikely to be revealed by the conventional scale (Bond & Lader, 1974), visual analogue scales allowing responses ranging from 0 to 100 were used to enhance sensitivity (Van Honk et al., 1999). As physiological measures, heart rate and skin conductance were assessed. Heart rate was measured using a Finger Pulse Plethysmograph and skin conductance using a Self Balancing Skin Conductance Amplifier (Contact Precision Instruments, London, UK). Signals were sampled at 10Hz using analogue-digital converting devices and software for physiological measurements (Test-

point 2.3). Motivated attention was indexed using a dot probe task. Pairs of faces of the same actor appear 750 ms after presentation of a central fixation cross. One face is neutral and the other angry or happy. They are presented simultaneously to the left and right hemifield with 9 degrees of visual angle between the centers of the pictures. After 500 ms delay, the pictures are replaced by a target probe (the capital character A or O) in the position of one the faces and subjects are instructed to vocally identify this probe as fast as possible. Reaction times of vocal responses were recorded using a National Instruments data acquisition card (PC-TIO-10) connected to a Lafayette voice activated relais in an IBM-compatible PC running Testpoint software. We used 96 trials, depicting 8 female and 8 male actors displaying a neutral and an emotional face. After computer registration of voice response onset the probes would disappear and after 1500-2500 ms (quasi-random variation) a new trial would start. By subtracting the response latencies to probes appearing in the position of an emotional face from latencies to probes appearing in the position of the neutral face, one obtains an attentional bias score indicating vigilance for (bias score > 0) or avoidance of (bias score < 0) the emotional face.

Procedure

Before the experiment, on a separate day, individual MT was quantified using the left-thumb movement visualization method (Pridmore, Fernandes-Filho, Nahas, Liberatos, & George, 1998). Separate days were used for the placebo (coil angled 90%) and stimulation session. Order of sham and real stimulation were randomized and counterbalanced over subjects. In these sessions, subjects first completed the mood scales and physiological activity was measured continuously during the experiment. P4 electrode site, according to the International 10-20 EEG System was marked using an EEG cap and rTMS/placebo using a specially designed iron-core coil (Neopulse, Neotonus Inc., Atlanta) was applied at 90% MT with a frequency of 2Hz during 20 minutes. 5 Minutes after rTMS/placebo a second version of the mood scales was completed, followed by a final version 25 minutes later. Afterwards subjects performed the dot probe task. Each stimulation session was separated by at

least 24 hours. During the actual measurements the experimenter was in an adjacent control room, thereby minimizing the chance of a possible experimenter bias.

Results

The stimulations were well tolerated by all subjects. Analyses used related-sample (placebo vs. rTMS) Wilcoxon rank-order tests, with α set at .05, two-tailed.

Mood

There were no significant effects for the mood-scales anger and anxiety, however, there was a significant reduction in depressive mood just after [$Z = -2.06$: $p < 0.039$] and also 30 minutes after rTMS [$Z = -2.03$: $p < 0.042$]. See Figure 10.1.

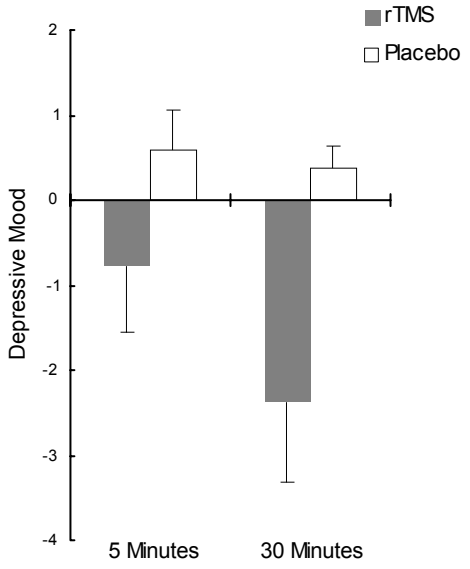

Figure 10.1. Mean (SEM) baseline-corrected changes in depressive mood 5 and 30 minutes after placebo and rTMS.

Motivated attention

There were no effects for happy faces, but rTMS resulted in a significant reduction in the avoidant response to the angry face (shown after placebo) when it appeared in the left-hemifield [$Z = -2.52$: $p < 0.012$]. See Figure 10.2.

Skin conductance and heart rate

No effects for skin conductance were observed. rTMS compared to placebo however showed significant elevations of heart rate during the performance of the dot probe task [$Z = 2.1$: $p < 0.036$], which is shown in Figure 10.2.

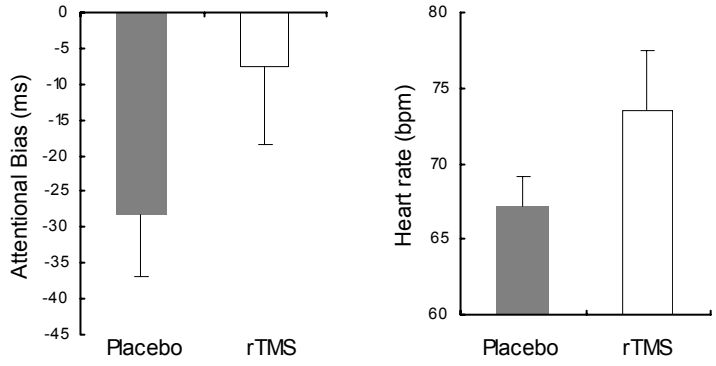

Figure 10.2. Mean (SEM) attentional biases for angry facial expressions in milliseconds (ms) in the left hemifield, and mean (SEM) heart rate in beats per minute (bpm) during performance of the motivated attention task after Placebo and rTMS.

Finally analyses were run to test for order effects of stimulation. The group who received rTMS on the first and sham on the second day was compared with the group who received sham on the first and rTMS on second day. No significant differences were found for the dependent measures (all Z's < 1.3, n.s.).

Discussion

To our knowledge this is the first rTMS study to investigate the role of the right parietal cortex in emotion. Compared to placebo, a single

session of rTMS induced slight, but significant reductions in depressive mood immediately after, and 30 minutes after stimulation. In addition, the avoidant pattern of responding to the angry face in the left hemifield (right hemispheric processing) was significantly reduced after rTMS, a reduction which was accompanied by a task-dependent elevation in heart rate, but not in skin conductance. Crucially, the role of the cardiac system in the modulation of motivated aspects of attention is well-documented (Öhman et al., 2000). As noted in the introduction, a converging elevation, in specifically, sympathetic, cardiac activity was shown after right PFC low-frequency rTMS during an emotional Stroop task, and was again accompanied by less avoidant emotional responses to the angry facial expression (D'Alfonso et al., 2000). Autonomic control over attention and emotion fits the polyvagal theory of Porges (1995), which in fact suggests that difficulties in autonomic control may lead to depressed mood. For all measures, self-report, motivated attention and physiology, the present effects constitute reductions in the outputs of low mood and depression (Van Honk et al., 1999, 2001a, 2001b; Nesse, 2001; Flinn, Baerwald, Decker, & England, 1998). It is argued that during social confrontations (i.e., when confronted with dominant figures displaying anger), the adaptive regulatory function of low mood and depression is to avoid injury and energy loss by securing for inhibited behavioral and physiological responses (Sapolsky, 1990). It seems justifiable to assume that the elevations in mood here induced by rTMS lead to a reduction of the tendency to avoid a socially threatening confrontation.
It should be acknowledged that the small sample size and the lack of a third control condition (e.g., left parietal cortex stimulation) somewhat limits this study. Sham controlled TMS designs have been a longstanding issue in TMS research, however in the present study subjects were not only naïve of TMS, but also unaware of the aim of the study and unfamiliar with the dependent measures. Additionally, as can be read in the Result section, there were no order effects for stimulation days.
When discussing these findings in relation to clinical rTMS research, where the left PFC is the main target region, the theoretical notion of dys-communication between the right parietal and left prefrontal cortex

in depression is notable (Van Honk et al., 2001b). Moreover as noted in the Introduction, higher baseline levels of the (depression-related) stress hormone cortisol, are in fact associated with reduced EEG coherence, i.e. functional connectivity in this left prefrontal-right parietal brain circuit (Schutter et al., 2002), and EEG coherence between these regions seems to be highly sensitive to rTMS (Jing & Takigawa, 2000). It might thus be suggested that one of the effects of 2Hz rTMS over the right parietal cortex is an increase in functional connectivity between the left prefrontal and right parietal cortex (Schutter, D'Alfonso, & Van Honk., 2003).

Finally, the present study adds to the methodology by exploring the large parameter range of rTMS (Sackheim, 2000). The reliability of rTMS effects seems to depend on the number of pulses applied, stabilizing at 1600 pulses (Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000), and clinical studies show that the most pronounced anti-depressant effects also depend on pulse quantity (George & Epstein, unpublished data). To upgrade the quantity of pulses in the low frequency range the 2Hz frequency may be a promising parameter. A single session of 2400 pulses as reached here has not been reported in human research so far. Regarding the possible application of the present stimulation parameters in clinical studies it must mentioned that rTMS induced changes in mood in normal subjects and depressed patients not always point in the same direction. Nevertheless, given the relative safety of low frequency rTMS, the application of this parameter in clinical studies over both the left prefrontal and the right parietal cortex seems warranted. In sum, in the present sham-controlled design, 2Hz rTMS at 90% of the individual motor threshold (MT) was applied over the right parietal cortex of eight healthy subjects for 20 minutes continuously. Effects on mood, autonomic activity and motivated attention were investigated. Although all subjects scored at baseline in the lowest quartile on the scale measuring depressive mood, significant reductions in depressive mood were still observed immediately following, and 30 minutes after stimulation. Moreover, these findings were objectified by a concurring pattern of autonomically-mediated changes in the attentional processing of angry

facial expressions. These data suggest a role for the right parietal cortex in affective brain circuits regulating phenomenological, physiological and attentional aspects of depressive functioning.

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11

Cortisol and reduced interhemispheric coupling between the left prefrontal and the right parietal cortex

Journal of Neuropsychiatry and Clinical Neurosciences 2002, 14, 89-90.

Abstract

The present study investigated the role of the steroid hormone cortisol in cortico-cortical connectivity. Basal cortisol levels in healthy volunteers demonstrated to be inversely related to functional connectivity between the left prefrontal and right parietal cortex. Since cortisol is considered to be a biochemical marker for depression, reduced functional connectivity between the left prefrontal and right parietal cortex might be implicated in the pathophysiology of depression.

Introduction

Neuroimaging and electrophysiological studies have demonstrated the relation between hypoactivation in the left prefrontal cortex and depression (Davidson & Henriques, 2000). There is also strong evidence for the involvement of the right parietal cortex in this unipolar disorder. Davidson and Henriques (2000) proposes an interhemispheric circuit consisting of the left prefrontal and right parietal area to be dysfunctional in depression. Depression is often accompanied by defective feedback of the Hypothalamic-Pituitary-Adrenal axis, resulting in elevated levels of the steroid hormone cortisol (Holsboer, 2000). Interestingly, steroid hormones are involved in interhemispheric transmission (Hausmann & Güntürkün, 2000). A valid method for quantifying interhemispheric transmission or functional connectivity is EEG spectral coherence analysis which measures phase consistency at paired location (Nunez, 2000), while a reliable measure for cortisol reaching the target tissues in the brain can be taken from saliva (Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999). Here we investigated the relationship between salivary cortisol and EEG spectral coherence over the left prefrontal and the right parietal cortex.

Method

Thirty non-clinical, right-handed subjects (15 females) aged 20-28 years participated. Written informed consent was obtained. To control for circadian hormonal rhythms, the sessions were conducted between 1:30pm and 4:30pm. Salivary sampling was followed by a 10-minute EEG baseline recording from the F3, F4, P3, P4 electrodes, which were referenced to the right mastoid. The cortisol level in saliva is a valid measure of the unbound hormone fraction, and only unbound cortisol reaches the brain (Krishbaum & Hellhammer, 1993; Van Honk et al., 2000). Salivary cortisol levels were determined without extraction at the Department of Endocrinology of the University Medical Centre (UMC) using a in-house competitive radio-immunoassay (RIA) employing a polyclonal anticortisol-antibody (K7348). Following chromatographic

verification of its purity, 1,2-^{3}H(N)-Hydrocortisone (NET 185, NEN-Dupont-, Dreiech, Germany) was used as a tracer. Lower limit for detection was 0,5 nmol/l and a reference value for adults 3-28 nmol/l. Baseline cortisol did not ($p < 0.25$) and normally does not differ between the sexes (Kirschbaum et al., 1999). Artifact free EEG signal (Bandpass filter: 1-30 Hz) was extracted through a Hamming window and a fast Fourier transformation was used to derive estimates of spectral power (μV^2). Squared correlation coefficients (coherences) were determined for paired-electrodes in the 4-7 Hz (θ), 8-13 Hz (α), 14-30 Hz (β) frequency domain.

Results

Non-parametric correlations showed significant inverse relations between cortisol and the F3-P4 coherence in the fast α [$r = - 0.43$: $p < 0.01$] and β [$r = - 0.39$: $p < 0.03$] frequency bands.

Discussion

Already in this non-clinical subject group higher cortisol was accompanied by reductions in interhemispheric transmission between the left prefrontal and right parietal cortex. The present data might suggest a sensitive interhemispheric decoupling mechanism by which pathological levels of the steroid hormone cortisol could be implicated in depression.

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12

Counterintuitive antidepressant properties of slow rTMS over the left frontal cortex: A possible mechanism

Journal of Neuropsychiatry and Clinical Neurosciences 2003, 15, 243-244.

Abstract

The present commentary addresses the counterintuitive findings by Rosenberg et al. who demonstrated antidepressant efficacy of both slow and fast rTMS over the left frontal cortex (FC). It is argued that not the modulation of absolute activity in the left FC accounts for the effects per se, but that the left FC-right parietal cortico-cortical cross-talk is equally important.

In the Summer 2002 Issue of the Journal of Neuropsychiatry and Clinical Neurosciences Rosenberg et al. (2002) report antidepressant effects after both slow (1 Hz) and fast (5 Hz) rTMS over the left frontal cortex (FC) in posttraumatic stress disorder (PTSD) patients with comorbid depression. There were no therapeutical differences between the effects of slow and fast rTMS, which is in fact a striking observation. Depressive symptomes are often accompanied by hypoactivity of the left FC, and there is ample evidence that slow rTMS causes neural inhibition, whereas fast rTMS results in neural excitation of the targeted regions. Thus, the widely applied and obvious parameter in studies treating depression is the fast frequency. Moreover, it has been demonstrated by rTMS-neuroimaging studies that fast rTMS leads to normalization of left FC hypometabolism. Only a study by Klein et al. (1999) used slow rTMS but they targeted the *right FC*, assuming depression is accompanied by an imbalance in neural activity between the left and right FC, favouring the right. Dampening the right FC activity by slow rTMS would restore homeostasis.

The antidepressants effects of slow rTMS over the left FC in the Rosenberg et al. (2002) study are when theorizing from the abovenoted findings rather counterintuitive. The interpretation Rosenberg et al.(2002) provide in terms of rTMS effects adjunct to antidepressant medication and different patient populations does not seem to be sufficient to explain their paradoxal finding. A more plausible explanation is that slow rTMS restored the functional connectivity in a cortico-cortical depression circuit (Van Honk & Schutter, 2000), which connects the left FC with right parietal cortex (PC). This functional connectivity between different cortical areas can be measured by means of EEG coherence analysis. Interestingly, a recent endocrinological study published in the Winter 2002 issue of the Journal of Neuropsychiatry and Clinical Neurosciences demonstrated an inverse relationship between the functional connectivity of the left FC and right PC and cortisol, a biochemical marker for depression (Schutter, Van Honk, Koppeschaar, & Kahn, 2002). This finding suggests that the functional connectivity in this cortico-cortical circuit is reduced in depression. It

should be noted that the functional connectivity between different brain areas is not entirely dependent on cortical arousal, indicating that temporal coupling can be modulated without dramatic changes in activity. Crucially, it has been demonstrated that rTMS over the left FC is capable of modulating functional connectivity with the right PC (Jing & Takigawa, 2000). Working from a model comprising the abovenoted depression circuit and the capablility of slow rTMS to influence functional connectivity, a recent placebo controlled study by Van Honk and Schutter (2000) demonstrated reductions in phenomenological, attentional and physiological indices of depression after slow rTMS over the right PC. The latter findings are in line with our cortico-cortical depression circuit hypothesis (Schutter et al., 2002) and concur with the slow rTMS results of Rosenberg et al. (2002).

One of the mechanisms by which rTMS studies have etablished antidepressant effects is the normalization of hypometabolism in the left FC. However, the slow rTMS findings of Rosenberg et al. (2002) more likely involve the restoration of the functional connectivity in a left FC-right PC cortico-cortical depression circuit.

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13

Administration of testosterone increases functional connectivity in a cortico-cortical depression circuit

2003, *submitted.*

Abstract

Increasing evidence suggests that the steroid hormone testosterone enhances libido and decreases depression. Even a single administration of testosterone (0.5 mg sublingually) in healthy young women is sufficient to enhance physiological sexual responsiveness. Such physiological evidence is not yet available for the link between testosterone and depression. However, recent research has revealed that lowered functional connectivity in a specific cortico-cortical pathway may be a sensitive physiological index for depression. This cortical pathway is, comprised of the left prefrontal and right parietal cortex, has been named a cortical depression circuit. In the present study, a single dose of testosterone was administered to healthy young women to investigate the effects on the functional connectivity in this cortical depression circuit. It was hypothesized that administration of testosterone would lead to an increase of functional connectivity. In a double-blind placebo-controlled, crossover design fourteen, healthy females received (sublingually) a single dose of 0.5 mg testosterone or placebo in a randomly assigned fashion. Three hours after drug administration the functional coupling between the left prefrontal and right parietal cortex was established by means of calculating the interhemispheric EEG coherence for the different frequency bands. Compared to placebo, testosterone administration significantly increased the functional connectivity in the delta frequency range between the left prefrontal and right parietal cortex. Results showed that testosterone increases functional connectivity in the delta frequency range in the cortical depression circuit. Reductions in interhemispheric coherence in the delta frequency range have been observed in clinically depressed patients. Thus the present findings may provide for the first insights into the neurobiological mechanisms by which testosterone decreases depression. The fact that only a single dose of testosterone was able to induce the effect in healthy female subjects suggests that the mechanism is highly sensitive. A feasible contributing application of testosterone treatment in the struggle against depression is discussed.

Introduction

Recent studies have demonstrated that the steroid hormone testosterone improves well-being especially in women (Davis & Tran, 2001) and decreases depression (Rabkin, Wagner, & Rabkin, 1999). However, the research focus on well-being has mainly been on sexual desire and, in particular, a decline in sexuality after a drop in androgenic functions has been demonstrated. Relatively, low levels of testosterone have been associated with reductions in coital frequency and diminished sexual desire (Bachmann & Leiblum, 1991; McCoy & Davidson, 1985). Testosterone substitution alone in androgenic deficient women seems, however, not sufficient to completely restore sexual functioning. A discrepancy has been observed in woman suffering from hypothalamic amenorrhea, whereby sexual physiological arousal increased after testosterone treatment, but the subjectively measured excitement remained unchanged (Tuiten et al., 1996). It was suggested that in the future testosterone treatment should be accompanied by appropriate psychotherapeutical interventions. Two recent fundamental studies have provided further insights into the mechanisms by which testosterone enhances sexual functioning. A transient effect on both subjective and physiological sexual arousal with a time course of three to four hours was shown after a single administration of testosterone in healthy young women (Tuiten et al., 2000). Interestingly, however a further study revealed that the effect of testosterone on the subjective component in the latter study was a priming confound of the repeated measurements in search for this time course (Tuiten et al., 2002). This finding again reveals the earlier observed discrepant effects of testosterone administration on subjective and physiological sexual functioning (Tuiten et al., 1996). The above noted fundamental research has not been done with respect to the proposed link between testosterone and depression (Davis & Tran, 2001).

Evidence suggests that the left prefrontal (PFC) and the right parietal cortex in depression are dysfunctional in depression (Davidson, 1984; Flor-Henry, 1979; George et al., 1997). A sensitive electrophysiological marker for depression was, however, missing until recently. Interestingly,

recent endocrinological studies in healthy human volunteers have demonstrated that a biochemical marker for depression, heightened baseline levels of the stress-hormone cortisol (Holsboer, 2000; Schutter, Van Honk, Koppeschaar, & Kahn, 2002) are related to lowered functional connectivity between the left PFC and right parietal cortex. A further study in healthy volunteers showed that cortisol was indeed associated with depressive mood (Van Honk et al., 2003), as often demonstrated in clinically depressed patients (Holsboer, 2000). Together, these findings suggest a sensitive relationship between the functional connectivity (cross talk) in the left prefrontal-right parietal cortico-cortical circuit and depression. In such a way that 'lowered' functional connectivity in the latter brain circuit might predispose to depression. Findings from a brain stimulation technique, repetitive transcranial magnetic stimulation (rTMS) seem to provide further evidence for the existence of such a left prefrontal-right parietal depression circuit. Not that the effects of rTMS depend on stimulation parameters, whereas the fast frequency rTMS ($\geq$ 5Hz) produces neural excitation, the slow frequencies cause neural inhibition of the targeted regions (George, Lisanby, & Sackeim, 1999; Wassermann & Lisanby, 2001). The antidepressants effects of fast (rTMS) over the left PFC are concordantly argued to be due to normalization of hypometabolism in the left PFC (George et al., 1997). This may, however, not be the main mechanism responsible. Importantly, a study of Jing and Takigawa (2001) demonstrated an increase in functional connectivity in the above noted left prefrontal-right parietal cortico-cortical depression circuit after high frequency rTMS over the left PFC. Increases in functional connectivity between different cortical regions have also been demonstrated after slow rTMS (Strens et al., 2002). Crucially, Rosenberg et al. (2002) showed comparable antidepressant efficacy after both slow and fast rTMS over the left PFC. The latter findings are paradoxical in terms of the traditional 'normalization of left PFC hypometabolism' claim, since slow rTMS should in fact further decrease left PFC metabolism (George et al., 1999; Wassermann & Lisanby, 2001). The Rosenberg et al.'s findings can however be interpreted in terms of the strengthening of the

functional connectivity in the left prefrontal-right parietal cortico-cortical depression circuit by both slow and fast rTMS (Schutter, D'Alfonso, & Van Honk, 2003). Finally, working from a heuristic model constituting this depression circuit, and assuming that rTMS would also be capable of strengthening functional connectivity when stimulating the right parietal cortex, a recent placebo controlled study by Van Honk and Schutter (2001) demonstrated reductions in phenomenological, attentional and physiological indices of depression in healthy volunteers after slow rTMS over the right parietal cortex.

As noted, there are indications that testosterone has antidepressant efficacy (Davis & Tran, 2000), but physiological evidence is lacking. In search for such evidence we investigated whether a single administration of testosterone in healthy young women would be capable of strengthening the functional connectivity in the left prefrontal-right parietal cortico-cortical depression circuit.

Method

Participants

Volunteers were recruited among students at Utrecht University, Utrecht, The Netherlands. Fourteen non-smoking, healthy, right-handed women participated in the study (mean ± SD age, 21.6 ± 1,9 years). All women used oral contraceptives and did not have a history of psychiatric or neurological illness. Only women participated, because the time course and the dosage of T necessary to establish physiological and psychological effects after a single administration have yet not been established in men (Tuiten et al., 2000; Van Honk et al., 2001). There were no signs or symptoms of pituitary or endocrine diseases. All volunteers were unaware of the aim of the study. Informed consent was obtained and participants received payment for taking part in the study. The protocol was approved by the Medical Ethics Committee of the University Medical Center in accordance with the Declaration of Helsinki.

Procedure

Participants were tested twice in a double blind, placebo-controlled crossover design. Both testing days were separated by at least twenty-four hours. Prior to experimentation, the procedure was explained in full detail and participants were instructed to refrain from using medication and psychoactive drugs, such as coffee and alcohol on both testing days. Eating was not allowed an hour prior to each session. In the morning, between 8.30 and 10.30 a.m., upon arrival at the Psychological Laboratory of the Utrecht University, volunteers sublingually received 0.5 mg of either testosterone with cyclodextrines as carrier or placebo. Recent experimental studies in our laboratory have established the time course of 0.5 mg sublingual testosterone administration on blood levels and physiological responsivity. These studies showed without exception at least a tenfold increase in the levels of total testosterone in plasma (with no changes in binding globulin) fifteen minutes after intake, with a return to baseline within ninety minutes (Tuiten et al., 2000). Furthermore, it was repeatedly observed that this single dose of testosterone significantly elevated different indices of physiological responsivity approximately three to four hours after intake (Tuiten et al., 2000; Tuiten et al., 2002; Van Honk et al., 2001). Based on these previous findings, the time course effects of testosterone administration on subjective and physiological arousal were taken into account. Three hours after testosterone administration, volunteers returned to the lab where the mood states, i.e. depression, anger and anxiety were assessed. After completion of the mood inventory, EEG recording preparations were made, which took on average about thirty minutes. Participants were seated in a comfortable chair in a dimly lit, quiet room, while the experimenter was in an adjacent control room. To obtain baseline measurements of background EEG, subjects were instructed to relax and to sit as motionless as possible. One-minute intervals of background EEG with eyes-open (O) and eyes-closed (C) for a total of four minutes (Sequence: O-C-O-C) were recorded three and a half hours after testosterone administration.

Dependent Measures

Baseline EEGs were recorded from twelve scalp positions (Fz, Fp1, Fp2, F3, F4, Cz, C3, C4, Pz, P3, P4, Oz) according to the International 10/20 System of EEG electrode positions, using an electro-cap with Ag/AgCl electrodes (Neurosoft, Inc.). The reference electrode was placed on the right mastoid. Electro-oculogram (EOG) was recorded by placing Ag/AgCl electrodes to the supra- and suborbit of the right eye and on the external canthi of each eye, in order to correct for vertical and horizontal eye movements. ECI EEG gel was used as conducting medium for both EEG and EOG electrodes and all impedances were lower than 5,000 Ω. An acquisition amplifier (Ampligraph) was used to filter incoming signals (low pass cut-off frequency was 70 Hz with a time constant of 3s). Amplification was set at 20,000 for both the EEG and EOG leads, and the sample rate was set at 250 Hz. For the actual EEG registration, recording and data processing, NeuroScan Software was used. Raw EEG signals were digitally filtered offline with a 1-30 Hz bandpass filter setting. EEG signal containing eye and/ or muscle movements, or other forms of artifacts, greater than -50 μV and +50 μV were rejected for further analysis. After artifacts were discarded, data were corrected for horizontal and vertical eye movements using linear regression analysis. For the quantitative analysis of interhemispheric coherence, one electrode pair of interest, i.e. the functional connectivity between the left prefrontal and right parietal areas was selected on the basis of our a priori hypothesis, stating that testosterone would increase cross talk between these two cortical regions. The four frequency bands were extracted using a fast Fourier transform algorithm (Hamming window: length 10%). Cross-spectra for the different frequency bands were calculated and normalized by the autospectra to compute coherence, according to the following equation (1):

$$(1) \qquad |R_{xy}(e)|^2 = \frac{|G_{xy}(e)|^2}{G_{xx}(e) * G_{yy}(e)}$$

In equation (1), $G_{xx}(e)$, $G_{yy}(e)$ and $G_{xy}(e)$ are values of the auto- and cross-spectra at a given frequency band *e* respectively. Coherence indexes the linear synchronization between electrode pairs and ranges from absence (0) to perfect (1) association. The fronto-parietal coherence was determined for the delta (1-3 Hz), theta (4-7 Hz), alpha (8-13 Hz) and beta (14-30 Hz) frequency bands.

Self-reports on state depression, anger and anxiety were quantified using a Visual Analogue Scale (VAS) computerized version of the POMS (Profile of Mood States) questionnaire (Shacham, 1983).

Statistical analyses

Separate MANOVAs for repeated measurements with Greenhouse-Geisser corrected p-values were carried out for the delta, theta, alpha, beta frequency bands as within-subject variables and with Order of drug intake as between-subjects factor, respectively. In order to detect possible changes in mood states as a result of drug, separate MANOVAs for repeated measurements with Greenhouse-Geisser corrected p-values were performed with depression, anger and anxiety as within-participants variables and Order of drug intake as between-participants factor. The alpha level of significance (two-tailed) was $p \leq 0.05$ throughout.

Results

Electrophysiological data

Multivariate testing revealed a statistical significant increase in interhemispheric coherence in the delta frequency range after testosterone compared to placebo [$F(1,12) = 7{,}4$: $p < 0.02$]. There was no effect of Order ($p > 0.8$), indicating no carry-over effects of administration. No significant changes after testosterone administration were found for the theta, alpha, beta frequency bands (all p's > 0.5). Figure 13.1 displays the left prefrontal (F3) and right parietal (P4) functional connectivity and functional connectivity across the different frequency bands after 0.5 mg of testosterone and placebo.

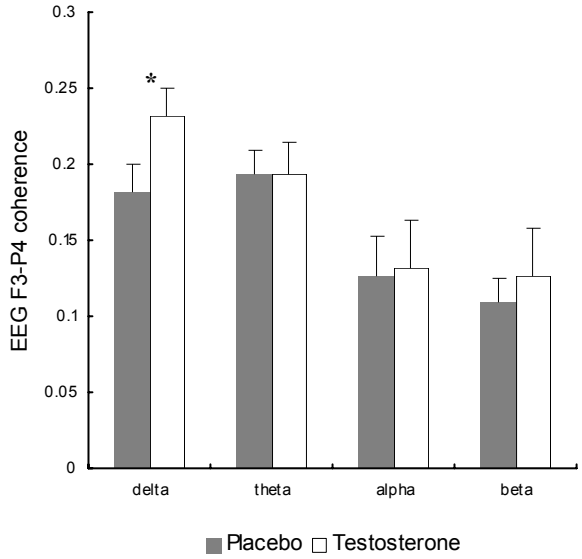

Figure 13.1. Mean fronto-parietal (F3-P4) coherence (and SEM) in the delta, theta, alpha, and beta frequency bands for the testosterone and placebo condition. * P < 0.02.

Mood states

Separate MANOVAs were used to investigate possible effects of 0.5 mg testosterone on self-reported mood states of depression, anger and anxiety. Statistical analyses did not show any significant changes in mood (all p's > 0.5).

Discussion

The present study investigated whether a single administration of testosterone would increase the functional connectivity between the left PFC and right parietal cortex. In line with our hypothesis, testosterone as compared to placebo induced a significant increase in the functional connectivity in this left prefrontal-right parietal cortico-cortical depression circuit (Schutter et al., 2003). Although EEG coherence between different cortical regions is largely established by both cortico-cortical and thalamo-cortical interactions (Nunez et al., 1997), other subcortical brain areas contribute to both inter- and intrahemispheric functional

communication as well (Davey, Victor, & Schiff, 2000). Especially the lower bandwidths such as the delta frequency in the EEG coherence spectrum are associated with limbic contributions to the cortico-cortical coupling (Locatelli, Cursi, Liberati, Franceschi, & Comi, 1998). Interestingly, the hormone testosterone establishes its effects on emotional processing by binding to specific steroid responsive networks in the limbic system (Wood, 1996). Presently, the testosterone-induced changes in these networks may have lead to a cascade of biochemical events resulting in the strengthening of the functional connectivity in the delta frequency band of the left prefrontal-right parietal depression circuit (Cottingham & Phaff, 1986).

In crucial defense of this notion, a study by Roemer, Shagass, Dubin, Jaffe, & Katz (1990) demonstrated lower interhemispheric coherence in the *delta frequency range* in depressive patients compared to healthy controls. The authors suggested subcortical abnormalities to be responsible for the lowered coherence. The absence of effects on self-reported depressive mood in the present study might, at first sight, seem somewhat paradoxical.

However, these findings concur with earlier research whereby single doses of 0.5 mg testosterone administration in healthy human volunteers induced similar discrepancies between physiological and self-reported variables (Tuiten et al., 2002; Van Honk et al., 2001). Moreover, as already noted in the Introduction, the same discrepancies have also been observed in a clinical testosterone treatment study (Tuiten et al., 1996). Apparently, testosterone induces changes in physiological affective processing which cannot easily be captured by self-report (Gray, Jackson, & McKinlay, 1991).

Importantly, it was recently demonstrated that increased amygdala responses to masked fearful faces normalized after antidepressant treatment (Sheline et al., 2001). Strikingly, in a placebo controlled cross-over testosterone administration study, similar to the present study, we observed concurring reductions in affective responses to masked fearful faces (Van Honk, Schutter, & Peper, submitted). This provides further evidence for testosterone's antidepressant properties and points at the

likelihood of the involvement of limbic structures in these effects of testosterone.

Finally, of interest from a clinical perspective, it has been demonstrated that higher pretreatment interhemispheric coherence in the delta frequency range in clinically depressed subjects results in a more positive therapeutical outcome of electroconvulsive therapy (ECT). Hence, the present findings when taking together with earlier reports of testosterone administration (Tuiten et al., 1996; Tuiten et al., 2000, 2002) suggest that testosterone may lay a neurochemical basis for successful therapy. The strengthening of the functional connectivity in the delta frequency range by testosterone treatment in depressed individuals might for instance increase the success of behavioral and psychotherapeutical interventions (Tuiten et al., 1996). At this moment clinical trials are being prepared to test the hypothesis whether testosterone treatment in combination with psychotherapy has enhanced antidepressant efficacy.

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14

High frequency rTMS over the medial cerebellum induces a shift in the prefrontal electroencephalogram gamma spectrum: A pilot study in humans

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Abstract

In the present study the anatomical projections from the medial cerebellum to the prefrontal cortex (PFC) were investigated in healthy human subjects, using high frequency repetitive transcranial magnetic (rTMS) stimulation and electroencephalography (EEG). Medial cerebellar rTMS, compared to placebo induced a significant shift in anterior asymmetry, from left to right dominance in the fast (30-50Hz) EEG spectrum, whereas occipital and lateral cerebellum stimulation did not show such an effect. Moreover elevations in mood and alertness were reported again after medial cerebellar stimulation only. Taken together, these data confirm and further specify the assumed cerebellar modulation of PFC activity and affect.

Introduction

Traditionally, the cerebellum has been implicated in the learning, coordination and control of fine-grained motor movements (Thach, 1998). Reciprocal connections, through thalamic interfacing, between the cerebellum and primary motor cortex support this functional attribution. In addition, it has been shown that the cerebellum projects to other cortical areas of the brain as well, indicating a possible role in cognition and affect. Studies have demonstrated that electrical stimulation of the cerebellar dentate nucleus in monkeys elicits neural responses in the frontal association cortex (Sasaki, Jinnai, Gemba, Hashimoto, & Mizuno, 1979). Furthermore, Middleton and Strick (1994, 2001) found evidence for cerebellar connections to the prefrontal cortex (PFC) using a viral retrograde transneural transport method. Evidence for this connectivity is, however, primarily based on animal studies, thus further extrapolating these findings to a human model is of prime importance. A relative new technique in human research is repetitive transcranial magnetic stimulation (rTMS), which enables investigators to study the functional neuroanatomy of man *in vivo*. rTMS is a noninvasive technique, in which a pulsed magnetic field is passed virtually unattenuated through the skull inducing a secondary, electrical current in nearby nerve tissue. Except for the non-invasiveness of the electromagnetic induction method, rTMS shares the same properties as electrical stimulation at the tissue level, since they both cause ionic currents to flow in the brain (George & Belmaker, 2000). Using rTMS, neural processes can be studied in human subjects relatively easy and safely. Depending on stimulation parameters neurons can transiently be made more or less excitable. Fast frequency rTMS ($\geq$ 5Hz) over a particular target area seems to induce more neural excitability in that region, whereas slow rTMS ($\leq$ 1Hz) suppresses neural excitability after stimulation (Di Lazzaro et al., 2002; Meada, Keenan, Tormos, Topka, & Pascual-Leone, 2000). Indeed, several neuroimaging studies have demonstrated that alterations in neural excitability are accompanied by changes in activity of the stimulated region (Nahas et al., 2001; Speer et al., 2000). A method capable of indexing this ongoing

neural activity by computing power densities in different frequency bands is quantitative electroencephalography (qEEG) (Lopes da Silva, 1999). Especially elevations in power densities in the higher frequency domain (13-50Hz) have been argued to reflect underlying aroused brain activity. Moreover, brain asymmetries through log transformation can be calculated in order to identify relative hemispheric dominance in particular EEG frequency bands. In the present study we investigated the possible modulatory role of the cerebellum on PFC brain asymmetry, using high frequency repetitive transcranial magnetic stimulation and qEEG in healthy human subjects.

Method

Participants

In the present study five male, right-handed healthy volunteers, aged between 26-43 years, participated in this within-subject, three-way controlled, counterbalanced, crossover design. None of the subjects had a history of neurologic and/ or psychiatric disorder and were naive for the aim of the study. Informed consent was obtained from all participants. The study was approved by the local ethics committee, in accordance with the standards set by the declaration of Helsinki.

Transcranial magnetic stimulation

Individual motor thresholds (MT) for both hemispheres were determined using the thumb movement visualization method (Pridmore, Fernandes-Fihlo, Nahas, Liberatos, & George, 1998). The medial cerebellum stimulation area was defined as the position located half a centimeter below the inion (Hashimoto & Ohtsuka, 1995; Théoret & Pascual-Leone, 1997). The control sites consisted of occipital stimulation, that is the Oz lead electrode according to the International 10-20 EEG System, the area two centimeters lateral to the right of the target area and placebo stimulation over the medial cerebellum. Real rTMS was performed using a Neotonus stimulator (maximum output 2300 A peak / 1750 Vac peak) and an iron-core coil with a current magnetic induction field of ap-

proximately 2 Tesla. In the sham condition a specially designed placebo coil was used (Neotonus Inc., Atlanta). By placing a metal plate in the coil housing directly under the iron-core coil, the majority of the magnetic pulse induces an electrical current in the plate in stead of the brain tissue. Consequently, the brain is shielded and not actually stimulated although mimicking the sound click and sensation of real stimulation. The head of the participants was positioned in flexion which allowed the coil to be hold tangentially to the site of stimulation. A special built coil holder was used to keep the coil in place during the actual stimulation. Stimulation parameters were set at 80% of the lowest obtained MT with a frequency of 25Hz (10s. on, 5s. off) for a total duration of twenty minutes, resulting in a total of 20,000 pulses. Subthreshold stimulation studies in healthy human subjects have been widely used without incidence (Wassermann, 1998). The subjects were informed regarding the safety of rTMS and instructed to immediately indicate if they detected twitches in the extremities of the hand during or after stimulation. Furthermore, the stimulation sessions were attended by a physician.

Electrophysiological recordings

EEGs were recorded from the homologous Fp1, Fp2, F3, F4 scalp positions, using an Electro-Cap with Ag/AgCl electrodes (Neurosoft, Inc.). EEG signals were referenced to an electrode placed behind the subject's right ear. For the purpose of artifact scoring, vertical (VEOG) and horizontal (HEOG) eye movements were recorded. Ag/AgCL electrode pairs (bipolar) were placed at the supra- and suborbit of the right eye and at the external canthi of each eye. ECI EEG Gel was used for both EEG and EOG and all electrode impedances were less than 5,000 Ω. An acquisition amplifier (Ampligraph) was used to filter incoming signals. For the EEG recordings NeuroScan software was used. Amplification was set at 20,000 for both the EEG and EOG leads, and the sample rate was set at 250 Hz. After a 4-minute baseline EEG recording, rTMS (Neopulse Magnetic Stimulator; Neotonus Inc., Atlanta) was applied which was followed by a post-stimulation EEG recording of 15 minutes. Portions of each 1-minute EEG signal in the electrodes

containing ocular and muscular, or other sources of artifacts (± 50 μV) were rejected prior to further analysis. After artifact rejection, EEG data were corrected for horizontal and vertical eye movements and filtered (Bandpass: 4-50 Hz) off-line. Next, 1,024-s chunks of averaged artifact free EEG were extracted through a Hamming window (length 10%) in order to reduce spurious estimates of spectral power. For each chunk, a Fast Fourier Transform method was used to derive estimates of spectral power (μV^2) in the 1 Hz frequency bins for each electrode site. Spectral power values were averaged across all epochs within a single baseline. Values were then transformed to power density values ($\mu V^2/Hz$) for the 4-7 Hz (theta), 8-12 Hz (alpha), 13-30 Hz (beta) and 31-50 Hz (gamma) frequency bands respectively. Finally, the prefrontal log-transformed asymmetries for mean power density were calculated for Fp1-Fp2 and F3-F4 and collapsed, constructing a global prefrontal EEG brain asymmetry. rTMS was well tolerated by each of the participants and none reported adverse effects during or after the stimulation sessions.

Results

Non-parametric Friedman tests across the different frequency bands yielded a significant Stimulation difference in the gamma frequency range [$\chi^2 = 7.8$: $p = 0.05$]. Post-hoc Wilcoxon signed rank tests revealed that the EEG brain asymmetry after medial cerebellum stimulation (mean ± SEM, 0.12 ± 0.05) significantly differed from placebo (mean ± SEM, -0.08 ± 0.04) [$Z = -2.02$: $p = 0.04$] and Oz stimulation (mean ± SEM, -0.12 ± 0.04) [$Z = -2.02$: $p = 0.04$]. Because the medial did not differ from the lateral cerebellar stimulation, we cannot rule out the possibility that rTMS over the medial cerebellum resulted in more widespread effects to more lateral parts of the cerebellum and *vice versa*. However, it can be assumed that rTMS has its most profound effects over the stimulation site, since this stimulation significantly differed from placebo and Oz stimulation. Another potential confound might have been electromyographic activity (EMG) contaminating the recorded gamma activity in the frontal regions. In order to control for this confound baseline

EEG was recorded prior to each stimulation, controlling for possible EMG artifacts in the EEG after rTMS. Furthermore, if gamma activity was contaminated during the medial cerebellum stimulation, this would also have been apparent in the other rTMS sessions, given the small distances between the stimulation sites. Finally, we did not use the absolute power values, but calculated a baseline-corrected asymmetry index using log transformation, which reflects the relative brain activity between the prefrontal hemispheres (Davidson, 1988).

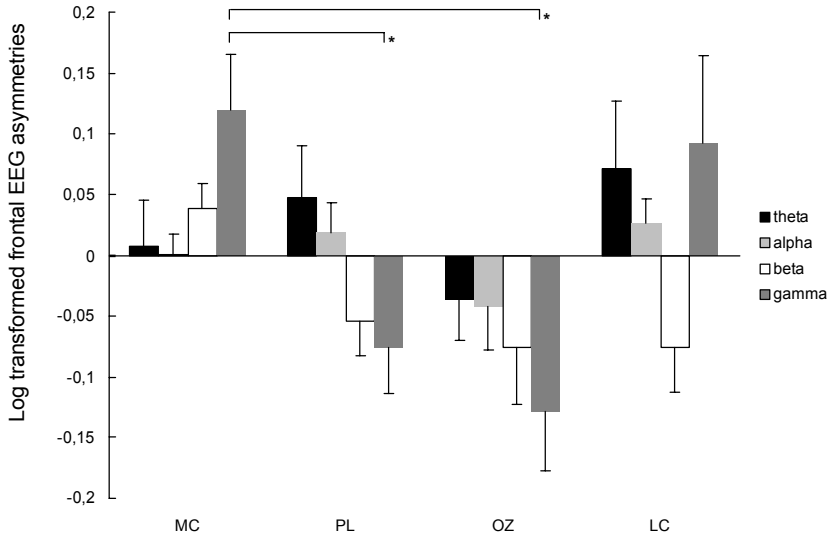

Figure 14.1. Mean (± SEM) baseline corrected prefrontal brain asymmetries for the theta, alpha, beta and gamma frequency bands across the different stimulation conditions (MC: Medial cerebellum, PL: Placebo, LC: Lateral cerebellum, OZ: Oz electrode). Positive value indicates relative right-sided dominance in the EEG gamma (30-50Hz) frequency range.
* P = 0.04.

Since there is no a priori reason to assume that EMG is not equally distributed over the skull, the contribution of EMG activity at the homologues electrode sites will cancel each other out in the calculation of the asymmetry index. Compared to placebo and occipital stimulation, rTMS over the medial cerebellum induced a shift in brain asymmetry to the right prefrontal cortex in the fast gamma frequency band extending for the 15 minutes recording period after stimulation. In other words, prior

to stimulation, relative power in the left hemisphere was higher, while after stimulation, relative power in the right hemisphere prevailed. Interestingly, although possible changes in mood were not objectively quantified, each subject independently and spontaneously reported elevations in alertness and elated mood *only* after medial cerebellum stimulation. Figure 14.1 shows the effect of rTMS for the different frequency bands across the four stimulations on the relative dominant cerebral activity.

Discussion

The present finding provides the first preliminary evidence from rTMS for a modulatory role of the medial cerebellum on the PFC. Although more detailed work is needed, a possible underlying mechanism might involve an increase of the inhibitory output of the GABAergic Purkinje cells via the dentate nucleus to the thalamus as result of the facilitatory properties of fast rTMS. Such increased inhibition arguably results in thalamocortical modulation of high frequency oscillations, and could therefore induce the observed gamma shift to the right PFC. Timofeev and Steriade (1997) demonstrated the cerebellar nuclei are major contributors to the induction of fast rhythms, which depend on the depolarization of thalamic and cortical neurons. Furthermore, Cooper, Riklan, Amin, Waltz, & Cullinan (1976) reported increases in alertness in subjects receiving cerebellar stimulation, which is in accordance with the here observed alleviations in alertness and mood. With respect to the present data, not only are the prefrontal regions of the brain strongly involved in affect modulation, but Müller, Keil, Gruber, & Elbert (1999) also provided evidence for the EEG gamma band being specifically implicated in affective information processing. Thus, the current results might be interpreted as the possibility of elevations in mood after a prefrontal-detected shift in brain activation. In further agreement, Blood and Zatorre (2001) found right orbitofrontal increases in regional cerebral blood flow (rCBF) during pleasant experience. Finally, the cerebellar "pacemaker" study of Heath, Rouchell, Llewellyn, & Walker (1981) historically support the involvement of the cerebellum in affective states

and also converges with the here-observed elevations in mood. More specifically, Heath, Franklin, Walker, & Keating (1982) suggested relations between cerebellar vermal atrophy, loss of its inhibitory control on forebrain regions and emotional dysfunction and assumed a functional relationship between the cerebellum and septum, suggesting the latter structure as an affective system playing a role in pleasure and positive affect. Of course such hypotheses cannot be evaluated with extracranial EEG. Nevertheless, the current results suggest that the medial part of the cerebellum is involved in emotional processes, which may be affected at least in part, through its regulation of the PFC brain asymmetry in the fast EEG band.

In sum, an anatomical pathway between the cerebellum and frontal regions of the brain has been established in primates. The present findings provide the first evidence for a similar cerebello-prefrontal link in humans by means of non-invasively mediating brain activity. Furthermore, the role of the medial regions of the cerebellum in affect and PFC modulation, suggests a possible therapeutic efficacy for cerebellar rTMS in mood disorders.

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15

Targeting alternative brain regions by repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression

2003, *submitted.*

Abstract

It is argued that clinical depression goes accompanied by reductions in cortical excitability of the left prefrontal cortex (PFC). In agreement, a method capable of enhancing cortical excitability, repetitive transcranial magnetic stimulation (rTMS), when applied over the left PFC has shown to exhibit antidepressant efficacy, although the overall therapeutic effects are inconclusive. The cerebral pathophysiology of depression is however not limited to dysfunctions in the PFC, targeting alternative brain regions by rTMS may provide for new therapeutic windows in the treatment of depression. Presently, the role of rTMS over the PFC in the treatment of depression as well as recent research in the field of affective neuroscience investigating the antidepressant effects of rTMS over other brain regions are discussed and framed in an heuristic model. Evidence from EEG and lesion studies indicates the involvement of the parietal cortex and cerebellum in depression. Moreover, rTMS over both the parietal cortex and the cerebellum exhibits antidepressant properties, at least in healthy volunteers. Together these findings support an rTMS-oriented innovative theoretical model on the neurobiology of depression. To further establish the therapeutic efficacy of rTMS and the neurobiology underlying depression, this theoretical model has to be further investigated. Clinical rTMS depression research targeting the parietal cortex and cerebellum is warranted.

Introduction

Epidemiological studies report that clinical depression has an annual prevalence varying from 1-6% in community samples world wide (Weissman et al., 2000). Estimates of the previous-year prevalence in the general population have shown a sharp increase in morbidity (2.1-7.6%), making depression one of the most frequent mental disorders in the Western countries (American Psychiatric Association, 2000). Most treatment protocols involve the administration of pharmacological agents, ranging from tricyclic antidepressants (TCA) to selective serotonin reuptake inhibitors (SSRIs) with or without psychotherapeutical support. Electroconvulsive shocktherapy (ECT), on the other hand, is usually reserved only for those patients who are refractory to any kind of treatment. Although its antidepressant efficacy is quite high, that is an 64-84% remission rate in patients diagnosed with non-psychotic depression treated with bi-temporal ECT, the application is invasive and goes accompanied by annoying but transient physical and cognitive side-effects.

With the advent of repetitive transcranial magnetic stimulation (rTMS) in 1985, a non-invasive technique based on focal electromagnetic induction was introduced. Hoflich, Kasper, Hufnagel, Ruhrmann, & Moller (1993) were the first who reported beneficial effects after applying rTMS over the left prefrontal cortex (PFC) in two refractory depressed patients. Presently, the most widely used rTMS treatment protocol involves the modulation of neural excitability of the left PFC. Although, recent reviews (e.g., Burt, Lisanby, & Sackeim, 2002; Fitzgerald, Brown, & Daskalakis, 2002; Wassermann & Lisanby, 2001) indicate that PFC rTMS does indeed possess antidepressant efficacy, the available data and results remain rather heterogeneous and somewhat inconclusive.

Interestingly, there is also evidence for a role of the parietal cortex and the cerebellum in the complex neurocircuitry underlying emotion and mood regulation, which is dysfunctional in depression. (Davidson, 1984; Heller, Nitschke, Etienne, & Miller, 1997; Schmahmann, 1998). The aim of the current article is to discuss rTMS studies targeting the PFC in the

treatment of depression together with recent research in the field of affective neuroscience investigating the antidepressant efficacy of rTMS over the right parietal cortex and the medial cerebellum. Moreover, findings are discussed within in an rTMS-oriented heuristic model for emotional processing in depression.

Transcranial magnetic stimulation

The underlying working principles of TMS are based on two physical laws, originally formulated by Ampère and Faraday. The firs law refers the generation of a magnetic field, using an electrical current and the second law describes the generation of an electrical current through an alternating magnetic field (Fitzgerald, Brown, & Daskalakis, 2002). Basically, TMS involves applying a brief magnetic pulse or train of pulses, the latter called repetitive TMS (rTMS) to the scalp using a coil of wire (Hallett, 2000). When the magnetic field of the magnetic pulse alternates rapidly enough, a secondary electrical current is induced which alters the local electric field near conductive nerve tissue. This secondary current, however, needs to create a strong transmembrane potential for neurons to depolarize and generate an action potential (Bohning, 2000). The effects of rTMS depend on the stimulation parameters, which include frequency and intensity. It is argued that slow rTMS ($\leq$ 2 Hz) results in reductions in neural excitability (Chen et al., 1997), as opposed to fast rTMS ($\geq$ 5 Hz) which enhances neural excitability (Pascual-Leone, Valls-Sole, Wassermann, & Hallett, 1994). Speer et al. (2000) demonstrated these opposite effects of slow and fast rTMS over the dorsolateral PFC by measuring decreases and increases in regional cerebral blood flow (rCBF) respectively. The second parameter, stimulation intensity is usually taken as a percentage relative to the motor threshold (MT). By applying TMS over the motor cortex, muscle contractions, usually the abductor pollicus brevis (APB) can be evoked. The MT is the lowest stimulation intensity needed to induce APB twitches 5 out of 10 consecutive trials (Wassermann, 1998). Stimulation intensities exceeding the MT are referred to as suprathreshold rTMS, whereas the term sub-

threshold rTMS is designated to stimulation intensities below MT. The average maximum field strength of TMS is approximately 1.5-2.5 Tesla (T), but this strength decays exponentially with distance. As a result only superficial brain tissue will be affected directly. It has also been argued that the effects of subthreshold rTMS are more locally, whereas suprathreshold rTMS result in more widespread and distant transsynaptic effects (Nahas et al., 2001). TMS is capable of modulating networks which are functionally connected. This was demonstrated by neuroimaging studies of Fox et al. (1997) and Paus et al. (1997), which show distant rTMS effects in such neural networks. rTMS cannot only be used to investigate the pathophysiology underlying mood disorders, but also to 'normalize' disrupted activity in the cerebral cortex.

Prefrontal rTMS and depression

rTMS research on depression started on the premise of a dysfunctional PFC (Drevets et al., 1997; Pizzagalli et al., 2002; Sackeim et al., 1982). Two related concepts have been postulated on the relation between prefrontal activity and depression. Depression is by most researchers and clinicians argued to involve a left hypoactive PFC, but some suggest a right versus left PFC-sided dominance in activity is the malefactor. A recent meta-analysis by Kozel and George (2002) tested the antidepressant efficacy of fast rTMS over the left PFC. They reported statistically significant effect sizes, as well as measurable clinical improvement. The antidepressant efficacy of slow rTMS over the right PFC has also been investigated. Klein et al. (1999) demonstrated that slow rTMS over the right PFC was more effective than sham stimulation, providing evidence for idea of an distorted homeostasis between right and left PFC activity in depression. Recently, Burt et al. (2002) conducted a meta-analysis for both left and right PFC rTMS across three categories of studies in clinically depressed patients. The categories included (i) open and uncontrolled trials, (ii) controlled designs, and (iii) comparisons with electroconvulsive shock therapy (ECT). Reductions in the Hamilton Rating Scale for Depression (HRSD) were taken as the dependent variables of

interest. Both open and controlled trials showed initially an antidepressant response, but the overall clinical significance was small for both left and right PFC rTMS.

The comparison of rTMS with ECT studies indicated that the duration of stimulation might be an important factor for achieving such clinical significance. In another meta-analysis McNamara, Ray, Arthurs, & Boniface (2001) also reported beneficial effects of rTMS over the PFC, but the overall clinical significance of rTMS treatment in depression is according to the authors rather unconvincing. rTMS research on depression is however still in its infancy and the extreme large stimulation parameter range is just beginning to be explored. Burt et al. (2002), for instance, suggested that the extension of the rTMS treatment sessions beyond the traditional 1-2 weeks might result in more pronounced antidepressants effects. Several other reasons could underlie the ambivalence of findings, it is likely that an effective treatment protocol has not yet been developed. Parameter settings such as stimulation frequency might also play an important role in establishing more clinically relevant outcomes. For instance, fast rTMS uses frequencies between 10 and 20 Hz, whereas slow rTMS uses frequencies of around 1 Hz. Based on the assumption that the total amount of pulses applied is a function of clinical efficacy, increasing the frequency up to 2 Hz for slow and 25 Hz for fast rTMS could result in more pronounced effects. Thus, intensification of stimulation parameters could be a first step (Gershon, Dannon, & Grunhaus, 2003), but the attempt to target other brain regions involved in the pathophysiology of depression by rTMS to explore the therapeutic efficacy might prove to be even more important.

Introducing alternative brain regions in clinical rTMS studies

As noted above, the antidepressant efficacy of PFC rTMS is still inconclusive and alternative treatment tools, such as nervus vagus (VNS) and deep brain stimulation (DBS) are currently being explored in preclinical and clinical trials (George, Nahas, Lomarev, Bohning, & Kellner, 1996). However, apart from the largely unexplored parameter range, rTMS

studies have not yet investigated other brain regions involved in the pathophysiology of depression. Presently we would like to propose alternative brain areas as targets for rTMS treatment in depression. Recent research suggests antidepressant efficacy of rTMS over the medial cerebellum (Schutter, Van Honk, D'Alfonso, Peper, & Panksepp, 2003) and the right parietal cortex (Van Honk, Schutter, Putman, De Haan, & D'Alfonso, 2003). The theoretical foundation and the implementation of a neurobiological model of depression comprising the medial cerebellum and right parietal cortex will be discussed below.

The parietal cortex: Evidence for a left prefrontal-right parietal depression circuit

There is evidence from lesion and neuroimaging studies for the involvement of the parietal cortex in depression (Davidson, 1984; Flor-Henry, 1974, 1979; Uytdenhoef et al., 1983). In particular a hypoactive right parietal cortex has been associated with depression. However, depending on whether depression is co-morbid with anxiety, right parietal hyperactivity has also been observed (Heller & Nitschke, 1998). This can be explained by the fact, that the right parietal cortex is involved in arousal (Heller et al., 1997), and hypoarousal is linked to depression, whereas hyperarousal is associated with anxiety. Problematically, a highly complex picture emerges when depression is co-morbid with anxiety, which is often the case (Kessler et al., 1996; Zimmerman, Chelminski, & McDermut, 2002).

A well known biochemical markers for depression is cortisol. Presumably due to an hyperactive hypothalamic-pituitary-adrenal (HPA) axis, depressive as well anxious subjects often demonstrate higher than normal basal levels of this stress-related hormone (Gold, Drevets, & Charney, 2002; Shulkin, Gold, & McEwen, 1998). Moreover, Belanoff, Flores, Kalezhan, & Schatzberg (2001) and Belanoff et al. (2002) recently demonstrated that the cortisol-receptor antagonist mifepristone was effective in the treatment of psychotic depression.

Furthermore, Schutter, Van Honk, Koppeschaar, & Kahn (2002) found that higher basal levels of cortisol are associated with reductions in the

functional connectivity between the left prefrontal and *right parietal cortex*. This functional connectivity or cross-talk between different cortical brain regions can be measured using EEG coherence analysis (Nunez et al., 1997), and may provide for valuable insights into the neurobiological mechanisms of depression. Cerebral atrophy, for instance, which has been reported in depression (Leuchter et al., 1997) goes accompanied by a breakdown in cortico-cortical cross-talk (Cook et al., 2000).

Recently, an rTMS experiment was conducted to investigate the involvement of the right parietal cortex in depression. In healthy human subjects, 2 Hz rTMS over the right parietal cortex as compared to placebo for 20 minutes continuously resulted in statistically significant decreases in phenomenological, attentional and psychophysiological indices of depressive mood (Van Honk et al., 2003). The fact that these reductions in several indices of depressive mood were already found in a non-clinical group after a single session of rTMS is strongly indicative for antidepressant efficacy, although it has been argued that rTMS induced effects on mood may differ between healthy and clinical depressed subjects. Crucially however, the above findings of Van Honk et al. (2003) concur with a study of Schutter et al. (2002) which showed that high levels of cortisol are related to reductions in cortico-cortical cross-talk between the left prefrontal and right parietal cortex. Moreover, it seems that the antidepressant effects of the steroid hormone testosterone are also established by increases in the functional connectivity in this prefrontal-right parietal depression circuit (Schutter et al., submitted). Together with the observation by Jing and Takigawa (2000) that cortico-cortical cross-talk between the left prefrontal and right parietal brain regions can be enhanced by rTMS, it can be argued that TMS might serve as a therapeutical probe.

In summary, recent research from multiple disciplines suggests that the information transfer between the left prefrontal and right parietal cortex plays an important role in depression. Moreover, the antidepressant effects of rTMS studies over the left PFC and recently the right parietal cortex may well be established by the enhancement of information

transfer between these cortical brain areas (Mayberg et al., 1999; Schutter, Van Honk, & D'Alfonso, 2003).

The cerebellum

For decades the cerebellum has been thought to be predominantly involved in motor performance and cognitive operations. Recently however a growing body of evidence indicates that the cerebellum is also involved in emotion. The first evidence for cerebellar involvement in emotion came from Robert G. Heath already during the early fifties. Although his initial work predominantly comprised of the electrical stimulation of the septum he commenced stimulating the cerebellum, which might provide for a better entry to the emotional circuitry of the brain. Several cerebellar pacemaker studies by Heath (1977) and Heath, Rouchell, & Goethe (1981) did indeed demonstrate positive effects on mood and personality in mentally disturbed patients after electrically stimulating the cerebellum. Moreover, Schmahmann and Sherman (1998) provided clinical support for the role of the cerebellum and particularly the vermis in the regulation of emotion and mood. Given its modulatory role on emotion, the midline cerebellar vermis together with the fastigual nucleus and the flocculonodular lobe have been designated as the limbic cerebellum (Schmahmann, 2000). Furthermore, additional evidence for the involvement of the cerebellum in mood disorders, such as depression was provided by structural MRI studies. Unipolar depression is not only associated with volumetric reductions of the frontal lobes, but also of the cerebellum (Soares & Mann, 1997). Leroi et al. (2002) recently found further evidence for this cerebellar depression relationship. In a study using patients with degenerative cerebellar diseases comprehensive psychiatric evaluations revealed that depressive disorders were associated with cerebellar degeneration. Starkstein, Robinson, Berthier, & Price (1988) even so found evidence for a relationship between cerebrovascular lesions in the posterior brain structures including cerebellum and depression. Finally, Beyer and Krishnan (2002) recently concluded after reviewing the literature that depression is associated with abnormalities

in the frontal lobes, the basal ganglia and the cerebellum. Given the structural deviations of the cerebellum, functional abnormalities are likely to be present also. However, reports of functional cerebellar deviances are lacking, most likely due to the practice of using the cerebellum as a reference for cerebral perfusion and activation patterns (Schmahmann, 2000). Interestingly, however, studies by Schmahmann and Pandya (1997), and Middleton and Strick (2001) demonstrated that the cerebellum and the prefrontal cortex are actually anatomically linked in a bi-directional fashion. The first loop consists of the thalamus which receives efferent input from the cerebellum and projects to the prefrontal cortex. The circuit is closed via prefrontal projections back to the cerebellum via the pontine nucleus of the brain stem (Schmahmann & Pandya, 1997; Middleton & Strick, 2001). Recently, Schutter et al. (2003) investigated the existence of the assumed projection from the medial cerebellum to the prefrontal cortex in healthy human subjects using high frequency rTMS and electroencephalography. rTMS targeting the medial part of the cerebellum indeed modulated ongoing electrical activity in the prefrontal cortex. Interestingly, in the latter study elevations in mood and alertness were reported spontaneously after medial cerebellar stimulation exclusively. Notably, animal studies already provided support for the cerebellar modulation via the mescenphale reticular formation on levels of EEG patterns and alertness (Schmahmann, Anderson, Newton, & Ellis, 2001). These findings of Schutter et al. (2003) do not only provide for the first evidence for a cerebello-prefrontal link in humans, but the observed increases in mood are also a further indication for a role of the cerebellum in affect regulation. Since the cerebellum has efferent pathways to the substantia nigra, and depression has been linked to deficiencies in the biogenic monoamines, cerebellar rTMS in the Schutter et al. (2003) study might have stimulated dopamine release, which resulted in the observed changes in PFC activity and the elevations in alertness and mood. In defense, Keck et al. (2002) applied 20Hz rTMS in rats over the left frontal cortex and observed increases in the release of dopamine in both the mesolimbic and mesostriatal system. These effects were explained in terms of the innervations of the descending glutamatergic

pathways from the frontal cortex to the striatal regions. Importantly, since there is evidence for dopaminergic effects of cerebellar stimulation (Albert, Dempsey, & Sorenson, 1985), it is a defensible notion that the elevations in alertness and mood after cerebellar rTMS in the Schutter et al. (2003) study are explainable in terms of dopaminergic stimulation. In sum, the cerebellum is involved in depression and given its role as pacemaker in the brain (Heath, 1977), cerebellar rTMS should be a highly effective method in the treatment of depression.

An rTMS-oriented heuristical model for the treatment of depression

Until now, the PFC has been the main target in the investigation of the therapeutical application of rTMS in depression. Antidepressant effects have been explained in terms of the deficient innervations of the descending glutamatergic pathways from the frontal cortex to the striatal regions. Enhanced turnover over dopamine in particular the subcortical structures has been argued to contribute largely to the beneficial effects. Although PFC rTMS has demonstrated antidepressant properties, its overall clinical efficacy is not yet clear. This might be due to the lack of insight regarding the precise physiological mechanisms by which rTMS establishes its effects as well as the difficult type of patient population receiving stimulation, since these subjects normally have failed all conventional treatments. Furthermore, the stimulation parameters could also play an important role in the inconsistencies found and the lack of therapeutical efficacy (Sackheim, 2002). Given the high inter-individual variability in both functional as well as structural anatomy, the use of faster frequency rates and longer stimulation times should induce more stable and stronger effects (Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000). Problematically, the issue of safety however puts a constraint on the stimulation parameter settings which can be used in humans (Wassermann & Lisanby, 2001). However, triggering seizures or inducing kindling through magnetic stimulation is not very easy to accomplish, at least in healthy subjects (Grunhaus, Schreiber, Dolberg, Polak, & Dannon, 2003). Further exploring the possibilities of the safe

utilization of rTMS at more intense stimulation parameters, such as faster frequency rates and longer duration, might be worthwhile (Grunhaus et al., 2003).

As noted, alterations in dopamine levels seem to be involved in the pathogenesis of depression (Heimer, Harlan, Alheid, Garcia, & De Olmos, 1997) there is in particular a growing body of evidence for the association between depression and lowered dopaminergic activity (Nestler et al., 2002). Crucially in the present respect, animal research indicates that the antidepressant effects of left PFC rTMS are likely caused by enhanced dopaminergic activity (Keck et al., 2002). Further evidence for enhanced dopaminergic activity after rTMS was recently provided by Zangen and Hyodo (2002). Interestingly however, these authors showed that stimulation over the caudal cortex caused a greater increase in dopamine levels than stimulation over the frontal cortex, which led them to suggest that the caudal parts of the cortex could have a greater potential for establishing antidepressant efficacy. This evidence from animal research suggests that the PFC might not be the ideal target location for rTMS in depression. There is evidence for the involvement of interconnected structures in depression, including the parietal cortex (Flor-Henry, 1974, 1979), the cerebellum and various subcortical nuclei (Davidson, Pizzagalli, Nitschke, & Putnam, 2002; Heath et al., 1981). Unfortunately, direct subcortical stimulation is not yet an issue for rTMS research. Based on findings from direct stimulation studies in human healthy volunteers (Schutter et al., 2003; Van Honk et al., 2003) patients (Heath et al., 1981) and animals (Keck et al., 2002; Davidson, Pizzagalli, Nitschke, & Putnam, 2002) it is however a defensible notion that the clinical application of rTMS over the parietal cortex and cerebellum is an exciting venture. Currently, clinical slow and fast rTMS treatment studies in depressed patients targeting the right parietal cortex and cerebellum are being prepared to further investigate therapeutical efficacy and the neural mechanisms underlying the pathophysiology of depression.

In the final section of this paper we would like to postulate an hypothetical model for rTMS research in the domain of depression, which builds on the specific involvement of the PFC, right parietal cortex and cerebel-

lum. The above presented findings suggest that these structures and their reciprocal connectivity are part of a neurocircuitry which is dysfunctional in depression. Figure 15.1 depicts this heuristic working model for rTMS applications in the treatment of depression, which includes besides the PFC, the right parietal cortex and the cerebellum. It should be noted that the model is limited because it focuses primarily on regions directly reachable by rTMS and it aims specifically at the involvement of the neurotransmitter dopamine in depression.

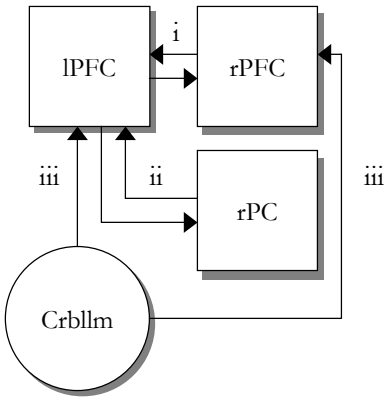

Figure 15.1. An rTMS oriented heuristic depression model comprised of the left (lPFC) and right prefrontal cortex (rPFC), right parietal cortex (rPC) and the cerebellum (Crbllm).

The connections outlined in Figure 15.1 are based on neuroimaging and rTMS electrophysiological studies. The connection between the left and right PFC (i) depicts the transcallosal inhibitory mechanism, whereas (ii) represents the functional connectivity between the left PFC and right parietal cortex. Finally (iii) shows the cerebellar projections to the PFC, directly via the thalamus and indirectly through dopaminergic activation. Also note, that the connections represent anatomical interdependencies based on the various neuroscientific methodologies and do not reflect inhibitory or excitatory links per se.

This rTMS-oriented working model enables us to distill several hypotheses regarding potential efficient antidepressant stimulation parameters. Moreover, the model might actually predict antidepressant efficacy for different subtypes of depression when applying rTMS with specific

stimulation parameters over selected brain regions. An hyperactive right parietal cortex has for instance been implicated in comorbid depression and anxiety (Heller & Nitschke, 1998). On the premise that 2 Hz rTMS over the right parietal cortex is capable of dampening cortical arousal and enhancing cortico-cortical functional connectivity with the left PFC, slow frequency rTMS might be especially effective in the treatment of this subtype of depression. Furthermore, elevations in mood and alertness after fast cerebellar rTMS (Schutter et al., 2003) are arguably due to increased dopaminergic activity, hence apathetically depressed patients may benefit from this kind of high frequency stimulation. On the other hand manic-depression (MD) could be treated by both slow and fast frequency rTMS depending on state of illness. Using carefully selected stimulation parameter settings, dopamine could in MD be partly enhanced or blocked in an attempt to set the brain proper and thus achieve euthymic stabilization. Although the above hypotheses are speculative and need further research, the current model aims at the development of a sophisticated theoretical foundation in clinical rTMS research and might break new boundaries in the treatment of depression by rTMS.

After a decade of research rTMS over the PFC has proven to be superior to sham stimulation in reducing depressive psychopathology, but the clinical efficacy remains inconclusive as of yet (Schlaepfer, Kosel, & Nemeroff, 2003). In the present overview the theorem was postulated that the investigation of the right parietal cortex and cerebellum by rTMS together with the intensification of stimulation parameters are the next steps and might provide for additional insights regarding the role of rTMS in the fundamental neurophysiological knowledge and its therapeutical applications in the treatment of depression.

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16 Discussion and prospects

The thesis started with a prologue (Chapter I) which states that neurophysiological methods for investigating the neural basis of function can provide substantive insight into the modern interdisciplinary and (anti)-reductionist neurophilosophical debates. This in particular holds for the relationships between brain functions and mental abilities. The research reported in the present thesis was specifically concerned with investigating the functional neuroanatomical substrates of affective processing in humans. The involvement of the left and right PFC and their functional connections with the parietal cortex, cerebellum and limbic system were considered to play a pivotal role in the "approach-reward-anger" (Engage) and "withdrawal-punishment-anxiety" (Retreat) systems of affective processing. In this closing Chapter, the main findings of the previous Chapters will be summarized and an extension of the heuristic motivational and affective balance model will be presented. Finally, some prospects with respect to forthcoming fundamental and clinical rTMS studies will be addressed.

The prefrontal cortex in affective processing

In Chapter 2, the involvement of the right PFC in anxious affect and the electrophysiological after-effects of slow 1 Hz rTMS were investigated in healthy volunteers. 1 Hz rTMS over the right PFC did not only result in decreased anxious mood, but also in a contra-lateral excitation of electrophysiological activity in the theta (4-7 Hz) frequency band of the EEG spectrum. This effect was explained in terms of transiently reduced transcallosal inhibition, the dominant anterior activity pattern shifted from the right to the left PFC, which resulted in attenuated anxiety. Evidence for an anterior asymmetry in negative affect was reported by D'Alfonso, Van Honk, Hermans, Postma, & De Haan (2000) and Van Honk, Hermans, D'Alfonso, Schutter, Van Doornen, & De Haan (2002). These studies demonstrated that slow rTMS over the right PFC in healthy volunteers induced an attentional bias towards the angry facial expression. Furthermore, this left PFC lateralized induced rTMS effect was accompanied by elevations in cardiac activity, which provided addi-

tional psychophysiological evidence for right PFC rTMS inducing a contralaterally driven approach-related behavioral state.

According to the motivational balance theory of affective processing, activation of the Engage system will result in deactivation of the Retreat system. Thus hypothetically, slow rTMS over the right PFC would result in an opposite attentional effect when using fearful instead of the angry facial expression (D'Alfonso et al., 2000).

In Chapter 3 this hypothesis was tested by applying 1 Hz rTMS for 20 minutes continuously over the right PFC of healthy human volunteers in a randomly assigned, sham-controlled, cross-over design. Vigilant attention for both the masked and unmasked fearful facial expression was observed after sham stimulation. After rTMS these vigilant responses to the fearful facial expression were significantly reduced, but only in the unmasked condition. These data provided further support for the anterior lateralisation of the approach-related emotion anger and withdrawal-related emotion anxiety in the PFC. The absence of an rTMS induced modulation of the attentional bias in the masked condition suggests that changes in affective processing after a single session of rTMS predominantly involve cortical affective pathways.

To investigate the role of the PFC in autonomic activity in Engage- and Retreat-related affective processing, the study discussed in Chapter 4 dealt with slow rTMS targeting the left orbital prefrontal cortex (OFC). Healthy volunteers received rTMS either at the left frontopolar area or at the left motor cortex, corresponding to FP1 and C3 electrode positions according to the International 10-20 EEG System, for 20 minutes continuously at 1 Hz (80% MT). After stimulation, electrodermal activity and heart rate were monitored in resting state as psychophysiological indices of autonomic activity. When neural excitability was decreased in the OFC, electrodermal activity decreased, but heart rate remained unchanged. Note that the OFC is implicated in motivational processes derived from reward-punishment contingencies (Rolls, 2001), and electrodermal activity is functionally associated with sensitivity for punishment (Fowles, 1980). In line with the Engage system of affective processing, Fowles (2000) more recently argued that low anxiety mediates an insensitivity for punishment, which is physiologically

insensitivity for punishment, which is physiologically reflected by reduced electrodermal activity. Interestingly, this punishment insensitivity is a characteristic of antisocial personality disorder (APD). Recently Raine, Todd, Bihrle, Lacasse, & Colletti (2000) investigated subtle PFC deficits in APD by assessing gray and white matter volumes. A striking similarity between our rTMS study and the findings of Raine et al. (2000) was observed. Similar to the rTMS study, Raine et al. (2000) found attenuated electrodermal activity, but no changes in heart rate. However, according to the left PFC implementation of the Engage system, local inhibition of neural activity by rTMS would have predicted increased electrodermal activity instead of the currently observed attenuation. However, Blair, Morris, Frith, Perrett, & Dolan (1999) did find evidence for the involvement of the right OFC in the processing of the Engage-related angry facial expression. Although the idea has been put forward that at the level of the OFC the anterior asymmetry is reversed (e.g., Papousek & Schulter, 2001), further research has to determine whether the dorsolateral oriented lateralisation model applies to the OFC and ventromedial areas of the PFC as well.

The Engage and Retreat systems of affective processing were further investigated using the Iowa gambling task in Chapter 5. Volunteers from a large subject pool (n = 525) were selected on high punishment-low reward sensitivity (group 1) and low punishment-high reward sensitivity (group 2). As hypothesized, group 1 (n=16) demonstrated intact punishment learning by showing advantageous gambling, whereas punishment learning was deteriorated in group 2 (n=16) resulting in disadvantageous gambling. Notably, APD which is characterized by a weak Retreat system and reduced electrodermal activity also goes accompanied by such disadvantageous gambling (Mitchell, Colledge**,** Leonard, & Blair, 2002). Neurophysiologically, the results from both our study and the Mitchell et al.'s study can be explained in terms of subtle differences or dysfunctions in PFC processing capability of somatic markers arising from the lower brain regions. Normally, the limbic system signals the PFC whenever a negative monetary outcome is anticipated prior to choosing a card from one of the four decks. These signals, termed so-

matic markers (Damasio, 1994), are necessary for guiding decision making effectively. In terms of adaptive choices, the Engage system promotes reward driven choices, whereas the Retreat system is responsible for a more cautious strategy.

In search for the cortical lateralisation theory of the Engage- and Retreat systems the left and right PFC respectively, Chapter 6 discusses an EEG-gambling study. Baseline alpha (8-12 Hz) activity was recorded over the left and right PFC in eighteen healthy volunteers before the Iowa gambling task was performed. Traditionally alpha activity is interpreted as cortical inactivity (so-called 'idling'), hence a relationship between risky, disadvantageous decision making and relatively reduced left-sided alpha activity was expected. However, contrary to what was expected, relatively more right frontal brain activity was significantly associated with these risky, disadvantageous choices. These results were explained in terms of recent theoretical accounts which state that the functional interpretation of baseline frontal alpha activity depends on the internal mental operations involved and does not necessarily imply inactivity. Positive relations between alpha waves and cortical inactivity have indeed reliably been observed over the visual cortex in the absence of *external* stimulation. However, recent research has provided evidence that the relationship between alpha activity and cortical inactivity is actually reversed during internal mental operations. Alpha waves generated during *internal* mental activity in the PFC, such as decision making is positively related to cortical activity. Recently, Schutter and Van Honk (unpublished data) replicated the finding reported in Chapter 6 by showing that predominant left-sided anterior alpha power asymmetry predicted a high percentage of risky decisions in a gambling task with random outcomes. More left-sided PFC activity predicted more risky decisions, indicating that left-sided dominant subjects were less punishment sensitive. These studies did not only demonstrate that the findings are in accordance with the postulated neurobiological model of Engage- and Retreat-related affective processing, but also defy the traditional functional interpretation of alpha waves in the PFC. The study in Chapter 6 demonstrated that baseline cortical activity predicts affectively mediated decision mak-

ing, but it would also be interesting to investigate the physiological basis of how the brain processes punishment and reward. How, for instance punishment and reward-related feedback processing is related to the individual's proneness to punishment (Retreat system) and reward sensitivity (Engage system). These issues were addressed in the study described in Chapter 7. Sixteen healthy subjects performed a gambling task in which participants could vary the amount of risk taking. After each decision, feedback was provided to record the electrical brain responses to winning or loosing after high and low risk gambling. A distinct increase of the feedback-locked P1 brain potential over the PFC was demonstrated after experiencing punishment after high risk. However, the P1 amplitude was inversely related to self-reported punishment sensitivity. Furthermore, the amplitude of a negative polarized brain potential recorded 200 ms after punishment feedback (MFN) was inversely associated with overall percentage risk taking. The P1 reflects an orienting response to relevant information and is generated in the thalamus through cholinergic innervations of the reticular activating system (Arai, 2003) and subsequently transmitted to the PFC. In sum, low punishment sensitivity is reflected by attenuated levels of experienced distress (P1 reduction), which seem to promote risky gambling behavior (MFN reduction). This finding provides an electrophysiological foundation of the involvement of the Engage and Retreat systems during punishment processing in high risk decision making.

The parietal cortex

Up until now the emphasis of our studies regarding the Engage- and Retreat system has been on the information processing in the frontal lobes. Affective processes are however not unitary concepts which can be implemented in straightforward modular localized fashions. There is increasing evidence that other association areas, such as the parietal cortex contribute to various aspects of affective processing. In Chapter 8, event-related potentials to the threatening angry facial expression were studied over both the anterior and posterior cortical regions. Whereas

the frontal regions were predominantly involved in fast evaluation processing (cf. Chapter 7), the parietal cortex seems more concerned with sustained attention to the threatening angry facial expression. In Chapter 9, the findings in Chapter 8 were further investigated by studying the involvement of the parietal cortex in the processing of anger. Relative more right-sided compared to left-sided parietal EEG activity was predictive of a more avoidant response to the angry facial expression. This finding suggests that asymmetrical parietal activity can be linked to the Retreat system, and concurs with a study of Heller, Nitschke, Etienne, & Miller (1997), which demonstrated an association between right parietal hyperactivity and anxious arousal. It was already outlined in Chapter 1 that depression often goes accompanied by high levels of anxiety (see also Heller, Ettienne, & Miller, 1995). Interestingly, Heller and Nitschke (1998) demonstrated that depression with comorbid anxiety is related to increased right parietal activity. This parietal hyperactivity might be interpreted as increased psychological arousal contributing to negative thought, ruminations, worrying and a weak Engage system. Evidence for the latter notion was provided in Chapter 9 where a relationship between right parietal activity and avoidant responses to the angry facial expression was observed. To elucidate the functional role of the right parietal cortex in affective processing, Chapter 10 describes a study wherein slow rTMS was applied over the right parietal cortex for 20 minutes continuously. Compared to sham, right parietal rTMS caused reductions in phenomenological, physiological and attentional indices of depression. Participants showed not only decreases in depressive mood but also more vigilant responses towards the angry facial expression. Furthermore, in line with the slow rTMS study by Van Honk et al. (2002), these vigilant responses were accompanied by increases in heart rate. Activation of the Engage system can account for the effects. Right parietal deactivation might have resulted in elevations of activity in the contralateral hemisphere, resulting in more Engage-related affective processing, and concurring reductions in low mood.

The left prefrontal and right parietal link

Research in the field of affective neuroscience has extensively relied on the localization of brain structures involved in affective processing through neuroimaging methods, including PET (e.g., Blair, Morris, Frith, Perrett, & Dolan, 1999), fMRI (e.g., Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003) and rTMS (e.g., Van Honk, Schutter, D'Alfonso, Kessels, & De Haan, 2002), or by means of studying the temporal dynamics using EEG (e.g., Bernat, Bunce, & Shevrin, 2000). Up to date relative few studies have investigated the connections between the different brain regions involved in affective processing. Obviously, affective information processing takes place in and between interconnected brain regions. Davidson (1984) already suggested a reciprocal relation between the frontal and parietal brain areas in affective processing. Although the precise functional interpretation remained elusive, Davidson (1984) argued that the left-sided PFC activation was balanced by right-sided parietal activation and vice versa. In order to fully comprehend how affective processing is instantiated within these functional networks, it is not only important to know which brain regions are crucial, but also to establish how they interact or communicate. Functional and effective connectivity can be distinguished (Horwitz, 2003). Functional connectivity relies on statistical signal correlation measured at two different brain sites, which can be quantified using EEG, PET and fMRI. Effective connectivity is based on measuring alterations of activity in brain areas distant from the target region, where the initial change in brain activity was induced by applying TMS for instance. Furthermore, the communication within neural networks is not only determined by anatomical connectivity, but is also influenced by neuromodulation of hormones such as the steroids cortisol and testosterone. A breakdown of cortico-cortical connectivity has been observed in patients with Cushing's disease, who are characterized by extreme high levels of cortisol (Schutter et al., submitted). Cortisol is a biochemical marker for depression and since both the left PFC (Sackheim et al., 1982; Drevets et al., 1997; Pizzagalli et al., 2002) and the right parietal cortex (Heller et al.,

1998) have been implicated in depression, lower functional connectivity between the left PFC and right parietal cortex was hypothesized to be associated with higher basal cortisol levels. Chapter 11 reports the verification of this hypothesis by means of demonstrating a significant inverse relationship between left PFC-right parietal cortical functional connectivity and basal cortisol levels. This result was further discussed in Chapter 12 in relation to recent counterintuitive findings by Rosenberg et al. (2002). These researchers investigated the antidepressant efficacy of slow and fast rTMS over the left PFC in depressed subjects with posttraumatic stress disorder. In clinical treatment trials of depression, fast rTMS over the left PFC is utilized to enhance neural activity, whereas slow rTMS is applied to dampen activity in the right PFC. The assumption underlying these treatment strategies is based on restoring the balance in activity between the left and right PFC (see also Chapter 15). Paradoxically, the study of Rosenberg et al. (2002) showed antidepressant efficacy for both fast and slow rTMS over the left PFC. Kimbrell et al. (1999) assessed cerebral glucose metabolism in major depressed subjects and found that antidepressant efficacy of either low or high rTMS depended on general baseline cerebral metabolism. Kimbrell et al. (1999) conjectured that depression can be accompanied by a hypo- as well as a hyperactive PFC irrespective of hemisphere. Rosenberg et al. (2002) compared the antidepressant efficacy of one group receiving slow rTMS with a group stimulated with fast rTMS. Unfortunately, no pre- and post treatment data of brain activity were available for the two groups. For these reasons the possibility cannot be ruled out that the antidepressant efficacy of slow rTMS is due to the first group having a hypermetabolic brain. In Chapter 12 it was posited that the absolute activity of the left PFC needs however not be involved per se. Instead, the increase in functional connectivity between the left PFC and right parietal cortex might have accounted for the amelioration of depression in the Rosenberg et al.'s study. Crucial evidence for this functional connectivity-depression hypothesis could be obtained by demonstrating that for instance testosterone, a steroid hormone having antidepressant properties (Rabkin, Wagner, & Rabkin, 1999), increases left PFC-right parietal

connectivity. In Chapter 13, a study is discussed wherein a single administration of testosterone was administered to healthy volunteers in a within-subject, double-blind, placebo-controlled crossover design. Significant increases in functional connectivity between the left PFC and right parietal cortex were indeed observed after testosterone administration. How these findings can be translated to pathological depression needs to be resolved by means of conducting more extensive testosterone treatment studies in clinically depressed populations.

The cerebellum and prefrontal link

Recent studies have also shown anatomical projections from the cerebellum to the PFC in primates (e.g., Middleton & Strick, 2001) and the cerebellar involvement in human affective states as evidenced by the cerebellar "pacemaker" studies of Heath, Rouchell, Llewellyn, & Walker (1981). Based on these two lines of evidence, Chapter 14 discusses an rTMS experiment, which investigates the anatomical connection of the cerebellum to the PFC in humans. EEG recordings were made over the PFC after fast rTMS over the medial portion of cerebellum. Medial cerebellar rTMS, compared to placebo and occipital stimulation induced a significant shift in PFC asymmetry from left to right dominance in the gamma (30-50 Hz) frequency band. Moreover, elevations in mood and alertness were spontaneously reported after medial cerebellar stimulation only. These data confirm the cerebellar modulation of PFC activity and affect in humans. However, right PFC dominance in activity after fast rTMS, which was accompanied by mood elevations seems to be at odds with the conceptualization of the right PFC involvement in withdrawal-related negative affect. The electrodes over the orbital and dorsolateral parts of the left and right PFC were however clustered, because the design does not allow us to draw conclusions regarding the exact source of the gamma activity. Nevertheless, the most pronounced effect of gamma induction was recorded over the right OFC. This is in accordance with theories adhering to the assumption that on the level of the OFC the anterior asymmetry of negative affect is functionally reversed

(Papousek and Schulter, 2001), and also agrees with the suggestion that reduced electrodermal activity after slow rTMS over the left OFC signifies reductions in punishment insensitivity (see Chapter 4).
Finally, Chapter 15 started by reviewing a longstanding issue in clinical research regarding rTMS as a potential treatment tool in major depression. As mentioned, clinical depression often goes accompanied by reductions in cortical excitability of the left prefrontal cortex (PFC). In agreement, a method capable of enhancing cortical excitability, repetitive transcranial magnetic stimulation (rTMS), when applied over the left PFC has been shown to exhibit antidepressant efficacy. The overall therapeutic effects of rTMS remain however inconclusive. It is common knowledge in the field of neuropsychiatry that the cerebral pathophysiology of depression is not limited to the PFC. The potential antidepressant efficacy of rTMS over the right parietal cortex (Chapter 10) and cerebellum (Chapter 14) warrants further explorations of the therapeutic efficacy of rTMS and the neurobiology underlying depression clinical research studies.

Extending the neurobiological model of Engage- and Retreat-related affect

The aim of current thesis was threefold:
(1) Further investigating the role of the PFC with respect to the Engage- and Retreat system.
The PFC remains one of the most important cortical regions in affective processing. Additional and corroborating behavioral and physiological evidence has been provided in Chapter 2 to 8 in favor of the PFC lateralisation model of affective processing.
(2) Modifying the heuristic neurobiological model, depicted in Figure 1.2, by introducing additional brain regions and their functional connection to the PFC.
Throughout the thesis it has become apparent that brain regions of interest, such as the PFC can not be treated in isolation. In particular the functional connectivity and interactions between these regions provide crucial insights into the understanding of human affective processing.

Based on the findings reported in Chapters 9-15, Figure 16.1 displays a modified and more elaborated version of the neurobiological model of Engage- and Retreat-related affective processing which was outlined in the introductory Chapter (Figure 1.2). The model now includes the role of the right parietal cortex and cerebellum in interaction with the PFC in affective processing. In particular the functional interaction/connectivity between brain structures and subsequently the construction of more dynamically brain models of affective processing will become increasingly important for the years to come.

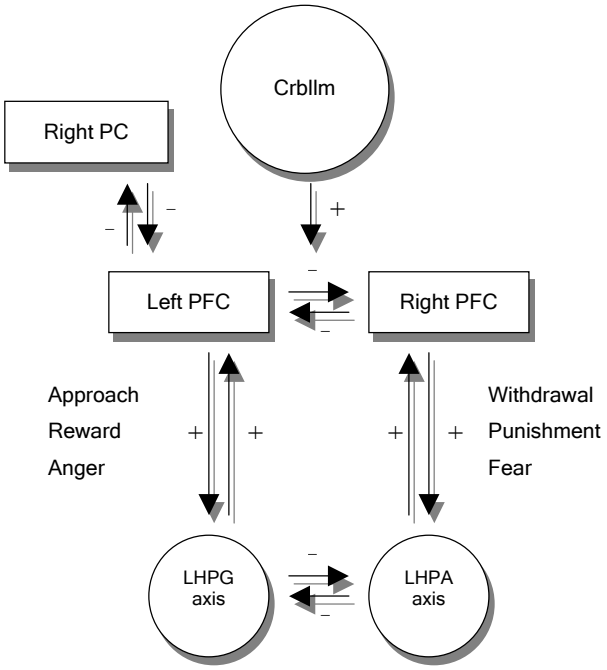

Figure 16.1: Modified heuristic neurobiological model of Engage- (left) and Retreat-related affective processing (right). Right PC; Right parietal cortex: Crbllm; Cerebellum: Left PFC; left prefrontal cortex: Right PFC; right prefrontal cortex: LHPA-axis; limbic-hypothalamic-pituitary-adrenal axis: LHPG-axis; limbic-hypothalamic-pituitary-gonadal axis: ⁻; inhibitory: +; excitatory projection.

(3) Introducing the heuristic neurobiological model of Engage- and Retreat-related affective processing in psychopathology of major depression and the potential role of rTMS in diverse treatment strategies.

In Chapter 15 an rTMS oriented heuristic model for the treatment of clinical depression comprised of the left and right prefrontal cortex, right parietal cortex and the cerebellum was presented (Figure 15.1). Fundamental research in the field of affective neuroscience has thus resulted into a hypothetical model of potentially more effective stimulation sites in the treatment of depression. Depression however reveals itself in several forms, and in particular the melancholic and lethargic forms of depression have their own distinct pathophysiology. The antidepressant effects of fast rTMS over the cerebellum might specifically be effective for lethargic depression, given the fact that medial cerebellar rTMS might in particular mimic the effect of mono-amine-oxidase (MAO) inhibitors. Patients with melancholic depression on the other hand might benefit more from slow rTMS over the right parietal cortex, since high levels of anxiety are observed in this clinical group (see Chapter 15).

Epilogue

Although our understanding of the brain has greatly expanded in the last decade, neuroscientists have to acknowledge that, in reality, the fathoming of brain functions remains elusive. Nevertheless, the present thesis has hopefully not only contributed to the scientific community in terms of providing additional insight into the biological mechanisms of affective processing, but also to the view that studying brain function more dynamically is a prerequisite. Firstly, by means of adopting an interdisciplinary approach in terms of utilizing and combining neuroimaging methods (e.g., EEG, fMRI and PET) and manipulation methods (e.g., rTMS and testosterone administration) in studying functional constructs, such as the Engage and Retreat system. Secondly, by means of promoting interaction-based architectures of function, since, to my opinion, relative dominant activity patterns (brain asymmetries of activity) and information transfer (functional connectivity) between different brain regions are more important and even crucial in understanding brain function, than studying brain function solely relying on localization methodology. TMS, for instance, might bring the suspicion about of

being a typical modern instrument to practice phrenology. Besides its property of causal inference, which can determine whether certain brain are critically involved in certain functional processing, TMS combined with neuroimaging techniques becomes a powerful tool, enabling us to expand our understanding of the neural basis of function in terms of interconnected networks. However, I am not suggesting that this approach will prove to be the holy grail in formulating the bridging principles between brain and function. Brain function can be studied at different explanatory levels ranging from macroscopic, such as mapping distributed neuronal networks, to microscopic approaches in terms of studying neurochemical processes at the synaptic level of the neuron. Nevertheless, although the progress made in both affective and cognitive neuroscience has been substantial, neuroscientists are still far away from resolving the brain-function relationship, making its further scientific endeavor worthwhile.

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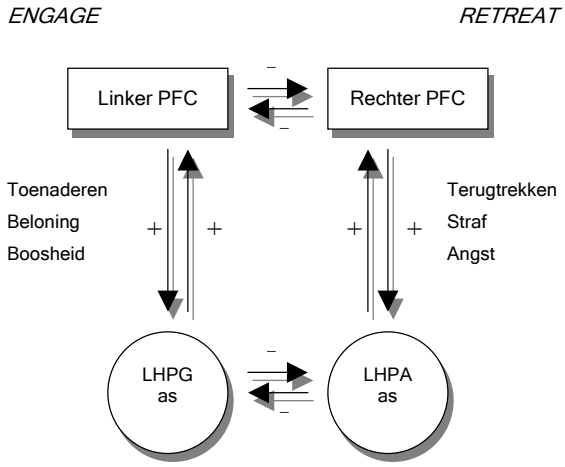
Samenvatting

De affectieve neurowetenschappen houden zich bezig met de bestudering van de ruimtelijke en temporele aspecten van het brein in relatie tot affectieve informatieverwerking. Wanneer naar het brein wordt gekeken kunnen een aantal deelsystemen worden onderscheiden, die elk op hun manier bijdragen aan de fysiologische en fenomenologische grondslagen van affect. Het limbische systeem, een evolutionair ouder deel van de hersenen wordt als het emotie centrum beschouwd, waar primaire emoties zoals angst en boosheid hun oorsprong vinden. Angst en boosheid worden vervolgens beschouwd als emoties die intrinsiek verbonden zijn met respectievelijk toenaderings- en terugtrekkingsgedrag. In deze dichotomie spelen de steroïde hormonen testosteron en cortisol een bangrijke rol als het gaat om selectieve motivationele en emotionele toestanden. Het gonadale hormoon testosteron wordt in verband gebracht met boosheid en agressie, terwijl hoge niveaus van het adrenale hormoon cortisol worden geassocieerd met angst. Het limbische systeem staat in direct contact met het hormonale systeem bestaande uit de hypothalamische-hypofyse-gonadale (HPG) en de hypothalamische-hypofyse-adrenale (HPA) as en speelt een belangrijke rol in de initiatie van de productie van respectievelijk testosteron en cortisol. Omdat het limbische systeem nauw betrokken is bij de regulering van de HPG en HPA as, worden deze assen tegenwoordig ook afgekort als LHPG en LHPA. Boven op het bovengenoemde limbische en hormonale systeem is nog een hersenstructuur geëvolueerd. Deze hersenschors wordt de neocortex genoemd en onderzoek heeft uitgewezen dat met name de voorste delen van deze hersenschors, de zogenoemde prefrontale hersenschors (PFC) een belangrijke rol spelen in de verwerking en regulatie van menselijk affect. De linker PFC zou betrokken zijn bij aan boosheid gerelateerd gedrag en een verhoogde actie bereidheid in termen van toenadering en exploratie, terwijl de rechter PFC vooral betrokken is bij terugtrekking, inhibitie; de emotie angst. De bovengenoemde vormen van affectieve informatieverwerking in de linker en rechter PFC hebben tevens direct te maken met respectievelijk de gevoeligheid voor beloning en straf. Hierbij is er sprake van een zogeheten balans in motivatie; een hoge mate van stafgevoeligheid en een verminderde drang naar beloning is te relateren

aan terugtrekkingsgedrag, terwijl een lage gevoeligheid voor straf in combinatie met een hoge drang naar beloning direct te koppelen is aan toenaderingsgedrag. Op fysiologisch niveau is er evidentie dat deze motivationele imbalans is te plaatsen in de eerdergenoemde linker en rechter PFC. De linker PFC lijkt vooral betrokken te zijn bij de gevoeligheid voor beloning, terwijl de rechter PFC meer in verband is te brengen met de gevoeligheid voor straf. Dominantie van activiteit in dan wel de linker of rechter PFC zou daarom bepalend zijn voor de motivationele toestand van het individu. Samengevat lijken de linker en rechter PFC neuroanatomische correlaten te zijn van respectievelijk een systeem bestaande uit beloning, boosheid en toenaderingsgedrag (*Engage* systeem), en een systeem bestaande uit straf, angst en terugtrekkingsgedrag (*Retreat* systeem). In een eenvoudig heuristisch model (Figuur S.1) kunnen deze twee systemen bovendien worden gekoppeld aan de LHPG (testosteron) en de LHPA as (cortisol).



Figuur S.1. Heuristisch neurobiologisch georiënteerd model van affectieve informatieverwerking. Linker PFC; linker prefrontale hersenschors: Rechter PFC; rechter prefrontale hersenschors: LHPA-as; limbische-hypothalamische-hypofyse-bijnier as: LHPG-as; limbische-hypothalamische-hypofyse-gonadale as: ⁻; inhibitoire: +; excitatoire projectie.

In dit proefschrift is allereerst gekeken naar verdere evidentie voor het heuristische werkmodel, waarbij de nadruk lag op de betrokkenheid van de PFC. Naast de PFC zal niet alleen een aantal nieuwe gebieden worden

betrokken bij het werkmodel, maar zal ook het belang van functionele connectiviteit tussen de verschillende gebieden worden verduidelijkt. Tenslotte zal een eerste aanzet worden gegeven om de pathofysiologie van emotionele stoornissen en de mogelijke klinische toepasbaarheid te kunnen voorspellen en te toetsen aan de hand van het gemodificeerde heuristische werkmodel. De gebruikte methoden van onderzoek betroffen onder andere elektroencefalografie (EEG), hormonale metingen en manipulatie, gedragsmetingen, repetitieve transcraniale magnetische stimulatie (rTMS) en combinaties van bovenstaande. De laatst genoemde methode van onderzoek is een relatief nieuwe techniek en in een theoretische verhandeling (Hoofdstuk I) wordt ingegaan op de mechanismen en de toepasbaarheid van deze techniek in neurowetenschappelijk onderzoek. TMS is een methode waarbij met behulp van een speciale spoel, die op het hoofd van de proefpersoon wordt geplaatst, zeer kortdurende, maar krachtige magnetische pulsjes onderliggende hersenactiviteit kortstondig kan worden beïnvloed. Op deze manier kan worden onderzocht welke functies veranderen als gevolg van deze beïnvloeding. Daar waar beeldvormingmethoden zoals functionele magnetische resonantie beeldvorming (fMRI) en positron emissie tomografie (PET) alleen een verband kunnen aantonen tussen een oplichtend hersengebied en een functie, zo kan TMS uitsluitsel geven aangaande de vraag of dit gebied wel of niet cruciaal betrokken is bij de betreffende functie (causale inferentie).

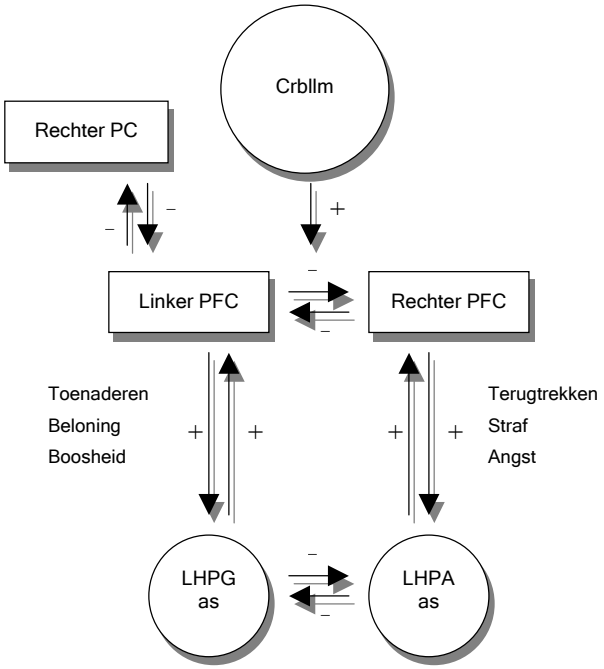
In Hoofdstuk 2 werd rTMS vervolgens toegepast op de PFC om de onderliggende fysiologische en gedragsveranderingen in kaart te brengen. EEG registraties na afloop van de TMS lieten een contralaterale toename in theta (4-7 Hz) activiteit en een afname in angst zien. Normaliter inhiberen de linker en rechter hemisfeer elkaar via het corpus callosum, de fysiologische realisatie van het balans model. Het reduceren van de rechter PFC activiteit door TMS leidde tot een verminderde transcallosale inhibitie naar links, waardoor de linker PFC in activiteit kon toenemen. De geobserveerde reductie in angst is in overeenstemming met de rechter PFC betrokkenheid in deze emotie. Onderzoek heeft bovendien een positieve relatie laten zien tussen theta activiteit en angst, hetgeen in het

rTMS onderzoek de variabelen waren die significante veranderingen lieten zien. De studie besproken in Hoofdstuk 3 liet vervolgens zien dat rechter PFC rTMS zorgt voor minder aandacht voor angstige gezichten tijdens de emotionele Stroop taak. Deze bevinding is wederom in overeenstemming met PFC lateralisatie theorie, alsmede met de bevindingen in Hoofdstuk 2. In de emotionele Stroop taak moeten proefpersonen zo snel mogelijk de kleur (rood, groen, blauw en geel) van neutrale en emotionele gezichten benoemen. Studies hebben laten zien dat angstige mensen langer doen over de benoeming van de kleur van een angstig kijkend gezicht, terwijl niet angstige mensen deze benoeming significant sneller doen dan de benoeming van neutrale gezichten. Dit laatste effect werd in Hoofdstuk 2 na TMS over de rechter PFC ook gevonden en lijkt dus een gevolg te zijn van een reductie in angst. Wanneer echter het gezicht heel kort wordt aangeboden (14 milliseconden) en vervolgens wordt vervangen door een 'masker' kunnen mensen niet meer bewust waarnemen wat voor een soort gezicht er zojuist werd getoond. Desalniettemin, laten angstige mensen hogere reactietijden zien bij de benoeming van de kleur van het masker wanneer dit was voorafgegaan door een angstig gezicht. Een gezaghebbende emotie theorie stelt dat er een bewuste corticale en een onbewuste limbische routes in de hersenen bestaan. Wanneer emotionele gezichten onder het bewustzijnsniveau worden aangeboden, wordt de corticale route niet geactiveerd en de emotioneel relevante informatie alleen op limbisch niveau verwerkt. Wanneer de gezichten op bewustzijnsniveau (ongemaskeerd) worden aangeboden worden beide routes geactiveerd, waarbij normaal gesproken de corticale route de overhand heeft. In het rTMS experiment werden alleen effecten gevonden op de ongemaskeerde en niet op de gemaskeerde versie van de taak. Dit lijkt in overeenstemming met het gegeven dat rTMS in eerste instantie alleen corticale gebieden kan beïnvloeden. De limbische informatieverwerking leek dus intact gebleven te zijn. Naast de gemeten gedragseffecten op affectieve informatieverwerking, zijn fysiologische veranderingen in huidgeleiding en hartslag zeer informatief met betrekking tot de emotionele toestand van lichaam en geest. Huidgeleiding blijkt een fysiologische maat te zijn voor strafgevoeligheid,

terwijl hartslag te koppelen is aan beloning. In Hoofdstuk 4 is gekeken naar de rol van het orbitale deel van de PFC (OFC) op huidgeleiding en hartslag. Het remmen van OFC activiteit door middel van rTMS resulteerde in een afname van huidgeleiding, terwijl hartslag onveranderd bleef. Deze bevinding is in overeenstemming met neuropsychologische data, die hebben laten zien dat schade in de OFC kan leiden tot afname van huidgeleiding en strafgevoeligheid. Afname in strafgevoeligheid kan leiden tot een onevenwichtige motivationele toestand, die gepaard gaat met een toename in gevoeligheid voor beloning. Twee extreme groepen werden geselecteerd op basis van een vragenlijst, die straf- en beloningsgevoeligheid meet en moesten vervolgens deelnemen aan een goktaak (Hoofdstuk 5). Conform de verwachting liet de groep die hoog scoorde op straf- en laag op beloningsgevoeligheid een voordelig, winstgevend gokpatroon zien in termen van het vermijden van grote beloningen, omdat deze gevolgd werden door nog grotere verliezen. De groep die daarentegen laag scoorde op straf- en hoog op beloningsgevoeligheid liet juist een nadelig, verliesgevend gokpatroon zien, omdat deze groep meer gevoelig was voor de grote beloningen en veel minder voor de nog grotere verliezen. Vervolgens werd de elektrische hersenactiviteit in de linker en rechter PFC gemeten (Hoofdstuk 6) om in een ongeselecteerde groep te kijken of een dergelijke motivationele onevenwichtigheid ook in de elektrofysiologie viel terug te vinden. Proefpersonen met relatief dominante linker PFC activiteit lieten een nadelig en risicovol gokpatroon zien. Deze gegevens zijn in overeenstemming met het heuristisch werkmodel, die stelt dat een dominante linker PFC gerelateerd is aan minder strafgevoeligheid en een grotere drang naar beloning. In Hoofdstuk 7 is vervolgens gekeken naar de invloed van strafgevoeligheid op het verwerken van straf door hersenen onmiddellijk nadat proefpersonen werden geconfronteerd met een hoge geldstraf na een risicovolle gok. Een lagere reactiviteit van de hersenen werd gemeten voor mensen die laag scoorden op strafgevoeligheid. Bovendien ging deze verlaagde reactiviteit gepaard met het nemen van hoge risico's. Tot dusver stond in de voorgaande Hoofdstukken de PFC centraal in affectieve informatieverwerkingsprocessen. Desalniettemin zijn er aanwijzingen in de litera-

tuur te vinden dat corticale structuren zoals het wandbeenkwab (parietale hersenschors) ook een belangrijke rol spelen in affect. In Hoofdstuk 8 worden empirische bevindingen besproken van een EEG studie waar proefpersonen naar neutrale en boze gezichten moesten kijken. De PFC bleek de snelle evaluatieprocessen voor zijn rekening te nemen, terwijl de parietale hersenschors de aandacht vasthield na aanbieding van een bedreigend gezicht. Deze bevindingen werden nader bestudeerd in Hoofdstuk 9, waarin werd gekeken of EEG activiteit in de parietale hersenschors de aandacht voor boze gezichten kon voorspellen. Een relatief dominante rechter ten opzichte van linker parietale activiteit resulteerde in de vermijding van de boze gezichten. Deze asymmetrie in de parietale hersenschors kan eveneens worden gekoppeld aan de PWF dimensie van affectieve informatieverwerking. Ander onderzoek heeft laten zien dat angstige opwinding gekenmerkt door symptomen van fysiologische *hyperarousal* en lichamelijke spanning gerelateerd is aan een overactieve rechter parietale hersenschors. De bevindingen laten zien dat affectieve informatieverwerking in de cerebrale hersenschors is te herleiden naar processen waar naast de PFC ook andere gebieden bij betrokken zijn. Hoofdstuk 10 bespreekt vervolgens een studie waarin de rol van de rechter parietale hersenschors door middel van rTMS verder is uitgewerkt. Vergeleken met een placebostimulatie induceerde rTMS een fysiologisch en gedragsmatig patroon, dat gekenmerkt werd door de activatie van het *Engage* systeem en een afname van depressieve stemming. Op basis van de bevindingen uit het voorgaande onderzoek lijkt het inhiberen van rechter parietale activiteit een angstgestuurde activatie van het *Engage* systeem te veroorzaken, die gekoppeld is aan een afname in depressieve stemming. Deze resultaten laten tevens zien dat emotionele stoornissen vaak gekoppeld is aan co-morbiditeit. In Hoofdstuk 11 werd een functionele verbinding besproken tussen de linker PFC en de rechter parietale hersenschors, waarvan de sterkte van connectiviteit wordt voorspeld door de activiteit van de LHPA-as in termen van cortisol niveaus. Deze studie liet zien dat niet alleen absolute hersenactiviteit in verschillende gebieden een rol speelt, maar ook de interactie tussen deze gebieden van belang is als het gaat om affectieve informatieverwer-

king. In Hoofdstuk 12 wordt op deze kwestie ingegaan door een alternatieve verklaring te geven voor paradoxale bevindingen van een recente rTMS behandelstudie van Rosenberg en collega's. In deze studie werden vergelijkbare antidepressieve effecten gevonden voor zowel langzame als snelle rTMS over de linker PFC. De theorieën omtrent de effecten van rTMS voorspelden echter alleen een effect van snelle rTMS, omdat deze techniek activiteit juist laat toe- in plaats van afnemen zoals bij langzame rTMS het geval is. Een toename van functionele connectiviteit tussen de linker en rechter PFC zou een alternatieve verklaring kunnen zijn voor de antidepressieve effecten. Van testosteron is bewezen dat dit hormoon in tegenstelling tot cortisol een positieve invloed heeft op het welbevinden. In een placebo gecontroleerde studie (Hoofdstuk 13) werd gekeken of het toedienen van testosteron zou leiden tot een toename van de functionele connectiviteit tussen de linker en rechter PFC, wat vervolgens ook werd bevestigd. In Hoofdstuk 14 werd vervolgens een studie gerapporteerd die liet zien dat snelle rTMS over het cerebellum veranderingen in PFC activiteit en een spontane verbeteringen van stemming teweegbracht. Deze lange afstandseffecten benadrukken nog eens het belang van interconnectiviteit. In Hoofdstuk 15 werd een literatuurstudie beschreven over behandeling van depressie met behulp van rTMS. Mede op basis van de voorgaande hoofdstukken en de literatuurstudie is gebleken dat depressie niet alleen te maken heeft met afwijkingen in PFC activiteit. De antidepressieve effectiviteit van klinische rTMS behandelstudies loopt onderling nog al uiteen. Een mogelijke reden hiervoor zou kunnen zijn dat de PFC niet de optimale plaats is voor de behandeling met rTMS. Daarnaast zou de duur en intensiteit van stimulatie een rol kunnen spelen. De conclusie is dan ook dat niet alleen de stimulatie parameters moeten worden geïntensifieerd, maar dat ook verder moet worden onderzocht of rTMS over de rechter parietale hersenschors en het cerebellum wellicht betere antidepressieve effectiviteit bewerkstelligt dan de traditionele PFC stimulaties. Figuur S.2 laat een gemodificeerde versie van het heuristische neurobiologische model van affectieve informatieverwerking zien.



Figuur S.2. Heuristisch neurobiologisch georiënteerd model van affectieve informatieverwerking. Rechter PC; rechte parietale hersenschors: Crbllm; Cerebellum: linker PFC; linker prefrontale hersenschors: rechter PFC; rechter prefrontale hersenschors: LHPA-as; limbische-hypothalamische-hypofyse-bijnier as: LHPG-as; limbische-hypothalamische-hypofyse-gonadale as: –; inhibitoire: +; excitatoire projectie.

Uit de resultaten van de hierboven besproken studies blijken niet alleen het limbische systeem en de interactie met de linker en rechter PFC een specifieke rol te spelen in respectievelijk het *Engage* en *Retreat* systeem van affectieve informatieverwerking, maar dat de parietale hersenschors en het cerebellum eveneens belangrijke structuren zijn. Omdat het brein opereert als een netwerk, zal de functionele connectiviteit tussen de verschillende gebieden logischerwijs meer inzicht geven in de affectieve informatieverwerking en affect gerelateerde stoornissen dan activiteit in uitsluitend geïsoleerde hersengebieden. Tenslotte kan worden geconcludeerd dat fundamentele studies gericht op de werking van het brein in affectieve processen veel kennis opleveren met betrekking tot de psychopathologie en onderliggende pathofysiologie.

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Curriculum vitae

Dennis Schutter werd geboren op 18 juni 1975 in Numansdorp. In 1995 ontving hij het VWO diploma aan de Willem de Zwijger Scholengemeenschap in Papendrecht. Een jaar later behaalde hij de propedeuse Psychologie aan de Universiteit Utrecht. Hij specialiseerde zich vervolgens in theoretische en biologische psychologie en studeerde in 2000 af in de richting "Cognitie en emotie". In 2000 kreeg hij een VSB beurs en werkte vervolgens als speciale vrijwilliger/ onderzoeker op de afdeling cognitieve neurowetenschappen van het *National Institute of Neurological Disorders and Stroke* (NINDS) aan het *National Institutes of Health* (NIH) in Bethesda, de Verenigde Staten. In augustus 2001 begon hij als assistent in opleiding aan de capaciteitsgroep Psychonomie van de Universiteit Utrecht met het project *Corticale en subcorticale routes van emotionele informatieverwerking in het menselijk brein*. Op dit moment is hij als onderzoeker verbonden aan de capaciteitsgroep Psychonomie van de Universiteit Utrecht.

Dennis Schutter was born on June 18, 1975, in Numansdorp, the Netherlands. In 1995 he completed his secondary school education at the Willem de Zwijger Scholengemeenschap in Papendrecht. A year later, he passed his first-year examination in Psychology at the Utrecht University. He majored in theoretical and biological psychology and in 2000 he obtained his master of science's degree in the direction "Cognition and emotion". In 2000 he received a VSB scholarship and worked as a special volunteer/ researcher at the cognitive neuroscience section of the National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH) in Bethesda, United States of America. In August 2001 he started working as a Ph.D. student in the department of Psychonomics of the Utrecht University on the project *Cortical and subcortical affective pathways in the human brain*. Currently, he works as a researcher at the Psychonomics department of the Utrecht University.