Our Biased Brain

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(met een samenvatting in het Nederlands)

Proefschrift

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door

Dennis Hofman

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Promotor: Prof.dr. J.L. Kenemans

Co-promotor: Dr. D.J.L.G. Schutter

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Chapter 1

"An impractical man - which he not only seems to be, but really is - will always be unreliable and unpredictable in his dealings with others. He will engage in actions that mean something else to him than to others, but he is at peace with himself about everything as long as he can make it all come together in a fine idea."

Robert Musil, The man without qualities, part 1.

The man without qualities as painted by Robert Musil in his 20th century novel is intriguing through his apparent impossibility. As every thought or action of the man without qualities would be the result of a brain with neither premeditation nor history, they are stripped of affective valence, motivational direction or ancestry. Any reflection on future or past of the man would be meaningless. In general however, man can be taken to possess qualities.

Evolution has endowed us with a brain that is shaped by the experience of our predecessors. Such 'continuity of mind' as proposed by Charles Darwin in his The Descent of Man, describes how, similar to many other qualities, the human mental faculties can be understood in terms of one *common descent*: they are the result of evolution through natural and sexual selection (Darwin, 1871). Common descent dictates that fundamentally, there are no differences between the faculties of man and any other species, or as Darwin himself formulates '*If no organic being excepting man had possessed any mental power, or if his powers had been of a wholly different nature from those of the lower animals, then we should never have been able to convince ourselves that our high faculties had been gradually developed*' (page 35, Darwin, 1871). As the most recent manifestation of the proposed continuity of mind, the workings of the brain offer an outlook on what behaviors have proven successful in the descent of man. Man has shown capable of coping with environments pervaded with threat, has contrived social structures that harbor strong as well as weaker members, and in the process of doing so has maintained sufficient variability in its individual members to cope with future challenge.

The present thesis aims to describe what mechanisms enable man to successful cope with social challenge. The focus in the first two parts of this thesis the delicate balance between individual safeguarding and the maintenance of social coexistence. As social coexistence is dependent on stable social hierarchies, individual factors in the motivation to dominate or aggress are studied. This description may vary from normative when pertaining to universal mechanisms, to an individual differences approach if that would yield a greater insight in the causing mechanisms of human social behavior. To do so, we have in the following chapters adopted an approach rooted in social neuroscience methods and guided by evolutionary doctrine.

A theoretical approach to Social Neuroscience

As the chair of our mental faculties, the brain provides a window for the study of our cognitive abilities, emotions and behavior that constitute the foundation for our personality. In recent years, especially the neuroscientific study of human social behavior gave rise to an impressive body of knowledge. In their hallmark 1992 paper, Cacioppo and Berntson first named the discipline Social Neuroscience, and formulated a doctrine for the newly born in the 'decade of the brain' (Cacioppo & Berntson, 1992). What they advocated in their work was a multilevel, integrative approach to the study of mental and behavioral functioning, since the traditional levels of analysis employed in the psychological and neuroscience disciplines might have concealed communalities in their respective contributions to the explanation of psychological phenomena (Cacioppo & Berntson, 1992). In their view, '*levels*' refer to the different scales into which the brain can be represented, and are defined by physiological constraints, but more importantly, their potential to add to the understanding of a biological, psychological or phenomenological observation (Cacioppo & Berntson, 1992). Therefore, a multilevel approach in social neuroscience should be able to bring about comprehensive accounts of psychological and behavioral phenomena (Cacioppo & Berntson, 1992).

Indeed, the years of the 'decade of the brain' as the 1990's were declared by American Congress, have seen vast accumulation of data and the flourishing of social neuroscience under the true advent of functional brain imaging techniques. The rapid accumulation of knowledge on human brain function has, however, not necessarily led to an increased *understanding* of how our ssocial brain gives rise to our emotions, motivation and behavior. Along with growth, dispersion came, and despite increased awareness of work done multi-disciplinary, the main call as formulated in 1992 still stands, and can be taken as a guideline for modern social neuroscience.

In a recent reconceptualization of social neuroscience, three levels of social information processing are proposed: social perception, social cognition, and social regulation (Adolphs, 2010). First, social perception is proposed to be driven purely by sensory input. In the olfactory and tactile domains, hard-wired pathways dedicated to the communication of socially laden sensory inputs have been identified, possibly reflecting that the triggering stimuli are generated by conspecifics, facilitating learning and bonding (Loken, Wessberg, Morrison, McGlone, & Olausson, 2009; Wang & Anderson, 2010). Also for the auditory domain, for instance in voles, trajectories dedicated to social differentiation have been identified (Margoliash, 1983). Finally, processing of sensory input in the visual domain has received a vast amount of empirical attention. In macaque monkey a cortical region almost entirely consisting of face-selective neurons has been identified (Tsao, Freiwald, Tootell, & Livingstone, 2006), possibly aligning with its human equivalent in occipitotemporal cortex, which was been shown to be particularly sensitive to human facial expressions (Bentin, Allison, Puce, Perez, & McCarthy, 1996; Vuilleumier & Pourtois, 2007).

Social cognition takes social perception beyond the processing of sensory input. Automatic inferences based on the stimuli originally triggering the sensory pathways are made, preparing the observer for appropriate action. We automatically infer danger from a fearful or angry face, recognize sadness from the trembling mouth and dejected eyes, suggesting the emotional facial expression to fulfill a *signaling* function. Indeed, the communicatory function of emotional facial expressions is widely recognized and investigated. In addition to accounts proposing that facial expressions are automatic displays of emotion that are modulated by the experienced intensity of the emotion (Buck, 1999; Darwin, 1872), it has also been shown that emotional facial expressions are dependent primarily on the social context, from early infancy onward (Fridlund, 1991; Hinde, 1985; Jones & Raag, 1989). For an emotional facial expression to be of worth to the observer, an observer must be able to infer the psychological state of the conveyer, and the emotional facial expression can therefore be regarded to provide a basis for 'higher cognitive functions' such as theory of mind (Frith & Frith, 2012). As such, it has been proposed that emotional content is to a certain extent simulated by the observer, which makes the relationship between conveyer and observer reciprocal in nature. This notion is reflected in phenomena such as facial mimicry: reflexive imitation of emotional expressions that has been argued to facilitate interpersonal bonding (Lakin & Chartrand, 2003). Taken together, social cognition is the sensory-fed process of (automatic) inferences, attribution and simulation and imitation, processes that are under modulatory influence of social context.

Finally, social regulation refers to the ability to employ metacognitive strategies to exert regulatory control over one's own thinking and behavior (Adolphs, 2010). Especially the importance of emotional control has been described extensively in the context of psychopathology, such as extreme aggression (Davidson, Putnam, & Larson, 2000). Arguably, abilities not necessarily confined to the social domain, such as impulse control (behavioral inhibition) play a key role in successful regulation of social behavior. Indeed, several studies have implicated impaired inhibition of behavioral responses in for instance antisocial personality disorder, characterized by often extreme patterns of impulsive aggression (Kiehl, Smith, Hare, & Liddle, 2000; Swann, Lijffijt, Lane, Steinberg, & Moeller, 2009). On a more general account, brain-based emotion regulation theory has been dominated by accounts of the 'cognitive' regulatory function that the prefrontal cortex has been awarded (Davidson, 2002). Therefore, the extent to which these metacognitive abilities are dedicated to the regulatory control of behavior in the social domain is debatable, as they most probably are shared across domains of human cognition.

Before turning to the studies that are performed to inform the above described theoretical framework at the end of this prologue, the following pages will in short introduce the techniques that are the instruments of description.

The nuts and bolts of Social Neuroscience – brain recording and stimulation techniques employed in the present thesis

The electroencephalogram

Electroencephalogram (EEG) refers to the non-invasive recording of electrical activity generated by nervous tissue underneath sensors placed on the scalp. The human EEG reflects post-synaptic potentials, generated by large assemblies (typically 10 million up to 1 billion cells/sensor) of pyramidal cells throughout the cerebral cortex (Nunez & Srinivasan, 2007). The transmission of electric current through biological tissue, or volume conduction, results in a negligible delay in the generation and recording of electric fields, and therefore EEG is able to describe spontaneous as well as event-related electrophysiological activity with millisecond accuracy in its relation to the generating processes. The spatial resolution of EEG is hampered by the skull, which has only weak conductive capacity and therefore spreads activity over parts of the superjacent scalp. This attribute renders it difficult to determine sources of EEG activity, and confines EEG to the description of distributions of activity over the scalp.

Its discovery is generally attributed to Hans Berger, a German psychiatrist who in 1929 first published a paper on the human EEG in which he described the successful recording of oscillatory activity at occipital brain regions with a frequency of around 10 Hz, which he named α-waves (Berger, 1929). Figure 1, bottom panel shows two head plots of α-activity during a 60 second period with the eyes opened, and with eyes closed. Note the increase in alpha power at posterior electrode sites, showing that occipital areas are the main generators of alpha band activity

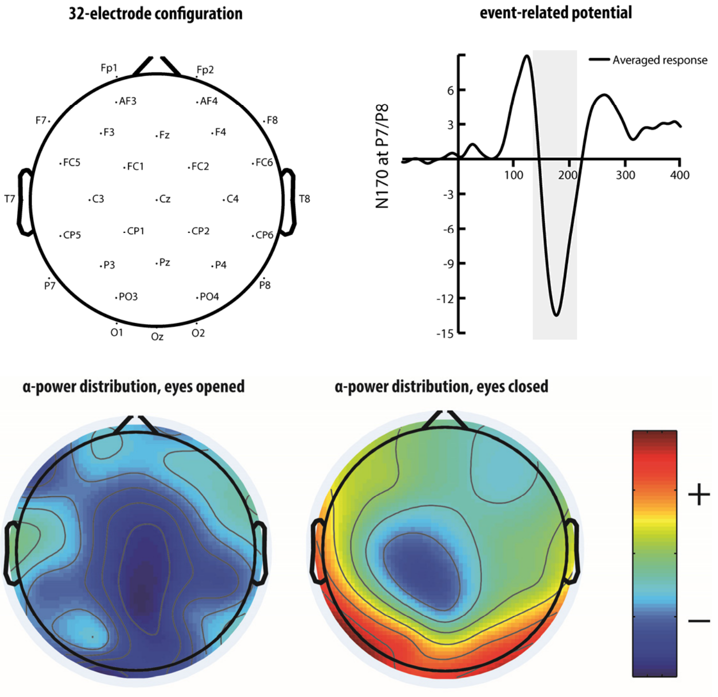

Figure 1.1. Upper panel, left figure: 10/20 electrode locations as used in a 32 sensor configuration. Upper panel, right figure: example of a group- and electrode averaged brain response to the presentation of an angry facial expression, measured from P7/P8. Bottom panel: examples of power distributions for the alpha frequency band, measured during a 60 sec eyes opened period (left) and a subsequent 60 sec eyes closed period.

In the present thesis, two approaches to the quantification and analysis of EEG data are undertaken. First, in chapters 6, 7 and 11, the spontaneous EEG, also referred to as resting-state EEG, is recorded from 32 electrodes placed on the participants' scalp according to the international 10/20 system for electrode placement (Jasper, 1958). The voltage traces in the time domain are then typically transformed to be represented in the frequency domain, usually in a power spectrum (Harmon-Jones & Peterson, 2009). Through the computation of absolute or relative contributions to the EEG signal as a whole, asymmetries in power between homologues electrode sites, of ratios between frequency bands can be calculated which in turn can be related to, for instance personality characteristics or task performance (see figure 1, bottom panel for a α-power based example). Second, when recording EEG in the context of a task, electrophysiological changes time-locked to the presentation of stimuli or responses can be used to study brain processes associated with those stimuli or responses. Such an event-locked response is referred to as an event-related potential (ERP), and reflects the one end of an electrical dipole that is produced by synchronously firing neurons (Bartholomew & Amodio, 2009). Therefore, recording voltage deflections at a particular electrode provides information about the neural manifestation of processing activities associated with for instance a stimulus such as the presentation of an emotional facial expression. Figure 1, upper right panel shows the averaged response to an angry facial expression as measured over the P7 and P8 electrode location. Figure 1, upper left panel shows the 10/20 positions for the 32 electrode configuration used in the present thesis.

Surface electromyography

Electromyography (EMG) is an index of electric activity generated by muscle contraction. Motor nerves consist of hundreds of nerve fibres, which each innervate several muscle fibres (Whittaker, 2012). One motor nerve fibre together with all the muscle fibres it innervates comprises a motor unit, and the changes in electrical potentials that result from the conduction of action potentials along muscle fibers, known as motor unit action potentials (MUAPs) are recorded by the surface electrodes (Fridlund & Cacioppo, 1986; Hess, 2009). In the present thesis, we use EMG to quantify motor responses to magnetic stimulation of M1 (chapters 3 and 8) and the activity of facial muscles in chapter 4.

Transcranial Magnetic Stimulation

In the cognitive and affective neurosciences, one of the few instruments able to clarify both spatial and temporal characteristics of causal relationships between brain structures is transcranial magnetic stimulation (TMS) (Schutter, van Honk, & Panksepp, 2004). TMS is based on Faraday's law of electromagnetic induction, which states that a magnetic field with the appropriate orientation (e.g., angle of the TMS-coil relative to the head) will induce an electric current near conducting tissue, e.g., neurons. When strong enough, the electromagnetic field will cause a transmembrane potential in underlying cortical nerve cells that are tangentially oriented to the magnetic field, resulting in Na+ influx and neuronal depolarization, which in turn may cause action potentials. The propagation of this current along the axon membrane is the mechanism by which neurons carry information (George, 2007). Ultimately, administering TMS at the proper intensity over for instance the thumb muscle representation in the primary motor cortex results in actual movement of the contralateral thumb muscle as measured through EMG, the EMG response being referred to as the motor evoked potential (MEP) (Barker, Jalinous, & Freeston, 1985). Figure 1, panel A shows the typical setup for eliciting EMG responses to a TMS-pulse.

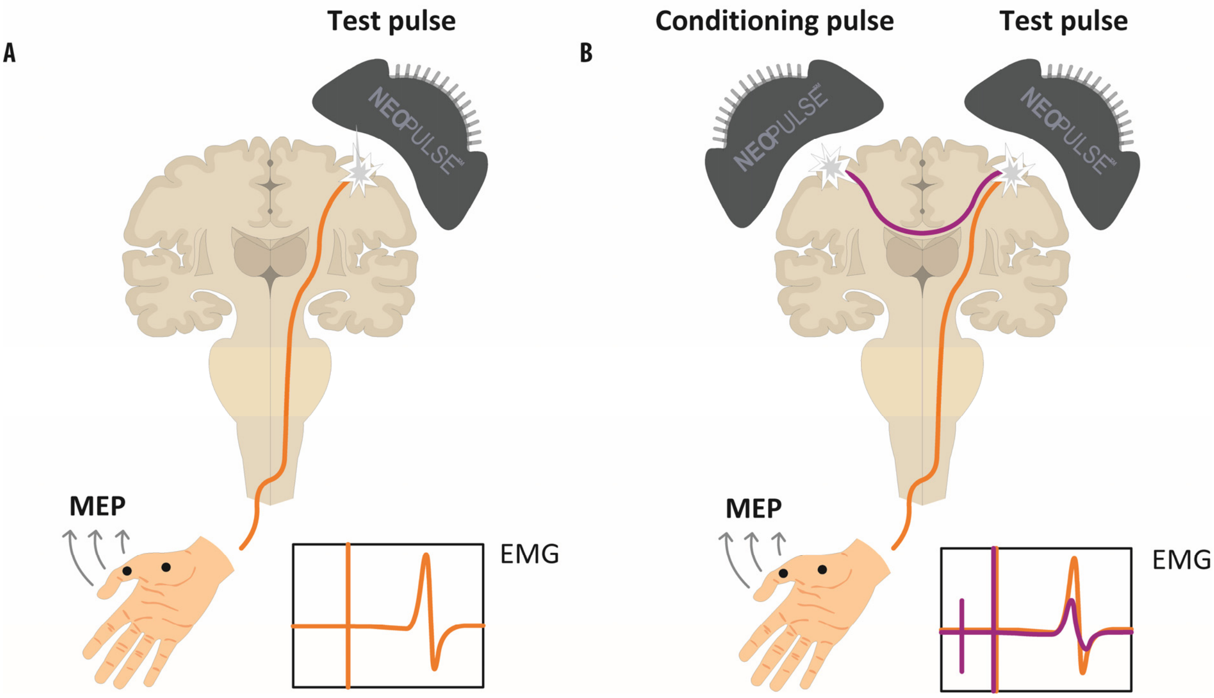

Figure 1.2. Magnetic stimulation of the cortical representation of the thumb muscle results in a MEP, quantifiable through surface EMG (panel A). Conditioning the magnetic pulse with a magnetic pulse of similar magnitude ~10ms before delivery results in an attenuation of the MEP of around 50% (panel B).

Interestingly, creating a set-up in which two stimulation coils (paired-pulse TMS) are combined to stimulate the cerebral hemispheres at homologous locations separated by latencies of ~10ms, allows for the quantification of functional interhemispheric connectivity (Ferbert et al., 1992). Interhemispheric signal transfer is mediated by the corpus callosum (CC), and excitatory fibers running through the CC are activated by the magnetic pulse. As these excitatory fibers innervate inhibitory interneurons in the contralateral cortex, the functional remainder of the conditioning pulse is inhibition of the motor response of the conditioned hemisphere, and the quantification of this inhibition can be taken as an index of interhemispheric communication. Figure 2, panel B schematically shows the principle of paired-pulse TMS, and its effect on the MEP.

Transcranial direct current stimulation

Transcranial direct current stimulation (tDCS) is in recent years undergoing renewed interest as a valuable tool for studying brain-function relationships non-invasively. The mechanism that is argued to bring about the effects of tDCS is the change in transmembrane potentials induced by the polarizing current (Stagg et al., 2009; Stagg & Nitsche, 2011).Generally, anodal tDCS (anode near the dendritic poles of radially oriented neurons) depolarizes neuronal cells, increasing firing rates, whereas cathodal polarization hyperpolarizes neurons, resulting in decreased firing rates (Wassermann, 2008). Figure 3 depicts a working model for the physiological effects of tDCS.

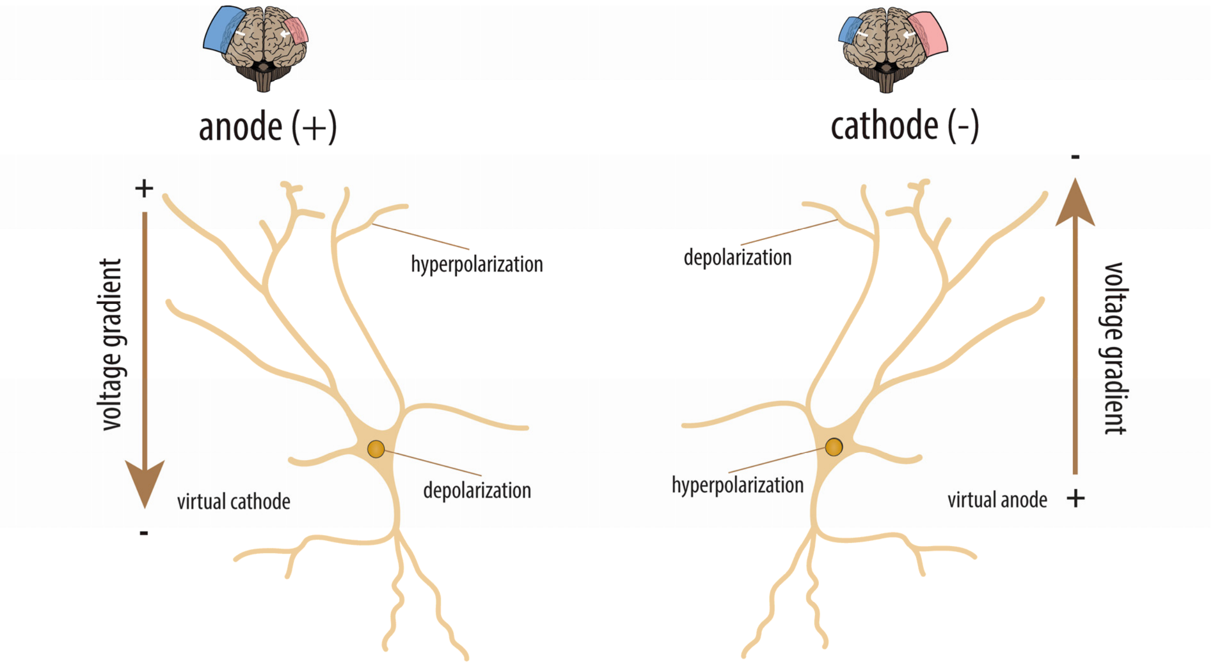

Figure 1.3. Working model for the mechanism by which tDCS modulates neural activity. For the anode example: a virtual cathode (negative polarity) is located near the soma. The extracellular increase in the concentrations of electrons (negatively charged) near the soma causes a reduction in the intra- and extracellular voltage difference and a state of depolarization near the cell soma.

Outline of the present thesis

This thesis takes a multilevel approach in addressing human motivated behavior, and through a series of experiments, attempts to show how the conceptualization of social perception, cognition and regulation are intertwined and can be framed to fit evolutionary views of human sociality. To this end, in parts 1 and 2, the research focus is on the balance between the safeguarding of individual interest versus the establishment and maintenance of social hierarchies. Part 1 focusses on mechanisms that are proposed to be universal, where part 2 takes an individual differences approach. Part three of the thesis is concerned with a methodological bias in the description of human social behavior, and suggests a new approach in social neuroscience studies.

Therefore, the present thesis consists of three parts: the normative bias, the individual bias and the methodological bias. Part one, *the normative bias* serves to investigate the extent to which our behavioral repertoire can be described in terms of universal mechanisms. In **chapter 2** a short neurocognitive account of the processing of emotional facial expressions and its possible functional repertoire in a perception-action model is presented. The notion of facial affect as an efficient form of nonverbal communication is tested directly in an experiment probing motor cortical responses to emotional facial expressions (**chapter 3**). Especially fearful facial expressions are assumed to annunciate impending threat, of which the functional resultant could be increased action preparation. To that end, we indexed corticospinal motor tract excitability through TMS of the primary motor cortex shortly after having presented fearful, happy and neutral facial expressions and our results are discussed along an evolutionary account of human perception-action coupling.

In **chapter 4**, following the coupling of perception and action tendencies, we harnessed the observation that in response to emotional expressions, observers tend to automatically imitate the expression observed. We tested the premise that in humans, mimicking facial affective display is more than a reflexive means of affiliation creation. As it has been suggested that mimicry is sensitive to contextual factors, (Lakin & Chartrand, 2003; Lakin, Chartrand, & Arkin, 2008) we here probed modulation of mimicry of happy and angry facial morphs during and after socioeconomic interaction, thereby manipulating immediate and distal goals. The results are discussed in context of human coexistence, and punishment of those who defy societal norms.

The **chapters 2-4** focus on normative biases in responses to facial affect without regard for individual differences in personality traits. However, such individual differences may well serve as powerful predictors of the response to challenge within the normative constraints defined by evolution. Therefore, *The individual bias* further zooms in on individual differences in these response patterns.

First, **chapter 5** provides a short overview of emotion processing theory with a special focus on the frontal cortex and its activity patterns. One of the most successful heuristic frameworks for the relation between cortical functioning and emotion is the frontal asymmetry of emotion model. This chapter introduces its principles, its main empirical achievements, and considerations for future research. **Chapter 6** directly investigates one of the hypotheses derived from the frontal asymmetry model, and further specifies its predictive power. Specifically, in this study we investigated whether individual differences in trait aggression and behavioral inhibition are reflected in asymmetrical patterns of frontal resting state inhibitory β-band oscillatory activity. In addition, the selective contributions of prefrontal and motor cortex areas to these associations were examined. **Chapter 7** conceptually builds on chapter 6 as it exploits the interpretation of β-band oscillatory activity as an inhibitory rhythm. Where chapter 6 tested whether β-activity modeled in a cortical interhemispheric asymmetry was predictive of aggressive behavior and impulse control, we here employed β-activity as an index of cortical control over subcortical drive, as expressed in low-frequency oscillatory activity in the δ-band. The ratio between the two yields an asymmetry in cortical – subcortical processing mode, an index of oscillatory activity that in the present study is implemented as a correlate of dominance motivation. Moreover, we now also included event related potentials (ERPs) to directly test the relationship between dominance motivation and the processing of facial affect. This led to the possibility of directly assessing the relation between dominance, resting-state as well as evoked brain activity and the related behavioral performance. Finally, chapter **8** investigates whether the main communicatory trajectory between the two cerebral hemispheres, the CC, could serve as a mechanism in the maintenance of frontal activity patterns - and thereby motivational stance. In line with the frontal asymmetry of emotion heuristic, we tested the hypothesis that left-to-right biased interhemispheric inhibition was associated with more approach-related personality characteristics, as well as increased interference when confronted with facial anger. Taken together, these experiments essentially test how social perception influences social cognition and social regulation, and how this relates to measures of self-reported motivation and emotion.

In *The methodological bias* a new avenue in human social function research is explored. Inspired by the findings from chapters 5-8, we here turned to the investigation of variation around the mean as a predicator of motivated behavior. Several studies have suggested that biological signal variability may also have functional properties in the neural system. In **chapter 9**, the importance of being variable as a proxy of plasticity is introduced and illustrated by discussing a recent study comparing mean- and variability based measures of cognitive functioning directly. In **chapter 10**, the versatility of variability based measures in predicting motivated behavior is tested in a sample of healthy subjects. Since behavioral approach has been shown to be reflected in left-lateralized frontal activity, and increased biological variability has been related to increased sensitivity to external events, we hypothesized that increased behavioral approach would be characterized by increased levels of state variability, particularly in the left hemisphere. Lastly, **chapter 11** evaluates whether transcranial direct current stimulation (tDCS) can affect variability in electrophysiological measures of cortical activity. In addition, possible interactions with steroid hormones known to affect cortical excitability are studied.

Conclusions and implications of our studies will be discussed in the epilogue.

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The normative bias

Introduction

Chapter 2

In societies complex and populated as ours, not all can be learned through direct experience. If one were to learn exclusively through personal interaction with the environment, chances of survival would decrease dramatically. Considering the fact that many mammalian species, including man, tend to live in groups, learning from conspecifics' encounters with threat would serve a wealthy secondary source of information that increases chances of survival. Carving these rules of engagement in a shared heritage would provide for a low-cost mechanism of incorporating a species' experience in its successors: a normative response bias.

Implicit transfer of social information can come in many forms; the cardinal form of non-verbal communication however is the emotional facial expression. When I use 'communicate', 'communication' or 'information transfer', I do not intend these phrases to be read as if the conveyer of the emotional expression wants to explicitly send a message to, or communicate with the observer. Rather, it states that the emotional expression in itself carries information about individuals, objects or situations, information that could be used to adjust on-going behavior of the observer (see also Blair, 2003). Facial expressions have a rich tradition of systematic investigation. Prevailing theories on the processing of facial identity and facial expression have proposed a dual-path framework for the processing of facial expressions (Bruce & Young, 1986; Calder & Young, 2005; Haxby, Hoffman, & Gobbini, 2000). Basically, the dual-path approach proposes a core system for the processing of invariant features of facial information, and an extended system for the information that requires further analysis to be of merit to an individual (for a graphic illustration see figure 1, adapted from Haxby et al., 2000).

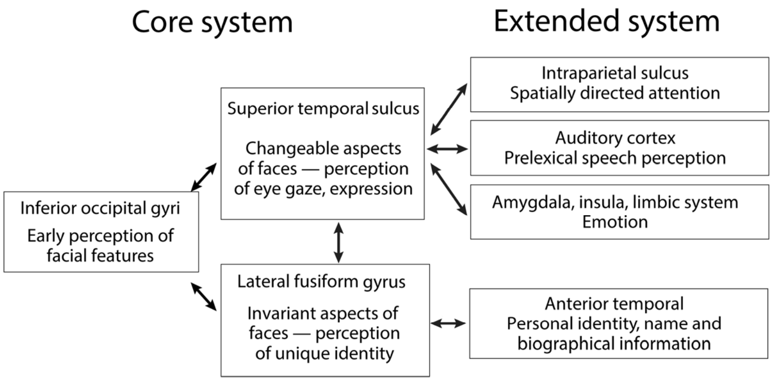

Figure 2.1. A distributed model for the processing of variant and invariant characteristics of facial information. At the core of the system lies a system dedicated to the visual analysis of faces, comprising occipitotemporal regions such as fusiform face area (FFA). The extended system is shared between the face processing system and other cognitive systems, and is fed by limbic structures such as the amygdala (AM), and by the intraparietal sulcus (IPS), and highly interconnected with auditory cortex and more anteriorly situated regions of temporal cortex.

The above model corresponds to the notion that in the course of evolution, a 'labeled lines' (i.e. central representations dedicated to a particular type of stimulus, Adolphs, 2010) system has evolved to incorporate the communicatory functions of facial expressions. This is implemented by the extensive anatomical interconnectedness of the core system with the rest of the brain, providing a highly integrated perception-action network. One of the most prominent propositions for the coupling of perception and response preparation and execution is the dual- model of saliency processing as formulated by LeDoux (1996). First, a fast thalamo-amygdaloid-response route for the processing of salient features in the environment is proposed, a process devoid of cortical involvement. This route enables rapid reflexive action, such as fight-flight behavior. Secondly, a relatively slower thalamo-cortical-response route operates in parallel with the fast thalomo-amygdaloid route. This route involving the frontal cortex allows for a more elaborate evaluation and, if necessary, regulation of the affective stimulus (LeDoux, 1996).

Facing Fear

Studies examining behavioral effects of emotional stimuli demonstrate that both negative and positive emotional facial expressions can bring about a series of central and peripheral physiological processes linked to action tendencies (Dalgleish, 2004; Vuilleumier & Pourtois, 2007; Williams et al., 2006). Especially fearful facial expressions play a crucial role in conveying social threat signals associated with fight-flight behavior (Adams, Ambady, Macrae, & Kleck, 2006; Frijda, 1986). Even outside conscious awareness, fear is able to elicit robust amygdala activity, enabling the rapid sensitization of response circuits bound to action preparation (Whalen et al., 2004). Experimental studies in primates have provided evidence for anatomical and functional coupling of limbic structures such as amygdala and the cortical motor areas. The supplementary motor area, which is highly interconnected with primary motor cortex (M1) and the spinal cord, is richly linked with motor cingulate areas (Morecraft & Van Hoesen, 1998). These motor cingulate areas are in turn connected to anterior cingulate areas and other components of the limbic system, providing an anatomical substrate for limbic modulation of motor control (Oliveri et al., 2003). TMS provides for a means to directly index stimulus-induced changes in cortical activity. When delivered over M1, the peripherally measured motor evoked potential (MEP) can be used to study the physiology of corticospinal conduction (Rösler & Magistris, 2008). Employing a paradigm in which TMS was delivered time-locked to the presentation of fearful, happy and neutral facial expressions, we directly tested the notion of increased M1 activation in response to social cues of threat.

Facing Fairness

A further question takes the notion of perception-action links orchestrating response patterns to emotional facial expressions a step further. This question is whether our evolutionary heritage that shaped the perception-action link is also reflected in social contexts that transcend the individual's direct interest. Throughout its development, mankind gave rise to societies based on a division of labour and resources between genetically unrelated individuals (Fehr & Fischbacher, 2003). In order for unrelated individuals to live together in such large groups, implicit social norms such as fairness enable cooperation and are therefore paramount in maintaining social homeostasis (Fehr & Fischbacher, 2004). Observational studies in our closest primate relatives have provided for a window onto the dynamics that shaped the development of our social relationships and response patterns throughout the course of human development (de Waal, 2012). The Perception-Action Model (PAM) as formulated by Preston and de Waal (2002) is the theoretical resultant of many of these observational and experimental studies, and still remains a guideline for the interpretation of many present studies. The PAM is a theoretical framework that aims to reconcile different empirical findings on the topic of empathy (Preston & de Waal, 2002). Empathy can be defined as a multi-layered construct, and encompasses a) the ability to share the emotional state of another, b) assess the reasons for the other's state and c) the ability to take the perspective of the other (de Waal, 2008). Importantly, empathy should not be confused with sympathy, as empathy can be *any* shared emotional experience as a result of perceiving the other, whereas sympathy is confined to the heightened awareness of the (distressing) situation the other is in, and the recognition that this situation should be alleviated (Wispe, 1986). Empathy therefore is a process, instead of a behavioral repertoire, and can thus be regarded a superordinate category including any kind of phenomenon that depends on this mechanism (Preston & de Waal, 2002). Figure 2 graphically depicts the PAM and its constituting motor and emotional behaviors. Modelling motor behavior as well as emotional behavior as dependent on the same mechanism provides a parsimonious explanation for human learning, social coordination (including the communication about impending danger) and the assistance of conspecifics in need (de Waal, 2012).

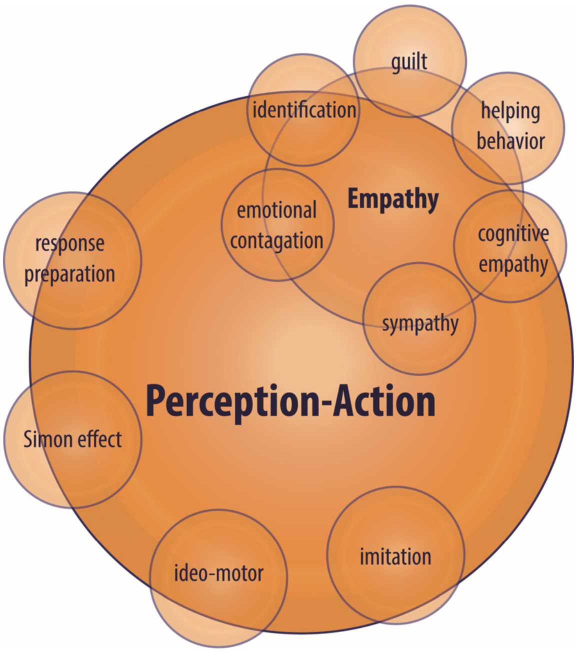

Figure 2.2. The perception-action model as proposed by Preston & de Waal (2002). The perception-action link is the base mechanism, or superordinate class, on which motor behavior as well as emotional behavior rely. Motor behaviors such as imitation and response preparation are regarded relatively simple forms of perception-action coupling observed in a wide variety of species, whereas empathy, with increasing levels of perspective taking capacities (e.g., cognitive empathy, helping behavior) requires higher forms of brain complexity and size. Adapted from Preston & de Waal, 2002.

A compelling demonstration of the perception-action link is the discovery of mirror neurons in the monkey premotor area F5 (di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992). In their 1992 study, the Rizzolatti group showed that neurons in the rostral part of the monkey premotor cortex not only discharge when performing goal-directed actions, but also when the monkey observed the experimenter perform a similar action (di Pellegrino et al., 1992). This mechanism provides for a parsimonious explanation for primate and human learning (Rizzolatti, Fogassi, & Gallese, 2001), and through overt behavioral imitation of facial expressions the observer is –literally- able to share intent or emotion (Bastiaansen, Thioux, & Keysers, 2009).

Furthermore, the PAM first distinguishes between proximate and ultimate causes of behavior (Preston & de Waal, 2002). Proximate causes for behavior govern responses of the individual to immediate factors in the environment, whereas ultimate causes eventually affect 'the particular DNA code of information with which individual of every species is endowed' (Mayr, 1961). A concept that is particularly sensitive to both proximate and ultimate causes of behavior is fairness. As noted, fairness is regarded a social norm that enables cooperation between unrelated individuals in large societies (Fehr & Fischbacher, 2004). Importantly, fairness arguably can be regarded a proximate as well as an ultimate cause of behavior, dependent on the current social relationship. In the present experiment, actors displaying emotional facial expressions were manipulated to be either fair or unfair in an economic bargaining game. During the expression of the facial emotions, the amount of facial motor imitation (mimicry) was recorded. While the game is on-going, we regard modulation of motor mimicry to result from proximate causes, whereas after the game, ultimate causes are expected to affect motor mimicry.

The *normative bias* aims to investigate how our brains through the course of evolution have been shaped to incorporate the experience of our ancestors. Through a mechanism of close coupling of perception and action-induced activation patterns, a low-cost mechanism for learning and social coordination is proposed.

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Fearful faces selectively increase corticospinal motor tract excitability: a transcranial magnetic stimulation study

Chapter 3

Schutter, D.J.L.G., Hofman, D. and van Honk, J. (2008).

Psychophysiology, 45(3): 345-8.

Abstract

Fearful facial expressions are danger signals that rapidly trigger a cascade of neurobiological processes defensibly associated with action preparation. However, direct evidence for the activating effects of fearful facial expressions on the motor system is absent. The current transcranial magnetic stimulation (TMS) study investigated whether fearful facial expressions selectively increase corticospinal motor tract (CST) excitability. Focal TMS was applied over the left primary motor cortex during the exposure of fearful, happy, and neutral facial expressions in 12 healthy right-handed volunteers. Changes in CST excitability using the motor evoked potential (MEP) were recorded. Results showed significant selective increases in MEP to fearful facial expressions. These findings provide the first direct evidence for selective increases in CST excitability to threat and contribute to evolutionary views on emotion and action preparedness.

Introduction

The ability to rapidly attend and react to emotional facial expressions is critical for social communication and survival (Blair, 2003, 2004). This notion is supported by numerous studies showing that emotional faces trigger a cascade of central and peripheral physiological processes associated with action preparedness (e.g., Dalgleish, 2004; Frijda, 1986; Vuilleumier & Pourtois, 2007). Positive emotions expressed by, for instance, happy faces have been argued to promote approach-related behaviors, whereas negative emotions expressed by, for instance, fearful faces would induce avoidance (Davidson, 1998). However, even though happy facial expressions may be inviting and thus have properties of reward, it is unlikely that they will rapidly activate approach systems (cf. van Honk & Schutter, 2006)From an evolutionary point of view, rapid action to facial expressions is only necessary in the case of threat (Ohman, 1986). Interestingly, increases in the corticospinal motor tract (CST) excitability to emotional stimuli have been demonstrated with transcranial magnetic stimulation (TMS) (Baumgartner, Willi, & Jancke, 2007; Hajcak et al., 2007; Oliveri et al., 2003). Baumgartner and colleagues found evidence for increased CST excitability in response to simultaneously presented emotional pictures and congruent music. Comparable findings were reported by Hajcak and colleagues, who measured higher CST excitability in healthy volunteers while they viewed pleasant and unpleasant scenes. Oliveri and colleagues provided evidence that the supplementary motor cortex (SMA) may act as a neural gateway in conveying emotion-related information from the limbic system to the primary motor cortex for initiating action programs. Taken together, these findings show that emotional experience and the motor system are closely related. Facial expressions serve important communicatory functions in humans, but these functions differ between the expressions. Fearful facial expressions are silent threat signals and crucial for survival, as they rapidly prepare the organism for action (Anderson & Phelps, 2001). Happy facial expressions, on the other hand, may have inviting and rewarding properties but are less likely to induce the rapid action preparation associated with fight–flight behavior. The aim of the present study was to test these hypotheses by measuring CST excitability changes to fearful, happy, and neutral facial expressions by applying focal TMS to the left primary motor cortex in healthy volunteers.

Methods

Participants

Twelve healthy nonsmoking right-handed volunteers (4 men), aged between 19 and 29 years, mean±SD, 23.5±3.1, were recruited at Utrecht University, The Netherlands. None of the participants had a history of psychiatric or neurological conditions and all had normal or corrected-to-normal vision. The participants received oral and written information prior to the study, and informed consent was obtained. All volunteers were unaware of the aim of the study and were paid for participation. The study was in accordance with the standards of the Declaration of Helsinki.

Facial expressions

The facial stimuli consisted of photographs of seven actors taken from the Ekman and Friesen (1976) set and three actors from the Karolinska directed emotional faces set (Lundqvist, 1998). The 10 actors (5 women) each displayed a fearful, neutral, and happy facial expression. All stimuli were projected in the center of a 17-in. computer screen (70 Hz refresh rate) in gray scale on a black background at a distance of 150 cm. The images were 14 cm × 9 cm, the vertical and horizontal visual angles being 5.34° and 3.42°, respectively. To investigate the possible confound of luminance differences between the emotional facial expressions, luminance measurements (in cd/cm2) were performed with a PR-650 Spectroscan Spectrocolorimeter (Photo Research Inc., Chatsworth). An analysis of variance (ANOVA) demonstrated no significant effect of luminance between facial expression types, $F(2,8)=2.3$, $p=.16$, $\varepsilon=.63$. A fixation cross was visible continuously in between stimulus presentations. The facial expressions were presented for 250 ms, as previous studies have shown that presentation times of<250 ms evoke emotion-specific cortical brain potentials (Schutter, de Haan, & van Honk, 2004; Smith, Low, Bradley, & Lang, 2006). Ten fearful, 10 neutral, and 10 happy facial expressions were presented in random order. The interstimulus interval varied between 4800 and 5200 ms.

Motor evoked potentials

The electromyogram (EMG) was recorded using sintered 11 x 17 mm active Ag-AgCl electrodes with the ActiveTwo system (BioSemi, Amsterdam, The Netherlands) relative to the common mode sense (CMS) in a belly-tendon arrangement. The motor evoked potential (MEP) was recorded from the abductor pollicus brevis (APB). The active electrode was placed over the muscle belly of the APB. The reference electrode was placed over the proximal phalanx of the thumb. The ground electrode was attached to the wrist. The EMG signal was digitized at 16 kHz, low-pass filtered (-3 dB cut-off frequency: 3334 Hz; roll-off: 30 dB/octave), and high-pass filtered (-3 dB cut-off frequency: 20 Hz; roll-off: 24 dB/octave).

Magnetic brain stimulation

Focal TMS was applied with a modified 8-shaped iron core coil powered by a Neopulse biphasic magnetic brain stimulator (Atlanta, US), pulse duration was < 1 ms, maximum output 2300 A peak / 1750 Vac peak (~ 2 Tesla) over the left primary motor cortex.

Procedure

Upon arrival at the laboratory, participants were screened for contraindications to TMS (Keel, Smith, & Wassermann, 2001) and received oral and written information on the experiment. After informed consent was obtained, right handedness was assessed with the Edinburgh handedness inventory(Oldfield, 1971), mean±SD, 45±2.5. Next, volunteers were seated in a comfortable dentist chair and the EMG electrodes were attached. The right hand of the participant was placed on the upper part of the right leg. The arm was slightly flexed at the elbow (~140°). The subject was instructed not to the move the arm during motor threshold determination and the passive viewing condition. Resting motor threshold (MT) of the left hemisphere was then determined according to the standardized procedure as described by Schutter and van Honk (Schutter & van Honk, 2006), mean±SD, 55%±9.6% of maximum machine output. For determining the motor threshold, participants were seated upwardly in a dentist chair and asked to relax the arm contralateral to the site of stimulation by placing it on the upper leg with the palm of the hand facing upward. The coil was initially positioned on the scalp halfway between the vertex and the external auditory meutus. By moving the coil systematically in different directions by approximately 1 cm and gradually increasing TMS intensity (interstimulus interval: 5 s) the site for eliciting reliable thumb twitches (5 out of 5) was found. Next, intensity was decreased until 5 out of 10 consecutive pulses induced a visually identifiable twitch. Finally, the coil was moved again over the scalp to search for additional scalp sites that surpassed the 50% thumb movement criterion. If such a site was found, TMS intensity was further decreased according to the 50% criterion (Schutter & van Honk, 2006). The optimum scalp site for eliciting MEPs was marked with a waterproof felt-tip pen. Next, the room was darkened and MEPs were collected for the 30 facial expressions. The 120% MT TMS pulse was locked to the onset of face presentation with a latency of 300 ms. Earlier studies have shown that the onset of unmasked stimulus-driven changes in CST excitability is approximately 300 ms (Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000; Liddell, Williams, Rathjen, Shevrin, & Gordon, 2004; Oliveri et al., 2003).A levelling staff mounted on the coil secured the angle of coil throughout the experiment. In Figure 1 an overview of the procedure is shown.

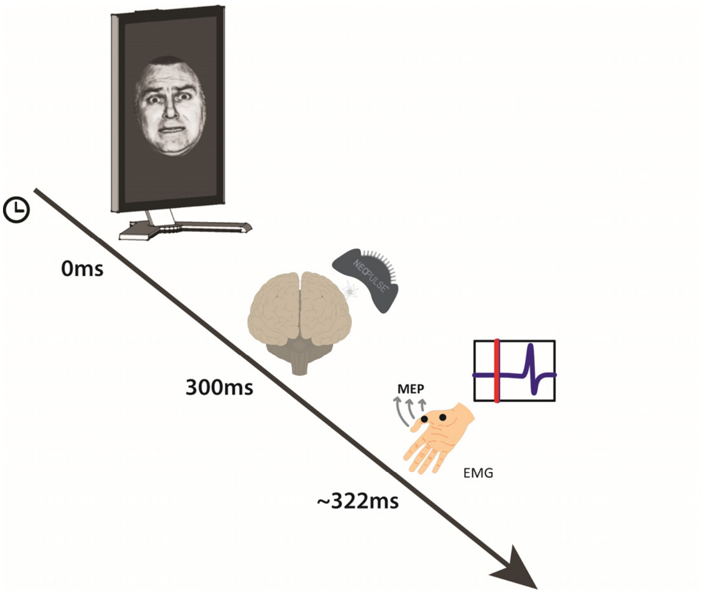

Figure 3.1. Schematic overview of the experimental procedure.

The experiment was concluded with an objective awareness check to verify that the participant could discriminate between the three different facial expressions with a 250-ms presentation time. The objective awareness task was a three-alternative forced-choice recognition check, using fearful, happy, and neutral facial expressions. In this procedure, the 30 faces used in the experiment were randomly presented for 250 ms. In advance, participants were explicitly told that the set contained the 10 neutral, 10 happy, and 10 fearful faces and were instructed to indicate whether the presented stimulus was a fearful, happy, or neutral emotional expression by pushing 1, 2, or 3 on the keyboard's numeric pad, respectively. Finally, subjects were debriefed and paid for participation.

Data reduction and analyses

The MEP was quantified as the peak-to-peak amplitude of the maximal EMG response. The mean rectified baseline EMG activity 1000 ms prior to the TMS pulse and the average MEP were calculated for each emotional facial expression. Analysis of variance (ANOVA) was performed to examine the effects of facial expressions on baseline EMG activity level and MEP. The Greenhouse–Geisser correction was applied to the p values and ε was reported when the degrees of freedom were greater than 1. The α level of significance was set at .05, two-tailed.

Results

TMS was well tolerated by all subjects. Binomial tests for deviation (33%) demonstrated that the participants were able to recognize the 250-ms presentations of the emotional facial expressions, mean±SD percentage correct, 95±4.4%, all ps<.001. The ANOVA showed a significant effect of facial expressions on MEP, F(2,10)=5.64, p=.01, ε=.97. Post hoc paired-samples t tests revealed significant MEP differences between fearful and neutral, t(11)=3.08, p=.01, and fearful and happy faces, t(11)=2.80, p=.02. MEPs following neutral and happy faces did not differ, t(11)=0.61, p=.56. The results could not be explained by expression-related differences in baseline EMG activity, F(2,10)=1.52, p=.24, ε=.54, or a relationship between baseline EMG activity and MEP as tested with Pearson's product moment correlations (all ps>.26). Figure 2 shows the significant increase in MEP after fearful as compared to happy and neutral faces.

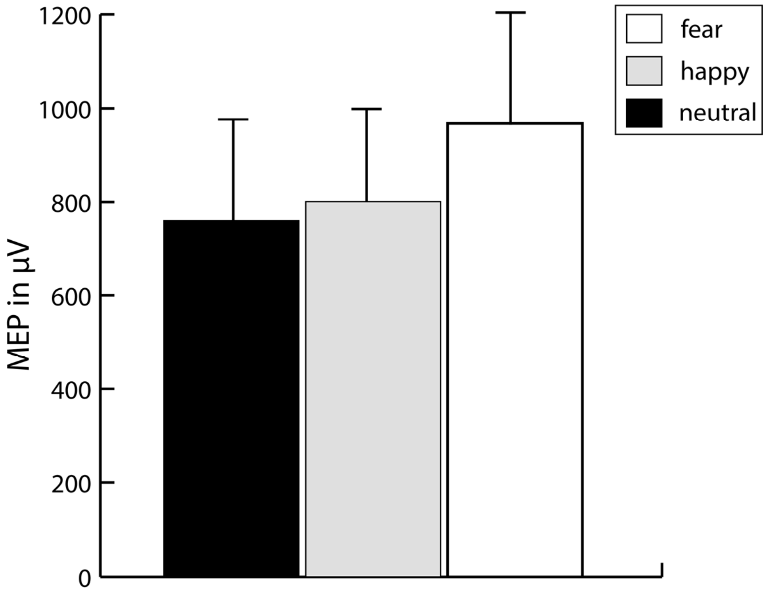

Figure 3.2. Mean MEP (in µV) to neutral, happy and fearful facial expressions. Error bars depict standard error of the mean.

Discussion

The present study provides the first direct evidence for selective increases in CST excitability to fearful facial expressions. These findings coincide with evolutionary views on the relation between threat signals and action tendencies (Ohman, 1986). Previous studies found significant increases in CST excitability for pleasant and unpleasant pictures from the International Affective Picture System as compared to neutral pictures (Baumgartner et al., 2007; Hajcak et al., 2007). The current results show significant CST increases to fearful as compared to happy and neutral facial expressions. This finding is in agreement with neuroimaging evidence demonstrating that fearful faces consistently activate brain structures underlying the detection and reaction to danger (Morris, Ohman, & Dolan, 1999). By silently signalling danger in the environment, fearful faces act as cues that rapidly prepare the organism for action that is critical for survival (Anderson & Phelps, 2001). A functional neuroanatomical link between threat perception and activation of the motor system has been provided by a previous TMS study with healthy volunteers that showed increased trait anxiety correlated to higher levels of CST excitability (Wassermann, Greenberg, Nguyen, & Murphy, 2001). CST hyper excitability may thus be a neurophysiological correlate of increased attention for threat as well as repetitive motor acts, commonly observed in anxiety disorders including obsessive compulsive disorder (Greenberg et al., 2000). Furthermore, selective attention to fearful facial expressions can be attenuated by reducing frontal cortical excitability with slow frequency repetitive TMS (van Honk, Schutter, d'Alfonso, Kessels, & de Haan, 2002). Our results show that the fearful facial expression is a physiologically more salient cue than the neutral and happy facial expressions, supporting evolutionary views of survival in asserting that environmental threat should immediately activate specific “defensive” brain circuits devoted to attention and action preparation (Davis & Whalen, 2001). According to the frontal asymmetry model of emotion, the processing of the avoidance-related emotion fear is associated with the right prefrontal cortex (Harmon-Jones, 2003; Schutter, de Weijer, Meuwese, Morgan, & van Honk, 2008; van Honk & Schutter, 2006); it can therefore be expected that the MEP of the APB muscle elicited from the right compared to the left motor cortex TMS following fearful face presentations will even be relatively larger. This asymmetrical increase will, however, be of a relative nature, as the organization of the motor system is primarily directed to functional cooperation between the left and right limbs. This makes it is highly unlikely that threat-related activation of the brain's defensive system will involve the right hemisphere exclusively. Furthermore, the APB muscle is often used in TMS studies because the muscle can be activated relatively easily due to strong cortico-spinal projections that results in lower motor thresholds (Brouwer & Ashby, 1990; Hajcak et al., 2007). Classifying intrinsic hand muscles in terms of flexor or extensor muscles, the APB functionally belongs to the group of extensor muscles and has been associated with approach-related behavior (fight). The adductor pollicis brevis, on the other hand, can be categorized as a flexor muscle and has been linked to withdrawal-related (flight) behavior (Rotteveel & Phaf, 2004; van Peer et al., 2007). This distinction allows for studying the frontal asymmetry of emotion in terms of differential activation of muscles groups in future TMS research.

In conclusion, this study provides the first direct evidence for selective increases in CST excitability to fearful facial expressions and concurs with evolutionary views of emotion and action preparedness

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Fairness modulates non-conscious facial mimicry in women

Chapter 4

Hofman, D., Bos, P.A.*, Schutter, D.J.L.G. and van Honk, J. (2012).*

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**: shared authorship*

Abstract

In societies with high cooperation demands, implicit consensus on social norms enables successful human coexistence. Mimicking other people's actions and emotions has been proposed a means to synchronize behaviour, thereby enhancing affiliation. Mimicry has long been thought to be reflexive, but it has recently been suggested that mimicry might also be motivationally driven. Here, we show during an economic bargaining game that automatic happy mimicry of those making unfair offers disappears. After the bargaining game, when the proposers have acquired either a fair or unfair reputation, we observe increased angry mimicry of proposers with an unfair reputation and decreased angry mimicry of fair proposers. These findings provide direct empirical evidence that non-conscious mimicry is modulated by fairness. We interpret the present results as to reflect that facial mimicry in women functions conditionally, dependent on situational demands.

Introduction

Implicit agreements underlie much of human social behaviour, to the extent that they orchestrate social relations and interactions, and promote organizational and social coordination (Henrich et al., 2001). Fairness has been proposed as an implicit shaper of social behaviour. For example, fairness has been shown to restrict profit seeking in economic markets (Kahneman, Knetsch, & Thaler, 1986), to shape behaviour in economic games as a function of reputation (Nowak, Page, & Sigmund, 2000) and to mould instant neural responses to economic offers (Sanfey, Rilling, Aronson, Nystrom, & Cohen, 2003). In general terms, for species with highly developed sharing and cooperation standards, answering to fairness principles is essential to all its members (de Waal, 2008).

In recent theoretical accounts of human fairness judgments, the role of emotions is progressively underscored (Haidt, 2001, 2007). Whereas earlier perspectives focused on cognitive development in moral reasoning (Kohlberg, 1969), emphasis has now shifted to the role of intuitions, stressing the automatic character of instant affective judgments (Haidt, 2001, 2007). A recent illustration of the automaticity of moral judgements is provided by a study of facial motor activity in response to several categories of disgust (Chapman, Kim, Susskind, & Anderson, 2009). In their study, the authors show facial expressions in response to moral disgust to be remarkably similar to the expressions in response to both toxic and contamination-based disgust, suggesting that the categories originally eliciting disgust have been enlarged to include the higher order forms of moral disgust (Chapman et al., 2009; Rozin, Haidt, & Fincher, 2009). Interestingly, the Chapman et al study (2009) shows that automatic facial motor activity as well as self-reported disgust are proportional to the degree of unfairness of offers made in the Ultimatum Game, illustrating its parallel relation with core motivational systems as well as human behaviours.

Facial motor activity has extensively been studied in the context of imitation (Niedenthal, Mermillod, Maringer, & Hess, 2010), and is generally referred to as facial mimicry. Mimicry has been proposed a low-cost, low-risk reflexive behaviour sub-serving the creation of affiliation and bonding (Bourgeois & Hess, 2008; Lakin & Chartrand, 2003; Lakin, Chartrand, & Arkin, 2008). The ‘chameleon effect’, as mimicry has been labeled

(Chartrand & Bargh, 1999) is suggested to result from a perception-action link; interindividual linkage arises from the integration of the behaviours of others into an individual's representations, thus facilitating coordinated activity (Chartrand & Bargh, 1999; Preston & de Waal, 2002). As described in the Perception-Action-Model (PAM) by Preston & de Waal, this interindividual linkage facilitates group living, with its critical dependency on social cooperation, and this group living further shaped this mechanism to form the foundation of empathic behaviours such as state matching and emotional contagion (Preston & de Waal, 2002). Therefore, through behavioural conformation to the interaction partner's attitudes, opinions and behaviours higher order social coordination is promoted (Jones, 1965; Lakin & Chartrand, 2003; Preston & de Waal, 2002). In other words, mimicry serves to automatically and non-consciously synchronize people's affect and promote social cohesion, but recent evidence shows that mimicry can also be motivationally driven.

Modulation of automatic affiliative mimicry has been illustrated by studies showing that social contexts such as group membership impact facial mimicry (Bourgeois & Hess, 2008) and that affiliative mimicry increases in response to social exclusion (Lakin et al., 2008). In the latter study for example, it was shown that to reinstate group membership after social exclusion, participants who were excluded in a cyber-ball game mimicked their interaction partner more than included participants (Lakin et al., 2008) .

Mimicry can thus be regarded as motor behaviour representing more than mere imitation (Lakin et al., 2008). It is affected by motivational systems and although non-conscious, it is an omnipresent characteristic of human non-verbal communication (R. van Baaren, Janssen, Chartrand, & Dijksterhuis, 2009). Social context modulates one's mimicry, and one's mimicking in turn promotes attachment (Lakin & Chartrand, 2003; Lakin et al., 2008). Mimicry facilitates and fosters interpersonal bonding, but to what extent it is able to further support successful human coexistence is unknown.

We here present an experiment in three blocks that incorporates measures of facial mimicry in response to emotional facial expressions during and after an economic bargaining game. First, we determine baseline facial mimicry to morphs of happy and angry facial expressions. In the second block, we manipulate fairness of offers in a bargaining game and investigate whether and how unfair offers directly affect facial mimicry. In the final block, facial mimicry in response to unfair and fair players is assessed to examine whether and how mimicry is affected by the reputation the players acquired in the encounters during the game.

Method & results

Participants

30 female participants (mean age: 20.8 years, S.D.: 2.1 years) performed a series of three experimental blocks. Only female participants were included since it has been shown that females are more facially reactive than males (Dimberg & Lundquist, 1990). Electromyographic (EMG) data from four participants were unusable due to absence of detectable changes in motor activity, yielding a final N of 26. Participants were told that the electrodes served to monitor 'physiological changes' as a cover story. None of the participants had a history of psychiatric or neurological conditions. Written informed consent was obtained and volunteers received financial compensation for participation. The study was conducted in accordance with local ethical guidelines.

Measures of facial motor activity

EMG responses were recorded from bipolar electrode montages from the left corrugator supercilii and zygomaticus major muscles to assess motor responses to angry and happy facial expressions respectively. (Fridlund & Cacioppo, 1986). The ground consisted of the active common mode sense and passive driven right leg electrodes (see www.biosemi.com) that were placed midline on the forehead. EMG was recorded at a sampling rate of 2048 Hz using a Biosemi ActiveTwo amplifier, and stored for off-line analysis.

Raw EMG traces were 30-500 Hz band pass filtered. For each trial, -1000 ms to +4000 ms response windows were selected time-locked to morph onsets. Baseline correction was applied by subtracting the averaged EMG activity 1000 ms pre-stimulus onset period from the post-stimulus onset values. EMG signals were then rectified and averaged in 250 ms intervals. The resulting 16 time bins were entered into statistical analyses.

Block 1: baseline facial mimicry

In the first block, 16 morphing neutral-to-happy and 16 morphing neutral-to-angry facial expressions were presented. The morphs were displayed by two female and two male actors, selected from the Ekman and Friesen Pictures of Facial Affect Set (Ekman, 1976). Each morph was displayed for 2000ms, and the last frame displaying the full emotional expression for an additional 2000ms. Each trial started with a 1000ms fixation cross followed by the morph, and ended with a variable intertrial interval of 3000-6000ms to avoid habituation to the presentation of the facial morphs, see figure 1A.

Results and discussion

The 2x2x16 (muscle x emotion x epoch) multivariate ANOVA revealed the typical emotional modulation of muscular activity: for zygomatic major greater activity in response to the happy morph, $F(1,15) = 102.8$, $p < .001$, $\eta^2 = .873$; for corrugator supercilii greater activity in response to the angry morph, $F(1,15) = 87.8$, $p < .001$, $\eta^2 = .854$. Group-averaged EMG traces recorded from zygomaticus major and corrugator supercilii in response to happy and angry morphs respectively served as reference data for the blocks 2 and three.

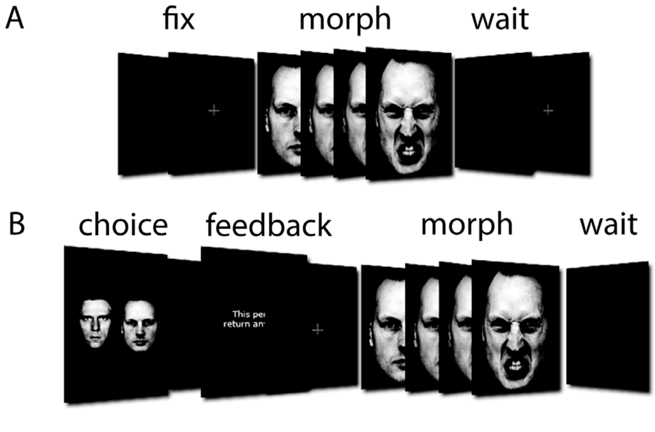

Figure 4.1. Panel a: single trial in blocks 1 and 3. Panel b: single trial in block 2.

Block 2: Facial mimicry and fairness behaviours

The fairness manipulation was incorporated in the second block. At the beginning of the game, participants were endowed with 1600 points, of which the remainder after the experiment had finished was converted to money and paid to the participant. Each of 64 trials started with a 2-option forced choice: two neutral looking confederates are presented, to one of which the participant has to donate 25 points. The confederates are pre-programmed to be either fair (75% of the trials the participant's donation is doubled and split, each player receives 50%), or unfair (75% of the trials the participant's donation is not returned, confederate receives 100%, participant 0%). After the feedback window, the confederate who was chosen by the participant displayed either the happy or angry 2000 ms morph, identical to those used in block 1. Figure 1B depicts a single trial of the bargaining game. Here, the instant impact of fair or unfair offers on EMG responses to happy and angry facial morphs during on-going interaction can be assessed.

Results and discussion

Compared to baseline mimicry, fairness during the bargaining game modulates mimicry of happy facial expressions as measured from zygomatic major, $F(2,30) = 46.7$, $p < .001$, $\eta^2 = .757$). Post-hoc analyses of the averaged activity of all epochs showed that the effect was due to the absence of mimicry after people were confronted with unfair offers, $t(15) = 9.62$, $p < .001$, $d = 1.87$. Fair offers trended towards a small decrease ($t(15) = 1.99$, $p = .066$, $d = .33$), see figure 2B for the group averaged EMG traces plotted against baseline mimicry. Corrugator supercilii also showed a fairness effect on mimicry of the angry morph, $F(2,30) = 3.5$, $p = .042$, $\eta^2 = .191$. Follow-up analyses however, were unable to further specify the effect as separate contrasts remained non-significant, p's > 0.24, see figure 2A.

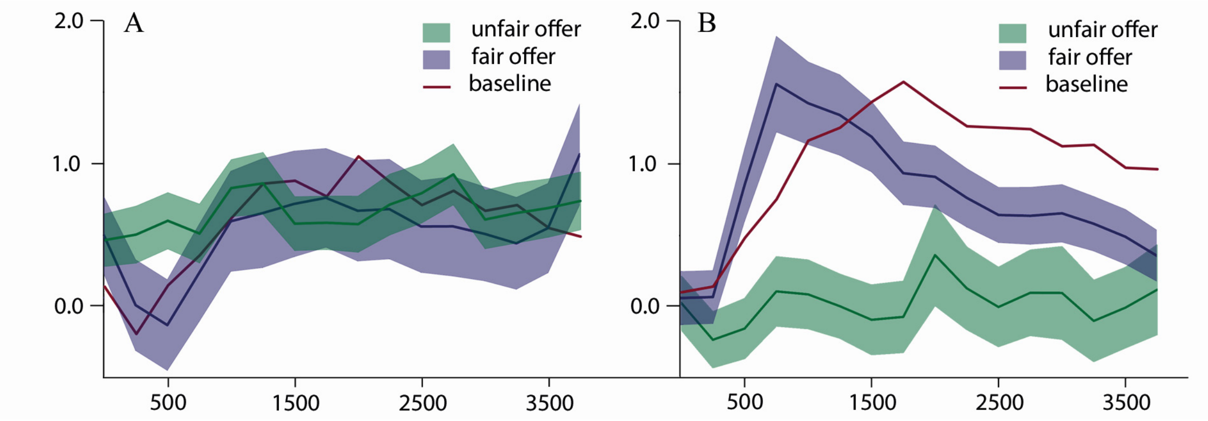

Figure 4.2. Panel a: mean rectified EMG responses in the corrugator supercilii to fair and unfair offers. Panel b: mean rectified EMG responses in the zygomaticus major to fair and unfair offers. Shaded colours depict standard error of the mean plotted around the mean EMG traces. X-axis depicts time from stimulus onset in milliseconds. Y-axis depicts EMG response in microvolts.

Block 3: Facial mimicry and fairness reputation

Experiment 3 essentially resembles experiment 1, but with the critical additional circumstance that now the confederates displaying the morph have earned the reputation of being either fair or unfair. Now, the interaction of fairness reputation with emotional expression can be assessed.

Results and discussion

Here, corrugator supercilii reveals modulation by reputation, $F(2,30) = 20.73$, $p < .001$, $\eta^2 = .58$), an effect quantified by increased angry mimicry towards unfair confederates, $t(15) = -4.21$, $p = .001$, $d = .26$, and decreased angry mimicry towards fair confederates, $t(15) = 3.66$, $p = .002$, $d = .36$, see figure 3A. Zygomatic major here showed no effect of fairness, $F(2,30) = 0.62$, $p = .54$, $\eta^2 = .04$, see figure 3B.

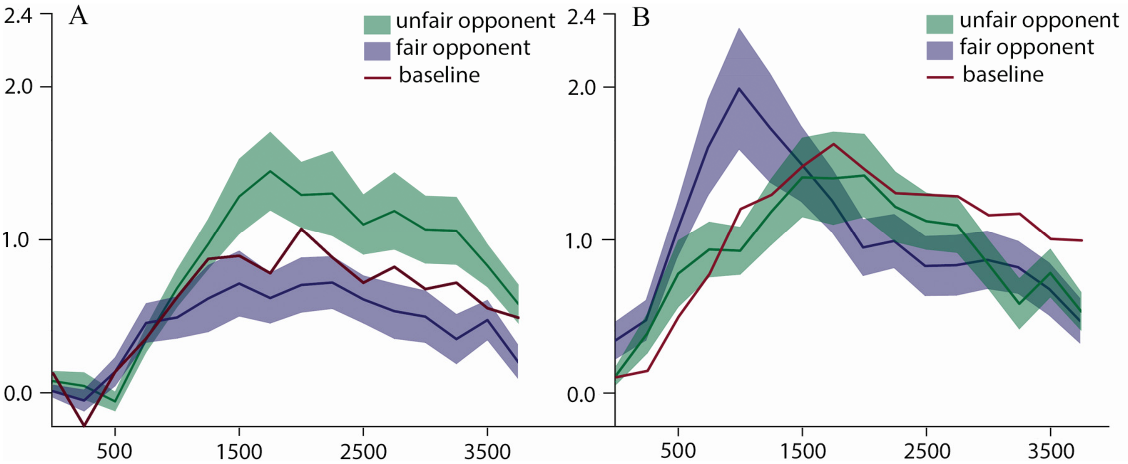

Figure 4.3. Panel a: mean rectified EMG responses in the corrugator supercilii to fair and unfair reputations. Panel b: mean rectified EMG responses in the zygomaticus major to fair and unfair reputations. Shaded colours depict standard error of the mean plotted around the mean EMG traces. X-axis depicts time from stimulus onset in milliseconds. Y-axis depicts EMG response in microvolts.

General discussion

In a series of three blocks, we recorded facial mimicry in response to emotional facial expressions. In the first block, baseline facial mimicry in response to emotional facial expressions was determined. In block 2, the instant impact of fair and unfair offers in an economical bargaining game on facial mimicry was assessed. Block 3 served to evaluate whether mimicry would show modulation by fairness reputation earned during the bargaining game.

We found that compared to baseline facial mimicry, unfair offers attenuate the imitation of emotional facial expressions during the bargaining game. Notably, mimicry of happy facial expressions after unfair offers is virtually absent. Here, we observe a remarkable divergence from the imitate-to-facilitate character mimicry has been ascribed. In the context of norm violation, facial mimicry, contrary to actively promoting interpersonal bonding in social interaction, shows clear attenuation. Attenuation of happy mimicry after unfair offers might passively communicate resentment, thereby discouraging the preceding behaviour by not providing reinforcing feedback. After the bargaining game has ended, mimicry displays distinct modulation by reputation as acquired during the game. Compared to baseline, mimicry of happy facial expressions is unaffected, irrespective of reputation. In response to facial anger however, mimicry reveals a selective modulation: attenuated in response to fair reputation but strengthened in response to unfair reputation. In line with studies illustrating the importance of social reputation in societies (Nowak et al., 2000; Tennie, Frith, & Frith, 2010), reputation selectively affects facial mimicry.

A possible interpretation of the observed modulation of facial mimicry is provided by the framework of the PAM as well as psychological theories stating that the extent to which an individual perceives the state of an interaction partner is affected by their interdependence (Holland, Roeder, van Baaren, Brandt, & Hannover, 2004; Preston & de Waal, 2002; R. B. van Baaren, Maddux, Chartrand, de Bouter, & van Knippenberg, 2003). This interdependence has been suggested to vary over time and between situations: proximate goals can increase interdependence to facilitate cooperation, but also decrease interdependence when efforts are frustrated (Preston & de Waal, 2002). Long-term goals in a similar fashion are modulators of interdependence, but here social relationships or groups might have goals spanning up to, or even beyond a lifetime (Preston & de Waal, 2002). Within this framework, the differential modulation of facial mimicry can be rooted in fairness-modulated interdependence, were proximate and distal goals show different modulation of facial mimicry. This remains speculative however, and future studies might incorporate further behavioural measures to be able to ascribe function to measures of facial mimicry.

Therefore, our data suggest mimicry to be a context-sensitive means of adaptive non-conscious communication. They empirically corroborate the recently coined suggestion that there are circumstances in which mimicry is not merely assimilative, but can act in a complementary way (van Baaren et al., 2009). Moreover, the data illustrate that implicit processes such as mimicry may serve one’s own as well as group benefit by reinforcing norm compliance (Frith & Frith, 2012). The pattern of mimicry modulation observed in the two experimental blocks may suggest a strategic and adaptive property arising from the repertoire observed: it not only is able to adopt a low risk strategy when profitable future interaction is at stake, but can turn to enforcement strategies when favourable.

These results may well inform and aide future research on the nature and purpose of non-conscious processes involved in human social interaction. Mimicry may, although involuntary and automatic, serve concrete and instant social goals, as well as goals that transcend immediate individual concern. It further demonstrates that non-conscious processes have adaptive properties (Bargh & Williams, 2006; Custers & Aarts, 2010), in that they are recruited dependent on situational demands (Bijleveld, Custers, & Aarts, 2009; Lakin et al., 2008) We conclude that fairness is a shaper of the process of non-conscious mimicry, and that mimicry should be regarded as a behaviour that extends beyond the facilitation of affiliation, and may be strategically employed to enforce norm compliance.

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The individual bias

Asymmetry in emotion: an overview

Chapter 5

Based on: Hofman, D. (2008).

Netherlands Journal of Psychology. 64 (3): 112-118

The emotional brain

Emotions are closely coupled to motivation and action preparation (Frijda, 1986). The processing and experience of emotions involves a circuitry comprised of cortical and subcortical structures (A.R. Damasio, 1994; James, 1884; LeDoux, 1996; Papez, 1937; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008). Even though researchers generally agree upon the brain structures involved in motivation and emotion, theories differ in their emphasis on either subcortical or cortical structures. The classical example here is LeDoux' dual pathway model in which one pathway involves a fast thalamo-amygdalar route, whereas the second pathway capitalizes on the evaluative and regulatory involvement of cortical brain areas. (LeDoux, 1996). Equally influential, the somatic-marker hypothesis, (closely related to the ideas of William James (1884)) is the formal proposition by Antonio Damasio stating that emotions arise from bodily responses generated by the autonomous nervous system in response to biologically relevant events. Somatic markers are initiated by the amygdala and evaluated in the ventromedial (vm) PFC allowing humans to consciously work their way through situations of complexity and ambiguity (A. R. Damasio, 1996).

Successful as normative research models, the propositions made by Ledoux and Damasio however do not pay particular attention to the effect of the regulatory influence exerted by the PFC in the processing of emotion and motivation. Individual differences in social and affective behavior may well arise from differences in the extent to which the PFC is able to successfully regulate and evaluate salient environmental cues. The basic action tendencies in coping with environmental stress are either to approach or to withdrawal from the situation. Such behavior is observed in the simplest of species up to primates, and is argued to be present at any level of phylogeny where behavior itself is present (Davidson, 1992, 2004). Particularly with the evolvement of networks complex as the human brain, functional asymmetries may have evolved to preclude conflicts between action tendencies (Davidson, 2004; van Honk & Schutter, 2006). Studies into the nature of PFC involvement in emotion and motivation have given rise to a successful cortical centred theory on affective and social processing: The frontal asymmetry of emotion model.

Frontal laterality and affective valence

The notion of asymmetrical hemispheric engagement in emotional processing was formulated as early as the late 19th century (Luys, 1881), but it took almost 100 years more for the first experimental paper on right hemispheric involvement in general emotional processing appeared (Schwartz, Davidson, & Maer, 1975). The authors demonstrated increased right hemispheric activation when confronting subjects with emotional questions as compared with non-emotional questions. Lateral eye movements were used to measure hemispheric engagement, and using this method, Schwartz and colleagues showed that increased right hemispheric activation was linked to emotional and spatial processing, whereas increased left hemispheric activity was associated with non-emotional and verbal processing (Schwartz et al., 1975). In 1979, the first publication using electroencephalographic (EEG) recordings in the study on the frontal lateralisation of emotion was published (Davidson, Schwartz, Saron, Bennett, & Goleman, 1979). In this paper, Davidson and colleagues proposed a lateralisation of positive emotions to the left PFC and negative emotions to the right PFC, a proposition that has become known as the *Valence Model*. Evidence supporting the lateralised involvement of the left and right PFC in positive and negative emotions cumulated through electrophysiological studies showing that positive-emotion eliciting questions yielded increases in left PFC activity, whereas negative-emotion eliciting questions showed decreases in right PFC activity (Ahern & Schwartz, 1985). In further support of the valence model, it was demonstrated that EEG asymmetries predicted the difference between experienced positive and negative affect (Tomarken, Davidson, & Henriques, 1990). In this particular study, positively rated video clips were associated with increased relative left activity, whereas negatively rated video clips were associated with increased relative right-sided activity. In addition to state-induced changes of PFC activity, it was also shown that the relation between resting state EEG asymmetries and positive and negative affect is stable over time (Tomarken, Davidson, Wheeler, & Doss, 1992). This suggests that frontal EEG asymmetries reflect stable trait-like personality characteristics in terms of the propensity to experience positive or negative affect.

In one of the first reviews on lateralized emotional processing the experimental results supporting the positive-negative distinction was discussed and three possible variants of emotion lateralisation were considered: (1) Emotions are better recognised by the right hemisphere, (2) Control of emotional expression generally takes place in the right hemisphere, and (3) The right hemisphere is specialised for dealing with negative emotions and the left hemisphere is specialised for dealing with positive emotions (Silberman & Weingartner, 1986). As noted by the authors, many of the results still needed replication and the mechanisms underlying frontal lateralisation were not well understood. Nonetheless, it was concluded that the available evidence provided support for the view that emotions are processed by the PFC in a lateralised fashion.

However, the vast majority of the research on the *Valence Model* was conducted using the Positive and Negative Affect Scale (PANAS) (Watson, Clark, & Tellegen, 1988). Properties assessed by the PANAS include attentiveness, interestedness, alertness, enthusiasm, excitement and inspiration for positive affect, and distress, hostility, irritability, anxiety and shame for the negative affect. Since the positive affect scale includes words such as ‘interested’, and the negative scale includes words such as ‘afraid’, several theorists argued that the self-report that results from the scale might be confounded with approach- and withdrawal-related motivation (Watson, Wiese, Vaidya, & Tellegen, 1999).

From affective valence to motivational direction

The lateralised involvement of the PFC in the processing of positive and negative emotions has yielded a substantial body of evidence in support of the valence model. However, in the late 1990s, research started to appear in the literature that yielded conflicting results. In these studies, the implicit assumption that approach-related motivation is associated with positive emotions was questioned. Harmon-Jones and Allen (1997) first introduced the concept of approach and withdrawal-related motivation in the PFC lateralisation theory of emotion. In one of their first experiments, participants’ baseline EEG asymmetry was determined to measure relative hemispheric dominance. The motivational tendency to approach was measured by the behavioural activation scales (BAS), whereas the motivational tendency to withdrawal was measured by the behavioural inhibition scales (BIS) (Carver & White, 1994). Results showed that the BAS score was related to a dominant left-sided PFC asymmetry. Trait BIS, however, yielded no significant relation with relative right PCF activity, possibly due to conceptualisation differences between the withdrawal system as defined by Davidson (1992) and the BIS system as defined by Gray (1990).

Anger and motivational direction

The introduction of approach- and withdrawal-related motivation in the asymmetry model of emotion has resulted in an alternative model that discarded the valence component. In the motivational direction model, approach-related emotions are lateralised to the left PFC, whereas avoidance-related emotions are lateralised to the right PFC. In this model, the negative emotion anger is associated with approach-related behaviour and lateralised to the left PFC. This amendment to the original valence model allows for a direct test of the two models: 1) If the asymmetry in frontal cortical activity represents emotional valence, then higher trait anger should be reflected in relatively higher right hemispheric frontal activity; 2) If the asymmetry in frontal cortical activity represents motivational direction, then higher trait anger should be reflected in relatively higher left hemispheric frontal activity. In line with the motivational direction model, trait anger as measured by the Buss and Perry Aggression Questionnaire (Buss & Perry, 1992) was correlated to relatively greater left frontal activity (Harmon-Jones & Allen, 1998). Investigating the possibly confounding effects of attitude towards anger, it was shown that a positive attitude toward anger did not correlate with the relative left over right frontal activity (Harmon-Jones, 2004b). These results demonstrate that positive attitude toward anger could not account for the reported relation between trait anger and relative left over right frontal activity. Furthermore, the relationship between relative left over right prefrontal activity and state-induced anger was explored in an experiment where volunteers were deliberately insulted (Harmon-Jones & Sigelman, 2001). In accordance with their hypothesis, it was shown that insulted participants demonstrated a significant increase in left PFC activity and in turn were more likely to act aggressively. In sum, this research strengthens the claim that, despite its negative valence, the processing of the emotion anger is lateralised to the left PFC.

Manipulations of frontal asymmetry

Thus far, research demonstrating that approach-related tendencies are lateralised to the left and withdrawal-related tendencies are lateralised to the right prefrontal cortex has mainly been correlational by nature. These correlational findings show that brain activity and function are statistically related. However, it does not tell us whether this frontal brain asymmetry is cause or effect of the differences in approach and withdrawal-related behaviour.

In the cognitive and affective neurosciences, one of the few instruments able to demonstrate causal relationships between brain and behaviour is transcranial magnetic stimulation (Schutter, van Honk, & Panksepp, 2004). When TMS is applied repetitively (rTMS) with frequencies around 1 Hz cortical excitability is reduced, whereas stimulation frequencies of 5 Hz and greater increase cortical excitability (Wassermann, 1998).

The first low frequency rTMS study addressing the issue of PFC asymmetry in the processing of anger deployed a pictorial emotional Stroop task (d'Alfonso, van Honk, Hermans, Postma, & de Haan, 2000). In the pictorial emotional Stroop task, subjects are instructed to name the colour of facial expressions as fast as possible. The mean colour-naming latencies of emotional facial expressions minus the colour-naming latencies of neutral facial expressions result in interference scores, an index of the processing of the emotional content of the facial expression presented. It was hypothesised that positive interference scores would increase following right PFC rTMS and would decrease following left PFC rTMS. In line with the hypotheses, right rTMS PFC resulted in selective attention to angry facial expressions, whereas left PFC rTMS resulted in selective attention away from the angry facial expressions. These were the first results showing a direct association between the modulation of PFC and the processing of angry facial expressions in terms of approach- (i.e., interference scores) and withdrawal-related behaviour (i.e., facilitation scores). Additionally, this study introduced the concept of hemispheric balance into the motivational direction model.

Using fearful facial expressions, the motivational-direction asymmetry of emotion found further support by a sham-controlled low frequency rTMS to the right PFC (van Honk, Schutter, d'Alfonso, Kessels, & de Haan, 2002). It was hypothesised that the attenuation of right cortical activity would result in a motivational shift towards approach-related behaviour, causing reduced attention to fearful facial expressions. Results showed vigilant attention for fearful facial expressions in response to the sham rTMS. Importantly, rTMS significantly reduced attention for fearful facial expressions demonstrating the hypothesised motivational shift towards approach-related behaviour. The shift in hemispheric dominance was further demonstrated in an interleaved rTMS-EEG experiment which showed contralateral increases in brain activity following low frequency rTMS to the right PFC (D. J. Schutter, van Honk, d'Alfonso, Postma, & de Haan, 2001)

To provide further support for the motivational-direction model, anger but not necessarily happiness should be processed by the left frontal cortex. In a recent experiment, sham and active low frequency rTMS was applied over the left and right PFC and emotional memory for angry and happy facial expression was examined (van Honk & Schutter, 2006). In agreement with the motivational direction model, significant reductions in memory for angry faces was observed following left PFC rTMS as compared with both sham and right PFC rTMS. The processing of happy faces was not influenced by rTMS over the left PFC or the right PFC. In sum, these results support the notion of a motivational-direction model of emotion processing.

Discussion

There is ample evidence that the frontal cortex plays a central role in the conscious processing of emotionally laden stimuli. In the social and affective neurosciences, one the most successful cortical theories of emotion is the model of frontal asymmetry of emotion. Two core motivational action tendencies are suggested to be represented in the frontal hemispheres in a lateralised fashion, arguably to preclude conflict among action tendencies (Davidson, 1998; Harmon-Jones, 2003). Early pioneering work by Davidson and colleagues (1990) provided evidence for involvement of the left frontal hemisphere in approach-related positive emotions, whereas the right frontal hemisphere is concerned with withdrawal-related negative emotions. However, Harmon-Jones showed that negative emotion anger is processed by the left hemisphere and proposed to remove the distinction between positive and negative emotions from the affective valence model (Harmon-Jones, 2004a). In support of Harmon-Jones' proposal, van Honk and Schutter

(2006) recently demonstrated that low-frequency rTMS over the left PFC modulates the processing of angry, but not happy facial expressions. Figure 1 provides an overview of the development of the frontal asymmetry of emotion model.

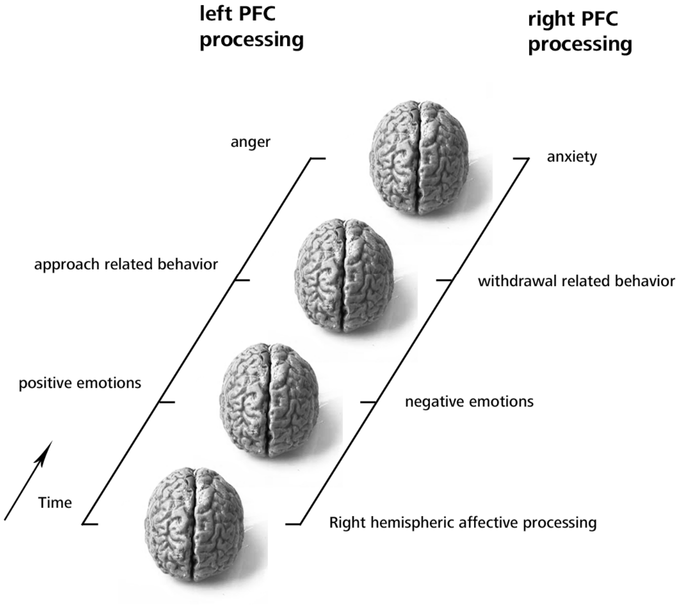

Figure 5.1. The frontal asymmetry model of emotion in developmental perspective.

Considerations for the asymmetry model

The vast majority of the studies reported on here used EEG recordings to examine frontal asymmetries in emotion processing, a technique that is only able to make coarse estimations on the actual neural sources of activity. Studies employing functional resonance imaging (fMRI) have yielded inconsistent results regarding the current state of the asymmetry model in terms of approach and withdrawal (Wager, Phan, Liberzon, & Taylor, 2003), but these inconsistencies may in part be confounded by the fact that most studies employing fMRI are not designed to assess frontal asymmetrical activity patterns in relation to motivational direction. The few fMRI studies that have done this, directly support the motivational direction instead of the valence model (Berkman & Lieberman, 2010).

Also, asymmetrical frontal activity patterns have predominantly used alpha frequency band activity as a (inverse) marker of cortical activity. A recent study however suggested a role for beta-band band in motivation related incentives (Schutter, de Weijer, Meuwese, Morgan, & van Honk, 2008) . In this study, the relationship between asymmetrical beta activity and the behavioral asymmetry in approach (BAS) and avoidance (BIS) motivation was examined. Results indicated a positive relationship between dominant right-hemispheric beta power and dominant BAS motivation, and were interpreted in terms of a left hemispheric functional dominance over the right cerebral cortex due to dominant right hemispheric inhibitory activity. Importantly, in this study M1 was also incorporated into measures of frontal asymmetrical activity, strengthening the coupling between trait motivation and action tendencies. How specifically the asymmetry model is able to harbor a distinction between prefrontal brain areas and more centrally situated regions, remains unclear.

Next to taking into account interhemipheric asymmetries in motivation research, the LeDoux and Damasio models clearly point out the importance of considering subcortical processes. A possible manner to incorporate such activity in measures of cortical activity patterns is to include additional frequency bands to compose a ratio. For instance, the ratio between δ and β activity in the context of incentive processing has been proposed an index of subcortical and cortical processing. Indeed, patterns of δ/β activity have been shown to predict behavioral responses to threat (Putman, 2011; Putman, Arias-Garcia, Pantazi, & van Schie, 2012). Combining the interhemispheric asymmetry approach with ratio measures of cortial/subcortical activity could prove a useful addition to the model, if it could be established that the measures are comparable conceptually.

Thus far, a clearly defined mechanism for the modulation of changes in patterns of frontal activity is lacking. Cortical asymmetries have been suggested to arise from differences in mutual inhibitory function of the left and right hemisphere (Chiarello & Maxfield, 1996). As noted in the prologue, the main trajectory for information transfer between the cerebral hemispheres is the CC, and probing patterns of functional interhemispheric inhibition in the context of approach motivation therefore could provide an anatomical basis for functional changes in asymmetry patterns. This proposition is in line with the concept of allostasis: in order to maintain stabitlity in response to challenge, an organism changes patterns of activity as a coping mechanism (McEwen, 1998). The CC would therefore be the prime candidate-substrate for the mediation of asymmetrical cerebral activity patterns, patterns that arguable reflect the balance in approach and avoidance related motivation.

The quantification of asymmetrical activity patterns thus yields a convenient means to establish an individual baseline-corrected (since based on relative dominance) measure of approach motivation. There is now abundant evidence that the left frontal cortex is predominantly involved in the approach-related negative emotion anger, whereas the right frontal cortex is mainly involved in the withdrawal-related negative emotion fear. In spite of conceptual and methodological issues, the model continues to provide a heuristic framework in which emotional processing can be studied, and is flexible to incorporate new propositions.

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Asymmetrical frontal resting-state beta oscillations predict trait aggressive tendencies and behavioral inhibition

Chapter 6

Hofman, D. and Schutter, D.J.L.G. (2012).

Social Cognitive and Affective Neuroscience, 7 (7): 850-7.

Abstract

Asymmetrical patterns of frontal cortical activity have been implicated in the development and expression of aggressive behavior. Along with individual motivational tendencies, the ability to restrain one's impulses might be a factor in aggressive behavior. Recently, a role for the inhibitory cortical beta rhythm was suggested. The present study investigated whether individual differences in resting state asymmetries in the beta frequency band were associated with trait aggression and behavioral inhibition. In addition, the selective contributions of the prefrontal and motor cortex areas to these associations were examined. Results showed that relative dominant right frontal beta frequency activity was associated with both heightened trait aggression, especially hostility, and reduced response inhibition. Moreover, asymmetries over the anterior electrode locations proved to be related closest to trait aggression, while asymmetries over the central electrode locations were associated with response inhibition. Together these findings show that right-dominant frontal beta activity is positively associated with aggressive tendencies and reduced behavioral inhibition.

Introduction

Over the last decades, scientific interest in human socio-emotive behavior has increased dramatically. Theorizing on the neural correlates of emotion and motivation has evolved into a rich branch of neuroscientific research which has increasingly gained the attention of scientists and the general public alike (Illes et al., 2010). Owing to its impact on society as well as individuals especially behaviors expressing aggressive intention defensively have become a topic of extensive investigation. Although several patterns of structural and functional connectivity (Nelson and Trainor, 2007; Hofman and Schutter, 2009; Hoptman et al., 2010) and frontal cortical activity (Harmon-Jones, 2003; Harmon-Jones et al., 2009) have been implicated in the development and expression of aggressive behavior, sources of individual differences that contribute to aggressive behavior however still remain relatively unknown.

A line of investigation particularly concerned with dispositional individual differences has been focusing on left and right frontal electrophysiological (EEG) activity and their respective relation with emotional processing (Davidson, 1988, 1992). The main tenet in this field has advanced from right hemispheric processing of negative emotion versus left hemispheric processing of positive emotion to a model of motivational direction in which the right cerebral hemisphere is associated with avoidance related incentive and the left cerebral hemisphere with approach related incentive (Harmon-Jones, 2003; Harmon-Jones et al., 2009). Recent empirical advances show asymmetrical frontal EEG activity to be directive in motivational incentives, and interestingly, have strongly linked anger and aggressive behaviors to approach motivation (Harmon-Jones and Allen, 1998; Harmon-Jones, 2007). The vast majority of the studies contributing to the frontal asymmetry of emotion model, as the framework has become known, has made use of the possibility to measure surface EEG activity from the scalp non-invasively (Harmon-Jones, 2003; Davidson, 2004). Manipulations of frontal EEG activity patterns strengthened the correlational claim of lateralized cerebral involvement in emotional processing (Peterson et al., 2008). Studies employing repetitive transcranial magnetic stimulation (rTMS), a method capable of changing local cortical activity transiently (Hallett, 2007), showed altered performance on emotionally laden behavioural tasks after changing anterior cortical excitability (d'Alfonso et al., 2000; van Honk and Schutter, 2006). Consequently, activity patterns in the frontal cortices can be regarded to be crucially involved in the processing of emotional stimuli.

The vast majority of the literature on asymmetrical frontal activity patterns has focused on the alpha (8-12 Hz) frequency band of the EEG spectrum. Prefrontal alpha EEG asymmetry has proved to be a consistent marker of motivational tendencies, in resting state as well as manipulation studies (for a contemporary review see Harmon-Jones et al., 2010) . As an assumed index of cortical idling, inverse alpha band activity has served a successful predictor of especially approach-related behaviors. Early studies employing alpha band activity have shown left hemispheric dominance to be predictive of approach motivation as measured by the Behavioral Approach (or behavioral activation system, BAS) and Behavioral Inhibition system (BIS) (Harmon-Jones and Allen, 1997), and were able to discern motivational direction and affective valence (Sutton and Davidson, 1997). Consistent with the latter notion, it was shown that anger, a negatively valenced emotion with clear approach-motivational inclination, could also be linked to left-hemispheric dominance (Harmon-Jones and Allen, 1998) as described in terms of inverse alpha power. Conversely, manipulation of patterns of prefrontal activity in the alpha band, for instance by contralateral hand contraction, have also been shown to relate to increases in approach motivation as well as anger (Harmon-Jones, 2006; Peterson et al., 2008).

A recent study however suggested a role for activity in the beta (12-30 Hz) frequency band in motivation related incentives (Schutter et al., 2008). In this study, the relationship between asymmetrical beta frequency range activity and the behavioral asymmetry in approach (behavioral activation, BAS) and avoidance (behavioral inhibition, BIS) motivation as indexed by the BIS/BAS questionnaire (Carver and White, 1994) was examined. The focus on beta band activity originates from earlier reports on its inhibitory function as illustrated by, for instance its relationship with the inhibitory neurotransmitter γ-aminobutyric acid (GABA) activity (Jensen et al., 2005). Results indicated a positive relationship between dominant right-hemispheric beta power and dominant BAS motivation, and were interpreted in terms of a left hemispheric functional dominance over the right cerebral cortex due to dominant right hemispheric inhibitory activity. These findings suggest that rather than focusing on local activity in one of the cerebral hemispheres, the balance of either excitatory or inhibitory activity between the cortices is of pivotal importance when considering functional dominance in terms of motivational tendencies. In a stimulus-dependent design, pre-stimulus beta activity measured directly from the cortex in a go-no-go task has been shown to predict successful inhibition of response (Swann et al., 2009b). Together these findings call for investigation of the relationships between beta frequency activity, motivational tendencies and behavioral inhibition.

Arguably, the ability to exert behavioral control over one's actions plays an important role in restraining aggressive tendencies. Studies on aggressive behavior in substance abuse have suggested a role for impaired self-control in aggressive and in particular hostile behavior (Dawe et al., 2009; Lapworth et al., 2009). Following from these studies, scrutinizing a possible role for impaired behavioral inhibition in the expression of aggressive behaviors might provide for additional insights in the relationship between frontal cortical activity and aggressive behaviors. Indeed, several studies have implicated impaired inhibition of behavioral responses in psychopathologies such as antisocial personality disorder (Kiehl et al., 2000; Swann et al., 2009a). Integrating these findings into a model of functional dominance on the level of the cerebral cortex therefore would petition the incorporation of the primary motor cortex (M1) into measures of cortical activity. As an important effector of human behavior, M1 is highly connected to the anterior parts of the cortex, and indeed, some of the physiological mechanisms by which M1 operates are highly similar to those of the prefrontal cortex (Kahkonen et al., 2005; Daskalakis et al., 2008). It therefore is not surprising that recent studies employing asymmetrical measures of cortical activity in motivation research have also either incorporated (Schutter et al., 2008; Hofman and Schutter, 2009) or made use of (Harmon-Jones, 2006; Peterson and Harmon-Jones, 2008; Peterson et al., 2008) the connectivity between the prefrontal and more central parts of the human frontal cortex.

The main objective of the present study therefore was to establish whether individual differences in asymmetrical resting state cortical activity in the beta frequency band were predictive of trait aggression and behavioral inhibition. Conform the inhibitory property of beta frequency activity and the asymmetrical involvement of the frontal cortices in approach and withdrawal related motivational tendencies we hypothesized relative dominant right-hemispheric beta activity to be related to higher trait aggression, and that activity recorded from anterior sites would be particularly predictive of trait aggression. Similarly, reduced behavioral inhibition is hypothesized to be related to relative right-dominant beta activity. In addition, we hypothesized activity recorded from the central electrodes would be closest associated with behavioral inhibition scores.

Methods

Participants

Thirty healthy non-smoking right-handed male volunteers mean ± SD age, 23.3 ± 2.0 years were recruited among the student population of Utrecht University, the Netherlands. None of the participants had a history of psychiatric or neurological conditions. Written informed consent was obtained and volunteers received course credit for participation. All volunteers were naïve to the aim of the study. The study was in accordance with the standards set by the Declaration of Helsinki (Edinburgh Amendments).

EEG recordings

Resting state EEG was collected during a four minutes eyes opened – eyes closed – eyes opened – eyes closed recording session. Recordings were made using the Biosemi ActiveTwo system (Biosemi, Amsterdam, The Netherlands) at a 256 Hertz sampling rate from 32 Ag/AgCl pin electrodes placed over the scalp according to the International 10/20 EEG system. The ground consisted of the active common mode sense and passive driven right leg electrode.

Buss Perry aggression questionnaire

Aggressive personality style was assessed with the Dutch translation of the 29 item Buss Perry aggression questionnaire (AQ) (Buss and Perry, 1992; Meesters et al., 1996). The ordinal response scale ranged from ‘1- extremely like me’ to ‘5- extremely unlike me’. The total AQ score provides a general index of trait aggression that can be further subdivided into four categories: Physical aggression (nine items), verbal aggression (five items), anger (seven items), and hostility (eight items).

Go–no-Go task

Behavioral inhibition was assessed in a Go-no-Go paradigm. The Go-no-Go (GnG) task consisted of three practice trials and 200 experimental trials. Participants were instructed to respond as quickly as possible, but accurately, to low and high frequency gratings by pressing the left or right mouse button respectively. This response had to be inhibited if the grating presentation was accompanied by a 400 ms, 1000Hz tone, presented at 50 dB (twenty percent of total number of trials, 40) as opposed to the trials accompanied by a low volume and frequency tone. Individual trials were delivered as follows: fixation cross against black background (500ms), grating presentation (1000ms) and a delay randomly varying from 750 to 1000 ms. Gratings were sized 800x800 pixels and presented on a 24” LCD monitor at approximately 100 cm viewing distance. Figure 1 depicts a single trial of the Go-no-Go task.

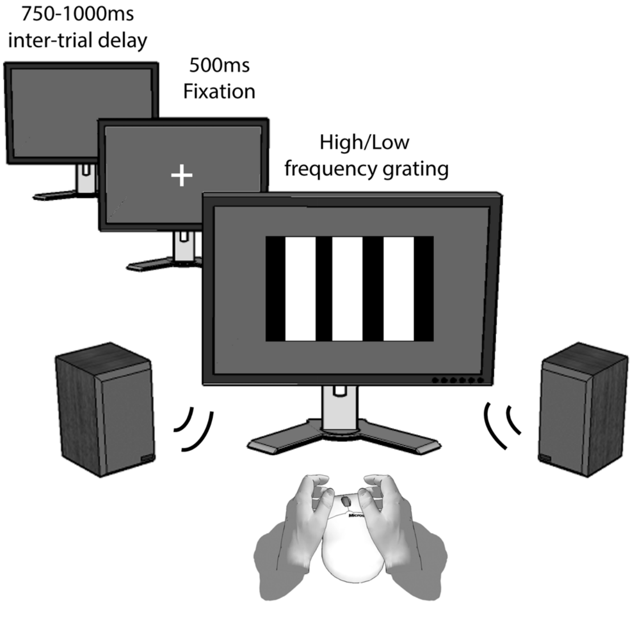

Figure 6.1. Single trial of the Go–no–Go task. Trials were separated by a time-varying intertrial delay, after which a fixation cross was presented. Participants were instructed to respond as quickly as possible to the high or low frequency grating, except for the trials that were accompanied by a loud high frequency tone

Procedure

Upon arrival at the laboratory participants received oral and written information on the experiment after which written informed consent was obtained. Next, participants were subjected to a short semi-structured interview to rule out history of psychiatric or neurological illness. The experiment continued with the resting state EEG recording session. Next, participants completed the AQ. The experiment continued with administration of the Go-No-Go task, and ended with debriefing.

Data reduction and statistical analyses

Go-no-Go data

Failed inhibition of response (i.e. response if response was to be inhibited) rates were calculated as the percentage of failed inhibitions of trials in which responses were to be inhibited ($i.e.: \frac{\#\,failed\ inhibitions}{40} * 100$).

Resting state EEG data

Raw EEG traces were re-referenced offline to the average activity of all electrode locations. Electro-oculogram recorded from electrodes placed on the suborbit and supraorbit of the right eye and on the external canthi of both eyes was used to correct for eye movements (Gratton et al., 1983). EEG was 1-30 Hz band pass filtered, with a 24 dB roll-off per octave. Data were subsequently divided in segments of one minute length, and the two remaining segments containing the eyes-closed data were segmented further in 2 second epochs. Next, artifacts greater than +/−50 mV were rejected before further analysis by removal of the containing epoch for all channels. Spectral power (μV^2) in the alpha (8-12 Hz) and beta (12.5−-30 Hz) frequency bandwidth was estimated by a fast Fourier transform (Hamming window: length 10%). Regions of interest were identical to the regions reported in earlier reports from our laboratory (left FC: C3, Fc1, Fc5, F3; right FC: C4, Fc2, Fc6, F4) and mean spectral power for the left and right frontal cortex was calculated by averaging the four corresponding electrodes. Asymmetrical power distribution was computed using the following equation: $\text{power}_{\text{asymmetry}}$ =

$\frac{\text{power}^{\text{right}} - \text{power}^{\text{left}}}{\text{power}^{\text{right}} + \text{power}^{\text{left}}}$ (Schutter et al., 2008), in order to control for individual differences in non-neurogenic variables including skull-to-cortex distance, skull thickness and orientation of underlying cortical tissue (Herbsman et al., 2009).

Statistical analyses

Pearson product-moment correlation analyses were run to assess the relations between asymmetrical frontal activity, AQ and behavioral inhibition scores. Exploratory follow-up Pearson product-moment analyses were performed to assess the relationship between asymmetrical frontal activity and the four factors of the AQ.

To test our hypotheses regarding the contributions of the anterior and more centrally located electrode pairs, separate stepwise linear regressions (method: probability of F to enter < 0.05; criteria probability of F to remove > 0.1) using F3/F4, Fc1/Fc2, Fc5/Fc6 and C3/C4 asymmetries as predictors were run for both AQ and behavioral inhibition scores if the Pearson correlations yielded a significant relation

Results

Data exclusion

Due to technical failure data of one participant were lost and one participant did not comply with instructions in the Go-no-Go task. Exploratory analyses indicated that data of two participants should be omitted from the analyses due to outlier values (>2 SD) on the $\beta_{\text{asymmetry}}$ variable. In Table 1 the group means and standard deviations of asymmetrical frontal activity, AQ scores, and percentages failed inhibition of response are depicted. All results reported in the following section are based on the analysis of the data from the remaining 26 participants.

Table 6.1. Means and standard deviations (SD) of the $\alpha_{asymmetry}$, $\beta_{asymmetry}$, percentages failed inhibition of response scores and AQ total and individual factor scores.

	Mean score	**SD**
$\alpha_{asymmetry}$	0.0067	0.0759
$\beta_{asymmetry}$	0.0142	0.0893
% failed inhibition (no-go trials)	8.31	6.583
% responses (go trials)	99.78	0.56
AQ total score	66.19	7.156
AQ_factor physical aggression	20.92	3.752
AQ factor hostility	17.19	4.079
AQ factor verbal aggression	13.15	2.866
AQ_factor anger	14.92	3.698

Relations between $\alpha_{asymmetry}$, $\beta_{asymmetry}$, trait aggression and behavioral inhibition.

First, Pearson product-moment correlational analysis showed that $\beta_{asymmetry}$ significantly predicted AQ scores, $r = 0.467$, $p = 0.016$. Next, the Pearson correlational analysis of the relationship between $\beta_{asymmetry}$ and percentage failed inhibition also resulted in a significant association, $r = 0.424$, $p = 0.031$.

Exploratory follow-up analyses of the relationship between $\beta_{asymmetry}$ and the four factors of the AQ (i.e., anger, hostility, physical aggression and verbal aggression) revealed that $\beta_{asymmetry}$ was significantly related to the AQ factor hostility solely, $r = 0.513$, $p = 0.007$, all other p-values > 0.172.

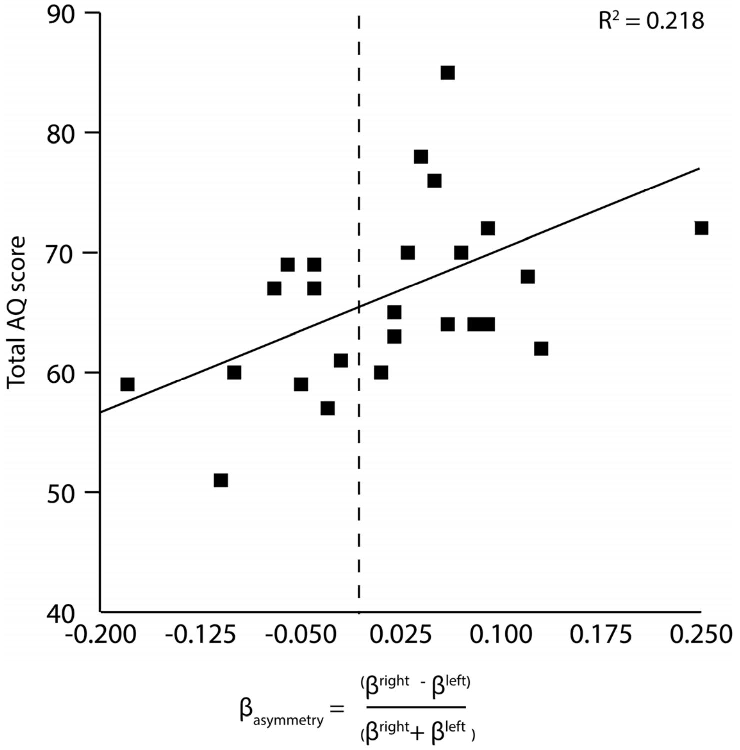

Figure 6.2. Dominant right hemispheric beta frequency activity is positively correlated to AQ scores.

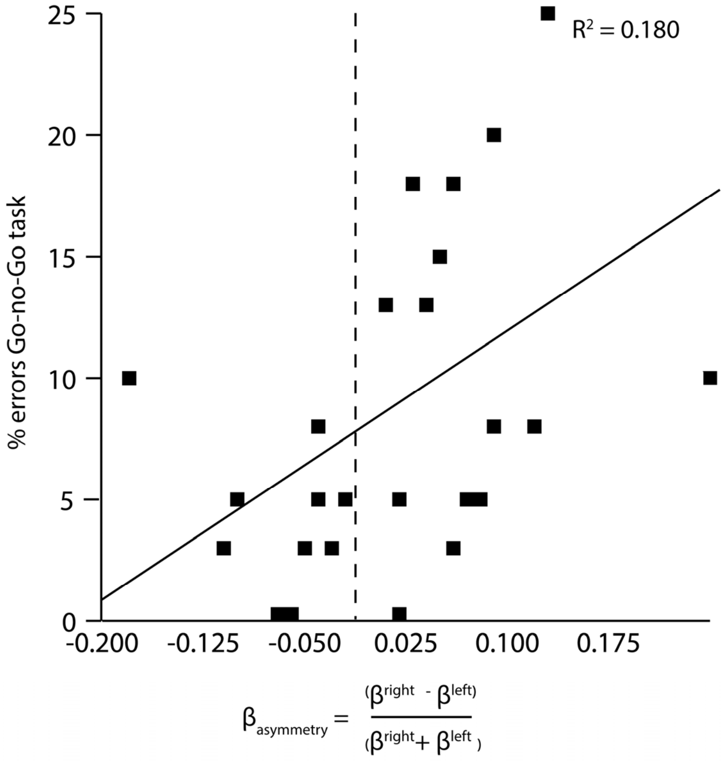

Figure 6.3. Dominant right hemispheric beta frequency activity is positively correlated to error percentages in the Go-no-Go task.

To examine contributions of individual electrode pairs in predicting trait aggression and behavioral inhibition, exploratory step-wise regression analyses in which F3/F4, Fc1/Fc2, Fc5/Fc6 and C3/C4 asymmetries were entered as predictors were run for AQ and behavioral inhibition scores separately. In line with our expectations, the step-wise linear regression in which F3/F4, Fc1/Fc2, Fc5/Fc6 and C3/C4 asymmetries were entered to predict AQ scores demonstrated that the $F3/F4_{\text{asymmetry}}$ was the only significant predictor, $F(4, 25) = 5.829$ $p = 0.024$ ($R^2 = 0.195$).

The step-wise linear regression in which F3/F4, Fc1/Fc2, Fc5/Fc6 and C3/C4 asymmetries served to model behavioral inhibition scores yielded two significant models. Model I consisted only of the $C3/C4_{\text{asymmetry}}$, $F(4, 25) = 4.873$ $p = 0.037$ ($R^2 = 0.169$). In model II however, adding the lateral fronto-central pair Fc5/Fc6 resulted in a significantly better fit, $F(4, 25) = 6.462$, $p = 0.018$ (R^2 change= 0.182). In table 2 and 3 the constants, betas, standard errors and the standardized betas can be found for the respective models.

Table 6.2: AQ *scores*

		b	***SE b***	***β***
Step 1 $\beta_{asymmetry}$				
	Constant	66.003	1.287	
	F3/F4	22.889	9.481	0.442*
Step 1 $\alpha_{asymmetry}$				
	Constant	65.818	1.288	
	F3/F4	39.669	16.085	0.450*

$\beta_{asymmetry}$ $R^2 = 0.195$ ($p < 0.05$). * $p < 0.05$.

$\alpha_{asymmetry}$ $R^2 = 0.202$ ($p < 0.05$). * $p < 0.05$.

Table 6.3: *Go-no-Go scores*

		b	***SE b***	***β***
Step 1				
	Constant	0.077	0.012	
	C3/C4	0.191	0.086	0.411*
Step 2				
	Constant	0.077	0.011	
	C3/C4	0.210	0.078	0.452*
	Fc4/Fc6	0.210	0.083	0.429*

$R^2 = 0.169$ for step 1, $\Delta R^2 = 0.182$ for step 2 (*ps* <0.05). * *p* <0.05.

To examine how the present data relate to the larger body of research on asymmetrical frontal activity, the statistical analyses were repeated for the asymmetries in the alpha band. In agreement with prior findings, Pearson product-moment correlational analysis showed that $\alpha_{asymmetry}$ significantly predicted AQ scores, $r = 0.391$, $p = 0.048$. However, the Pearson correlational analysis of the relationship between $\alpha_{asymmetry}$ and behavioral inhibition scores was not significant, $r = 0.275$, $p = 0.173$. The step-wise linear regression analysis in which F3/F4, Fc1/Fc2, Fc5/Fc6 and C3/C4 alpha asymmetries were entered to model AQ-scores demonstrated that the F3/F4$_{asymmetry}$ was the only significant predictor, $F(4, 25) = 6.082$ p = 0.021 ($R^2 = 0.202$)). In table 2 the constant, beta, standard error and the standardized beta can be found for the model.

Discussion

The present study aimed to explore the interrelations between frontal asymmetrical beta activity, trait aggression and behavioral inhibition. Additionally, we investigated whether activity recorded from anterior areas of the frontal cortex was especially predictive of trait aggression scores, whereas activity recorded from more central locations was hypothesized to be related closest to inhibition scores. We found asymmetrical frontal activity in the beta frequency range a significant predictor of both trait aggression as measured with the self-report AQ and behavioral inhibition as measured with a Go-no-Go task. Past research reporting interrelations between alpha asymmetries and trait aggression was replicated. However, whereas a significant relationship was found between frontal asymmetry and behavioral inhibition for the beta band, this relation was not found for the alpha band

Exploratory analyses of the relationship between AQ and beta asymmetrical activity indicated that the relationship originated from the strong association of the beta asymmetry with the AQ factor hostility. Further scrutinizing the contributions of separate electrode pairs yielded the frontal electrode pair F3/F4 as the most important predictor of trait aggression scores. For the behavioral inhibition scores, in a model which also included the lateral locations Fc5/Fc6, the most important predictor was the C3/C4 pair.

These findings confirm and extend earlier reports on the relationship between asymmetrical frontal activity and approach and withdrawal motivated behaviors, in particular the possibility of left hemispheric dominance on a functional level due to increased levels of inhibitory activity in the right hemisphere. This study corroborates previous results showing that dominant right hemispheric beta activity is paralleled by increased BAS motivation and left hemispheric cortical excitability (Schutter et al., 2008), and links this pattern of functional dominance to aggressive behavior, a relation that has already become apparent from studies employing alpha band EEG asymmetries (for reviews see Harmon-Jones, 2003; Harmon-Jones et al., 2009).

Beta frequency band activity is proposed to be indicative of active cortical inhibition (Jensen et al., 2005) and therefore may well play a role in the physiology underling hemispheric asymmetries. The beta inhibitory function is illustrated by its relationship with the inhibitory neurotransmitter γ-aminobutyric acid (GABA) activity (Jensen et al., 2005), and reports on beta frequency predicting successful inhibition of behavioral responses (Ruiz et al., 2010). Conversely, prestimulus alpha activity has recently been shown to, contrary to beta frequency activity, predict failure to inhibit motor response in a Go-no-Go task (Mazaheri et al., 2009). These findings suggest an organizing role for beta rather than alpha frequency activity in successfully regulating behavioral responses and inhibition.

A possible explanation for the higher predictive value of beta band activity may lie in the observation that specific brain regions have preferential natural rhythms, which tend to increase from posterior to anterior locations (Rosanova et al., 2009). In an interleaved TMS-EEG design, Rosanova and colleagues (2009) disturbed ongoing activity over occipital, parietal and premotor areas and observed the rate of subsequent oscillations (Rosanova et al., 2009). Applying this approach, it was demonstrated that the frequency of the observed natural rhythms following single-pulse TMS increased from around 10 Hz over occipital areas to around 20 Hz over parietal areas and around 30 Hz over premotor areas. Therefore, if the more frontal areas of the human brain tend to oscillate at frequencies of 20 Hz and higher, this might partly explain increased sensitivity of beta band activity over motor areas in predicting behavioral performance.

Moreover, M1 is considered to be a major output target of inhibitory control in the stopping network. Studies employing TMS while participants engaged in Go-no-Go tasks have shown rises in GABA mediated intracortical inhibition in no-go trials, suggesting that volitional inhibition of behavior is exerted at the M1 level, and is related to local GABA-ergic activity (Sohn et al., 2002; Coxon et al., 2006). Since beta activity has been suggested to reflect GABA-ergic activity (Jensen et al., 2005), this might also contribute to the observed increased sensitivity of beta activity over M1 in predicting response inhibition.

Involvement of the right frontal cortex in the regulation of affect is underscored by clinical studies involving patients suffering from selective damage to the frontal and anterior temporal lobes (Mychack et al., 2001). Frontotemporal dementia is a clinical syndrome marked by the selective degeneration of the frontal and anterior parts of the temporal lobes. Patients suffering from damage to the right frontal lobe are characterized by poorly modulated affect, poor impulse control and become highly critical of others (Mychack et al., 2001). These clinical observations fit the results presented here as relative hypo functioning of the right frontal cortex was marked by higher levels of impulsivity, trait aggression, and hostility in particular. Hostility can be described as a negative evaluation of people and objects (Ramirez and Andreu, 2006), and is proposed as a driving force behind angry and aggressive tendencies (Eckhardt et al., 1997).

In the present study, we show that the electrode pairs incorporated in the compound measure of asymmetrical beta power besides their ability to predict trait aggression and behavioral inhibition as a global measure of asymmetrical frontal cortical activity have selective explanatory power. Following our hypotheses, F3/F4 asymmetrical activity proved to be related to the measure of trait aggression in a selective manner. First, this finding is in line with the extensive body of work on asymmetrical frontal EEG activity (Harmon-Jones et al., 2009). Second, since participants were asked to judge the appropriateness of the statements in regard to their own personality and history, the questionnaire may partly implicitly probe successful non-aggressive coping in situations where participants had the opportunity to exert aggressive behavior. Therefore, since the prefrontal areas are implicated in emotional control (Davidson et al., 2000; Wager et al., 2008), activity as measured over these locations may be indicative for successful regulation of these behaviors over the lifespan. Conversely, the pair overlying the M1 (C3/C4) proved the strongest predictor for behavioral inhibition scores. This result suggests that in addition to the prefrontal locations, beta oscillations recorded over M1 are predictive of response inhibition. This finding is in line with earlier reports on beta band activity over the M1 and its involvement in successful stopping behavior (Swann et al., 2009b), as well as reports on M1 involvement in approach and withdrawal behaviors (Schutter et al., 2008; Hofman and Schutter, 2009) and studies employing the M1 as a proxy to induce prefrontal EEG asymmetries (Harmon-Jones, 2006; Peterson and Harmon-Jones, 2008; Peterson et al., 2008).

Some limitations on the generalizability and specificity of the present results must however be noted. First, it must be noted that the entire sample consisted of male university students without any history of psychiatric illness. In this sample, the relation between beta asymmetrical activity and hostility proved particularly strong. It would be conceivable that in more aggressive populations, other factors of the AQ would also become significantly related to asymmetrical beta activity.

Also, considering the characteristics of EEG regarding the localization of sources of cortical activity we cannot claim the activity as recorded over the locations reported originates from the cortical tissue directly beneath the electrodes.

Furthermore, the association between asymmetrical beta activity and aggressive behaviors and behavioral inhibition in particular may also be dependent on other personality characteristics which were not studied in the present study (Knyazev et al., 2008). For example, in a study employing a stop signal paradigm it was shown that synchronization of cortical electrophysiological activity post-response was modulated by trait anxiety (Savostyanov et al., 2009).

Finally, the correlational nature of the findings presented should be considered a limitation of the present study. Testing causality of the relationship between asymmetrical beta activity and aggressive behaviors and behavioral inhibition by manipulation of frontal activity patterns in the beta range, for instance by using transcranial alternating current stimulation (tACS), might be able to decide on the specificity and origin of the relation between asymmetrical beta activity patterns (Kanai et al., 2008; but see Schutter and Hortensius, 2010).

In conclusion, we here present data showing that resting state asymmetrical frontal beta activity is associated with trait aggression and response inhibition.

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Coalescence of dominance motivation and responses to facial anger in resting-state and event-related electrophysiology

Chapter 7

Hofman, D., Terburg, D., van Wielink, L. and Schutter, D.J.L.G.

(In revision)

Abstract

People vary in their proneness to dominate as a function of their motivation to fulfil their need for reward and social status. Recent research suggests that in humans dominant individuals respond vigilantly to angry faces, whereas non-dominant individuals rapidly signal submission. Dominance motivation has been suggested to reside in asymmetrical patterns of cortical and subcortical processing. The ratio between δ and β band oscillations has been proposed a proxy for this asymmetry, which we here aimed to map onto individual patterns of the event-related potentials (N170) as well as behavioral responses to facial anger in the context of dominance motivation. Results show that dominance motivation indeed predicts increased δ in the δ/β asymmetry; a pattern that further translates into behavioral vigilance as well as attenuation of the event-related response to angry faces. The present data are interpreted to suggest that dominance motivation is related to increased subcortical and decreased cortical processing, and that this translates into increased vigilance in dominance challenges, a motivational state that is further characterized by less detailed processing of angry faces as reflected in the attenuation of N170 amplitude.

Introduction

Social aggression is a common expression of dominance motivation in all vertebrate species and is, also still in humans, a driving force in the formation of social hierarchy structures (Mazur and Booth, 1998). Once considered the antisocial expression of an intention to damage another individual, aggression is now increasingly considered an adaptation to deal with competition for dominance and status (de Waal, 2000; Nelson and Trainor, 2007). In man, the motivation to pursue dominance, and thereby access to a variety of rewards, has cogently been linked to the Behavioral Approach System (BAS, Gray, 1990). More particular, variation in trait BAS drive and reward-responsiveness has been shown to predict dominance behavior (Putman et al., 2004; Terburg et al., 2011), as well as neural responses to challenge (Beaver et al., 2008; Hermans et al., 2010) and self–report measures of aggressive drive (Carver, 2004; Carver and Harmon-Jones, 2009).

A mechanism to assert dominance over conspecifics is sustained eye contact, especially when confronted with social challenge. Rivals attempt to out-stare each other in such dominance contests to the point at which one of the competitors averts gaze (Mazur and Booth, 1998). Building upon this notion, it has recently been established that dominance motives expressed in BAS are predictors of automatic keeping of eye contact with angry faces (Putman et al., 2004; Terburg et al., 2011). Moreover, administration of the steroid testosterone, a hormone linked to dominance motivation (Archer, 2006), also increased such reflexive dominant gaze behavior (Terburg et al., 2012). In addition, physical size has been suggested to be involved in dominance contests, and thereby attainment of resources through dominance contests (Brown, 1986). In general, animals that seek to become dominant can use physical and behavioral adaptations to their physique to appear larger, thereby increasing their apparent potential to obtain and hold resources (Parker, 1974). In humans, perceived as well as actual social status are also affected by size metrics (Deaux and Lewis, 1984; Frieze et al., 1990; Judge and Cable, 2004). In line, the open and expanded posture (i.e., enlarging physical presence) has also been linked to the expression of dominance in man (Hall et al., 2005), further suggesting a link between physical presence and social dominance. It is however not known if and how the physical size of an opponent affects reactive dominance behavior. It could be argued that a larger opponent constitutes a stronger dominance cue thereby evoking increased dominance behavior. Instead, it could also be the case that reactive dominance is attenuated towards larger opponents, as it involves greater risk of physical harm. In sum, dominant responding to angry facial expressions can be taken as a basic mechanism for the pursuit of social dominance, and this behavior might might be modulated by physical size of the opponent.

Direct interactions between attention for facial expressions of aggression and neural responses related to the processing of faces depicting anger have only been scarcely investigated. Electrophysiological studies have yielded a substantial body of evidence for a neural mechanism tuned to detect human faces, a process reflected in the negativity peaking around 170 ms after stimulus onset at occipitotemporal sites (N170, Bentin et al., 1996). There is considerable debate on the extent to which the N170 is sensitive to modulation, as studies varying stimulus content have yielded inconsistent results (Vuilleumier and Pourtois, 2007). For instance, effects of emotional content on the N170 have been reported for fearful, happy as well as disgusted faces (Ashley et al., 2004; Campanella et al., 2002). Therefore, it is suggested that attentional modulation instead of interstimulus variation such as emotional content accounts for modulatory effects on the N170 (Eimer and Holmes, 2007; Vuilleumier and Pourtois, 2007). More particular, this implies that rather than taking into account stimulus features per se, the interaction between observer and stimulus might be critical for the N170. This has led to the hypothesis that structural face processing, and thereby N170 amplitude, is subject to modulation by competing information processing (Senholzi and Ito, 2012). In terms of variation in dominance motivation, this premise would then lead to attenuation of the N170 as dominant individuals could take for instance an anger face as a sign of provocation, resulting in a relative disregard of the actual configural information constituting the face.

Further indications of trait-induced modulation of neural responses to facial affect come from studies with populations marked by aberrant expression of aggressive behavior. Such individuals have been shown to be more error-prone in the categorization of facial affect (Best et al., 2002), and to demonstrate attenuated cortical and exaggerated subcortical responses to facial threat (Coccaro et al., 2007), suggesting that the balance between cortical and subcortical processing might be indicative of aggressive motivation. This notion is supported by studies showing that inter-individual variation in BAS predicted amygdalar as well as frontal cortical responses to angry facials expressions such that increased BAS was related to increased amygdala, and decreased prefrontal activation (Beaver et al., 2008). To what extent this asymmetry in cortical and subcortical processing is able to predict variation in behavior however, has received little empirical attention.

Asymmetries in slow- and fast- wave oscillatory activity may provide for a window to study the relative contribution of cortical and subcortical processes to human behavior (Laufs, 2008). Basic motivational systems have been suggested to be reflected in oscillatory activity in the δ-frequency (1-4 Hz) band, one of the slowest rhythms in the human EEG that has been attributed functional characteristics (Knyazev, 2007). In the awake brain, δ-band activity is generated largely in limbic and subcortical structures and has been related to basic motivational processes (Knyazev, 2007, 2012; Steriade et al., 1993; Uhlhaas et al., 2010). For instance, increases in δ-band amplitude as well as coherence have been related to the inclination for food and sexual arousal (Knyazev, 2007), and also the rewarding properties of drug intake (Reid et al., 2006). As such, δ-band activity is a pervasive feature of intrinsic brain activity that seems closely related to reward pursuit. In the high-frequency end of the EEG spectrum, β-band (12-30 Hz) activity is commonly regarded as a rhythm that is generated in the cerebral cortex, and on a functional level β activity in frontal areas is involved in top-down modulation (Buschman and Miller, 2007). This view of high frequency oscillatory activity as an active top-down modulatory mechnism is consistent with observations of pre-stimulus β-band activity being predictive of succesful control over behavioral response (Swann et al., 2009). Recent studies suggest that β-band oscillations reflect activity of GABA (γ-aminobutyric acid)-ergic inhibitory interneurons as β activity is typically observed in cognitive– and motor states that require no voluntary change to them (Engel and Fries, 2010; Pfurtscheller et al., 1996). Not surprisingly, the study of the asymmetry in δ- and β-band activity has proven successful in a variety of experimental contexts. The asymmetry in δ/β activity has been shown to decrease as a function of salivary cortisol (CRT) and increase after testosterone (T) administration (Schutter and van Honk, 2004, 2005b), patterns interpreted as a CRT induced increase in cortico-subcortical communication, whereas T produced the opposite pattern. Taken together, the empirical observations above advocate considering the asymmetry in δ- and β-band oscillatory activity as a marker of the human drive for dominance.

The present study therefore was designed to test the hypothesis that increased dominance motivation is reflected in increased δ/β ratios as a proxy for the asymmetry in cortical and subcortical processing. Further, increased dominance motivation was hypothesized to be predictive of an attentional bias toward facial anger. Possible modulation of this vigilance through physical dominance was tested in a newly developed emotional vigilance task. Finally, we investigated the premise that with increasing dominance motivation processing depth of angry facial expressions decreases as a result of attentional interference by the emotional category.

Method

Participants

Twenty-six healthy participants (15 female, mean age= 22.5 ± 3.0 years) were recruited at Utrecht University campus in the Netherlands. None of the participants reported a history of psychiatric or neurological conditions. Participants received course credit or financial compensation for participation. All volunteers were naïve to the aim of the study, and written informed consent was obtained from all participants. The study was in compliance with the standards set by the Declaration of Helsinki (Seoul Amendments).

Dominance motivation

Dominance-motivation was determined by summing participants' scores on the two BAS scales closest related to reward sensitivity and aggression: BAS drive (BASD) and BAS reward-responsiveness (BASR) (Carver and Harmon-Jones, 2009; Carver and White, 1994; Putman et al., 2004; Terburg et al., 2011). For testing the magnitude of group effects of dominance motivation, participants were also divided in a low-dominance and high-dominance group by median split on basis of their dominance scores (see also statistical analyses). BAS fun-seeking (BASF) scores were obtained to control for non-dominance related approach motivation.

Attentional Bias for facial expressions of anger and happiness

Vigilance to emotional facial expressions was determined in a modified version of the Emotional Stroop Task (EST). The original EST is an index of vigilant and submissive responses to pictures of facial affect, and anger in particular that has been used in a variety of experimental contexts (for review see Van Honk and Schutter, 2007). To assess the role of physical dominance, the original EST was modified to consist of colorized face stimuli (red, green and blue) expressed by 18 actors (nine male, nine female) each expressing either an angry, happy or neutral emotion (Ekman, 1976; Lundqvist, 1998). Physical dominance of opponents was manipulated through stimulus presentation on three different positions on the computer screen (+30°, 0°, -30° visual angle at 50cm viewing distance, 162 trials in total). Each trial started with a 1250 ms fixation screen, in which the fixation cross always indicated the location where the emotional facial expression would appear. Participants were instructed to name the color of the face as fast as possible regardless of the expression of the face. Offset of the emotional facial expression was initiated by detection of the vocal response by a sound-activated relay, followed by an inter-trial black screen with a variable 1500 - 2500 duration (100 ms steps). Throughout the EST, the participant's EEG was recorded for evaluation of the event-related potentials in response to the presentation of the emotional facial expressions.

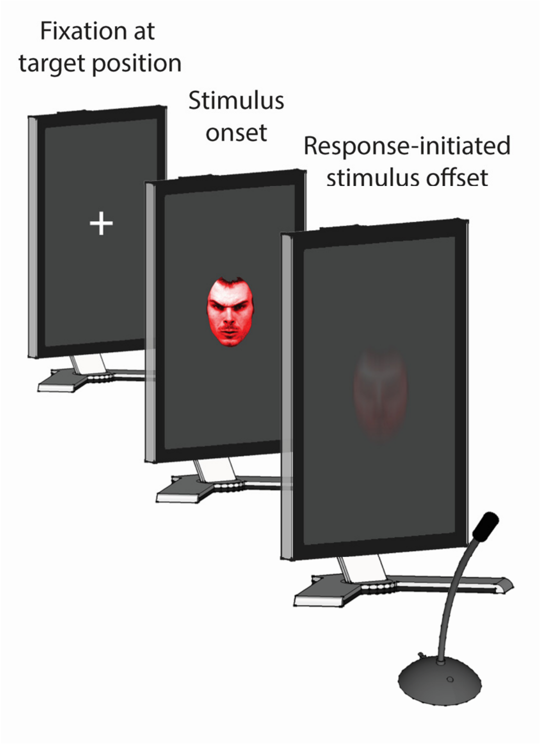

Figure 7.1. Single trial of the Emotional Stroop Task. Trials were separated by a time-varying intertrial delay, after which a fixation cross was presented at target position. Participants were instructed to name as quickly as possible the color of the face presented.

Resting state EEG recordings

Resting state EEG was recorded during a four minute eyes opened – eyes closed – eyes opened – eyes closed recording session. Recordings were made using the Biosemi ActiveTwo system (Biosemi, Amsterdam, The Netherlands) at a 2048 Hertz sampling rate from 32 Ag/AgCl pin electrodes placed over the scalp according to the International 10/20 EEG system. The ground consisted of the active common mode sense and passive driven right leg electrode.

Procedure and data reduction

Upon arrival at the laboratory, participants received oral and written information on the experiment after which written informed consent was obtained. Next, participants were subjected to a short semi-structured interview to rule out history of psychiatric or neurological illness. The experiment continued with the resting state EEG recording session. Next, participants completed the BAS questionnaire. After the questionnaire, the EST was administered. The experiment ended with debriefing.

Data reduction and statistical analyses

EST

Outlier latencies below 300 ms and above 900 ms (3.7%) were excluded from the analyses as well as latencies more than 3 standard deviations above each participant mean (6.7%) (Putman et al., 2004; Putman et al., 2007). Attentional bias scores were computed by subtracting the individual mean response latencies for neutral faces from the individual mean response latencies for angry and happy faces for all three locations (i.e. top, centre and bottom). Positive scores are referred to as interference and negative scores as facilitation.

Resting state EEG recordings

EEG raw traces were down-sampled to 256 Hz and re-referenced offline to the average activity of all electrode locations. Electrooculogram (EOG) recorded from electrodes placed on the suborbital and supraorbital of the right eye and on the external canthi of both eyes was used to correct for eye movements (Gratton et al., 1983). EEG was 1-30 Hz band pass filtered, with a 48 dB roll-off per octave. Data were subsequently divided in 4 segments of one-minute length. The two segments containing the eyes closed data were segmented further in 2-second epochs. Next, artefacts greater than +/−50 mV were rejected before further analysis by removal of the containing epoch for all channels. A fast Fourier transform (Hamming window: length 10%) was used to estimate spectral power (μV^2) in the β (13-30 Hz) and δ (1-3 Hz) frequency bands. Resting state δ/β EEG ratios were calculated for the fz, f3 and f4 electrode locations (Putman, 2011; Putman et al., 2012; Schutter and Van Honk, 2005a).

N170 in response to facial expressions

EEG raw traces were re-referenced to the average activity of all electrode locations and down-sampled to 256 Hz. Electro-oculogram recorded from electrodes placed on the suborbit and supraorbit of the right eye and on the external canthi of both eyes was used to correct for eye movements (Gratton et al., 1983). EEG was 1-30 Hz band pass filtered, with a 48 dB roll-off per octave. ERP waveforms were computed by selecting -100 – 400 ms response windows time-locked to face presentation onset where the 100ms before stimulus onset served as the baseline for the 400ms post stimulus period of interest. Next, epochs were averaged within their respective conditions (anger$^{\text{top, centre and bottom}}$, neutral$^{\text{top,}}$

$^{\text{centre and bottom}}$, happy$^{\text{top, centre and bottom}}$). The face-sensitive N170 component was scored as the peak negative amplitude between 150 and 220ms after stimulus onset at the P7/P8 electrode locations. As stimuli were presented in both hemifields throughout the task, responses as measured over P7 and P8 were collapsed into one weighted N170 for statistical analyses.

Statistical analyses

Pearson product-moment correlational analysis served to quantify the relationship between dominance motivation and the δ/β ratio and the N170. Exploratory regression modelling (stepwise linear regression: probability of F to enter < 0.05; criteria probability of F to remove > 0.1) was performed to relate dominance motivation to vigilance to facial affect in physical subordinate, equal or dominant position. To further illustrate, and facilitate comparison of the current effects with earlier studies, independent samples t-tests (median-split) were performed to estimate effect sizes in between group contrasts (see also Calder et al., 2011). If Levene's test indicated that variances were not equal between groups, the adjusted degrees of freedom and p-values are reported. Overall, p-values < .05 were considered statistically significant (two-tailed).

Results

First, we assessed whether increased dominance motivation would show a concomitant increase in δ/β ratios. In line with our expectations, a significant linear relation between dominance motivation and δ/β ratio was observed, $r = .627$, $p = .001$. Group comparison, mean ± SD low-dominance, 13.230 ± 2.166; mean ± SD high-dominance, 19.153 ± 2.823, dominance group difference, $t(24) = -6.001$, $p = .000$, $r = .768$, confirmed that the high dominant-group indeed showed a higher δ/β ratio, $t(15.83) = -3.213$, $p = .005$, $r = .628$. Figure 2 shows the individual asymmetry scores plotted against dominance motivation as well as the δ/β group differences.

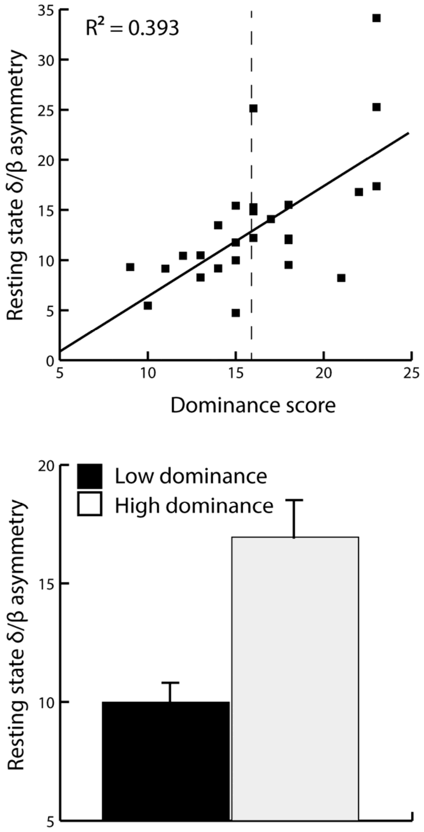

Figure 7.2. Upper panel: dominance motivation is correlated with SW/FW asymmetry. Bottom panel: means and error bars (SEM) for the median-split groups.

Second, we tested whether high dominance individuals would indeed show increased attention for facial anger as expressed in higher interference scores. Regressing (stepwise) the anger and happy bias scores for the three physical-relation conditions (anger bias$^{\text{top, centre and bottom}}$, happy bias$^{\text{top, centre and bottom}}$) on the dominance scores yielded a model in which the attentional bias towards the angry facial expression presented at eye-level provided a significant fit, $R^2 = .185$, $F(1, 23) = 5.439$, $p = .028$, $\beta = .430$. The test assessing the group difference demonstrated significantly higher interference scores for the high-dominance group, $t(24) = -2.250$, $p = .034$, $r = .417$. Figure 3 depicts the linear relation between dominance motivation and anger bias scores in the top panel, the median split analysis shows positive interference scores for the high-dominance group and negative interference scores for the low-dominance group.

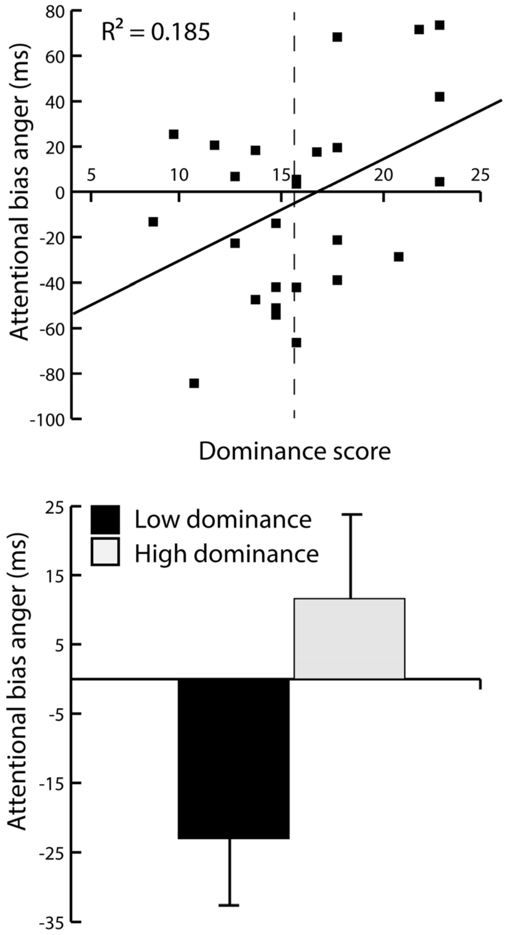

Figure 7.3. Upper panel: dominance motivation is positively related to vigilant responding in the EST, as determined by bias scores (positive scores indicate interference). Bottom panel: means and error bars (SEM) for the median-split groups.

Third, to further inform the above reported attentional bias, we evaluated whether dominance motivation would modulate processing of emotional facial expressions as indexed by the N170. As hypothesized, the N170s elicited by the angry, neutral and happy facial expressions showed attenuation with increasing dominance motivation: for angry facial expressions *r* = -.575, *p* = .002, for happy facial expressions *r* = -.530, *p* = .005 and for neutral facial expressions *r* = -.415, *p* = .035. Here, none of the subsequent group contrasts for the three emotional expressions reached significance, all *t*s <1.119, *ps> .249.* Figure 3 depicts the relation between the averaged face-sensitive N170 and dominance motivation, as well as the ERP grand averages for the high- and low dominance group.

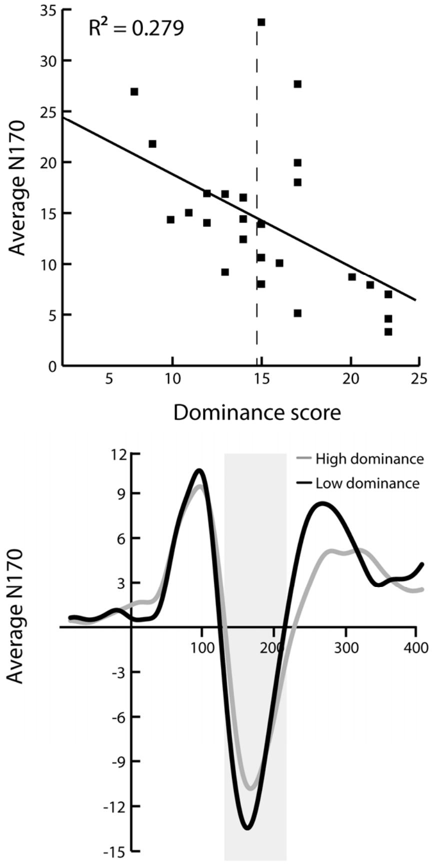

Figure 7.4. Upper panel: dominance motivation predicts N170 amplitude. Bottom panel: Grand Average waveforms for both median-split groups. Greyed-out areas indicates timewindow for scoring maximum peak amplitude.

Control analyses

We tested consistency in our model through computing the remaining two interrelations of our four measures, which confirmed that asymmetry in δ/β ratio towards subcortical processing also predicts increased vigilant responding to facial anger (r = .432, p = .028 and the related reduced N170 in response to facial anger (r = -.446, p = .022). As BASF and BAS dominance in our sample were significantly related (r = .422, p = .032), and have also been reported a compound measure of behavioral approach inclination, we also tested the above described linear relations with BAS dominance while controlling for BASF. All correlations remained virtually unchanged (see Table 1 for corrected second-order correlations), which confirms that the effects of dominance motives are independent from non-dominance approach motivation.

Table 7.1. Second order correlations between the variables of interest when partialing out BASfunseeking. **: Correlation is significant at the 0.01 level. *: Correlation is significant at the 0.05 level.

	Dominance motivation	SF/FW ratio	Attentional bias anger
SW/FW ratio	0.575**		
Attentional bias anger	0.403*	0.406*	
ERP angry faces	-0.561**	-0.419*	-0.418*

Discussion

Earlier studies showed that patterns of reduced cortical activity combined with exaggerated subcortical activity during processing of facial anger are associated with increased dominance motivation (Beaver et al., 2008). Increased dominance in turn predicts reflexive interference and attention towards angry faces (Putman et al., 2004; Terburg et al., 2011). In the present study, we sought to bring these findings together, and importantly, propose a predictive electrophysiological marker.

To this end, we explored the extent to which dominance motivation is reflected in the asymmetry in cortical and subcortical processing as expressed in resting state brain oscillations. We confirmed that with increasing dominance motivation, the δ/β asymmetry in oscillatory activity shifts towards greater δ prominence and reduced β presence, a pattern arguably reflecting a state of relative subcortical dominance over cortical activity. Configural processing of facial information as indexed by the N170 decreased with increased dominance motivation. This suggests that in-depth processing of facial features subsides as a function of increased dominance motivation, which might lead to increased behavioral vigilance towards facial anger. This behavioral pattern of reactive dominance was only observed towards the angry faces presented at eye-level, suggesting that this type of behavior is only prevalent towards opponents of equal physical size. This confirms earlier research with eye-level presentation of angry faces in emotional Stroop (Putman et al., 2004; van Honk et al., 2001) and gaze-aversion tasks (Terburg et al., 2012; Terburg et al., 2011), and further suggests that dominance behavior may be particularly a reflexive mechanism in situations where physical size of the opponents is relatively equal. This should however be confirmed in future studies. Together these findings suggest that dominance motivation is related to the behavioral response to signs of aggression presented at eye-level, which is reflected in the resting state asymmetry in δ/β activity, as well as in reduced configural processing of the opponent's face. Figure 5 schematically shows the empirical interrelations.

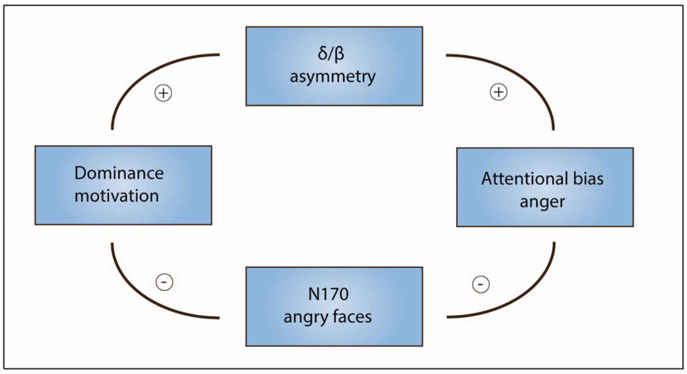

Figure 7.5. Schematic overview of the relationships observed.

As an index of basic motivational stance, measures of BAS drive and reward-responsiveness in particular have been shown to mediate a variety of behavioral as well as neural responses to social provocation. Direct involvement of the BAS in reward pursuit has been evidenced by studies showing that increased BAS significantly predicted the reward-related blood oxygenation level-dependent (BOLD) response in the ventral striatum, a brain area implicated in the motivational aspects of incentive processing (Hahn et al., 2009). A recent functional magnetic resonance imaging (fMRI) study involving testosterone administration replicated this relationship in its placebo condition, and showed that for low-BAS individuals, ventral striatal responses in the testosterone condition were brought up to the level of high-BAS individuals (Hermans et al., 2010). In parallel, after testosterone administration low-BAS individuals show similar reflexive dominance towards facial aggression as compared to high-BAS individuals (Terburg et al., 2012; 2011). In line with these findings individual variation in BAS was shown to predict the neural response to pictures of facial anger on the cortical and subcortical level (Beaver et al., 2008). More particular, increased BAS was related to increased amygdala activation and decreased ventromedial prefrontal cortex (vmPFC) activation. In a further experiment lowered connectivity between vmPFC and amygdala while viewing angry facial expressions was associated with increased BAS (Passamonti et al., 2008). This effect was interpreted in terms of reduced prefrontal control over the amygdala, and provides for a continuum in which BAS and its modulation of neural activation can be modelled ranging from extensive prefrontal regulation in low-BAS individuals to limited prefrontal regulation in high BAS individuals (Passamonti et al., 2008; Terburg et al., 2011). Combined, these studies suggest that activation patterns of cortical and subcortical structures implicated in reward pursuit and behavioural control are subject to individual variance in dominance motivation, and that these patterns translate into the behavioral response to social challenge.

This proposed variation in subcortical and cortical activity was in the present study taken to be reflected in the ratio between δ and β activity in EEG recordings of the brain's resting state. In the context of incentive processing, the asymmetry in δ/β activity can be regarded a proxy for indexing asymmetrical subcortical and cortical processing. High-frequency oscillatory activity is thought to originate from cortical mechanisms, in which inhibitory GABAergic interneurons play a central role (Traub et al., 2004; Uhlhaas and Singer, 2006). Support for this notion stems from studies showing that administration of the GABAergic agonist benzodiazepine increases power in the β-band (Jensen et al., 2005). This suggestion is further illustrated by studies showing that pre-stimulus rises in specifically β-band activity predicted successful inhibition of behavioral responses (Swann et al., 2009). Recent accounts of high-frequency oscillations have suggested that particularly β-band activity might reflect the inhibitory properties of GABAergic interneurons linked to the maintenance of the current cognitive or motor state (Engel and Fries, 2010), thereby possibly serving to control intrinsic motivation.

δ -Band activity is suggested to stem from limbic and subcortical generators, such as the brainstem, ventral tegmental area (VTA), nucleus accumbens (NAcc) and thalamus (Knyazev, 2007, 2012; Steriade et al., 1993; Uhlhaas et al., 2010). δ -Band activity has been related to motivational processes (Knyazev, 2007, 2012), and has recently also been related to aggressive pathology (Rosa et al., 2012). Through local field potentials recorded directly from the hypothalamus, it was established that in an excessively aggressive patient, slow wave activity in the δ range was significantly elevated as compared to activity recorded from the same location in a control patient. In combination with a decrease in α-band oscillatory activity, the authors propose the elevated δ-band activity as a marker for aggression (Rosa et al., 2012).

In line, studies considering patterns of δ/β activity have been linked to both vigilant and avoidant responses response to threat (Putman, 2011; Putman et al., 2012). For example, when presented with threatening words, individuals with high δ/β coupling, suggested to reflect high levels of cortical control over subcortical activity, showed lower levels of interference when instructed to name the color wherein the words were presented (Putman et al., 2012). These results directly concord with the vigilance effect reported in the present study in which, following the same rationale, lower control over subcortical motivation results in higher vigilance to anger display. A further demonstration of the role of δ/β asymmetry comes from a study showing that higher δ/β ratios were related to disadvantageous decision-making interpreted as impaired cortical control over the subcortical drive for reward attainment (Schutter and Van Honk, 2005a). Importantly, these empirical findings can be further framed in a model recently proposed in which the asymmetry in cortical and subcortical processing plays a pivotal role (van Honk et al., 2010). Herein, aggressive motivational tendencies are predicted to arise from imbalances at three different levels of brain functioning, one of which is the balance in cortical and subcortical processing. In particular, the asymmetry in cortical and subcortical in favour of the latter is predicted to result in increased aggressive motivation, a prediction met by the results from the present study.

Using the event-locked response to facial expressions of anger in the EST, we showed attenuation of the face-sensitive N170 as a function of increasing dominance motivation, possibly reflecting that dominance motives bias the brain in terms of subcortically driven dominance motivation at the expense of cortical control. The structural encoding of facial features as indexed by the N170 is suggested to be separate from the processing of the emotional content, in order to explain the divergent experimental finding reported (Ioannides et al., 2000; Vuilleumier and Pourtois, 2007). N170 effects have even been suggested to result from confounding differences between stimulus categories (Thierry et al., 2007), but see for instance Rossion et al. for a rebuttal (Rossion and Jacques, 2008). Rather, consideration of relevant personality factors might provide further insight in the interplay between brain areas involved in motivational and cognitive processing, even so in experimental designs contrasting different emotional conditions (Calder et al., 2011). Recent studies illustrate this premise: the N170 in response to black outgroup or white ingroup faces varied dependent on the instruction to either attend identity or racial category (Senholzi and Ito, 2012). Results showed that when focusing on identity, N170 amplitudes were increased for outgroup compared to ingroup members, whereas focusing on racial category resulted in the reversed effect. This suggests that when attention is captured by categories (i.e. race, or in the present study,emotional expressions), this could result in impaired processing of the facial stimulus per se. Likewise, Hahn et al. (Hahn et al., 2012) recently showed that rotating the eyes and mouth in facial displays of same or other race faces affected the same race faces most, showing that the relation between the observer and stimulus plays a significant role in the modulation of the N170. Therefore, in the present study modulation of N170 through trait motivational stance may also be the resultant of the interaction between observer and emotional facial expressions through attentional capture by the emotional category. As such, the observed asymmetry in the resting state EEG combined with the decrease in N170 when confronted with challenge might provide a physiological account for the differential behavioral response to, for instance, facial anger.

In conclusion, dominance motivation in man is reflected in a pattern of resting state asymmetrical cortical-subcortical processing, a pattern that translates into a δ/β asymmetry in the resting EEG that is correlated with dominance motivation. Both dominance motivation and δ/β asymmetry predict the event related neurophysiological response to displays of facial expressions such as anger, and ultimately the behavioral response to anger challenge. Together, the relations in the reported configuration may be taken as a marker of dominance behavior, and as such may well aid future research into the neural and behavioral manifestation of the disorders of aggression.

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Inside the Wire: Aggression and functional interhemispheric connectivity in the human brain

Chapter 8

Hofman, D. and Schutter, D.J.L.G. (2009).

Psychophysiology, 46, 1054-1058

Abstract

An aggressive personality style has been proposed to arise from a cortical asymmetry in activity of the left and right frontal hemisphere. In the present transcranial magnetic stimulation (TMS) study evidence was sought for a link between an aggressive personality style and functional interhemispheric connectivity between the left and right frontal cortex. Functional interhemispheric connectivity was quantified through interhemispheric inhibition (IHI) using TMS in twenty healthy right-handed volunteers, who were administered the Buss-Perry Aggression Questionnaire (AQ) and subjected to an emotional stroop task. Analyses showed higher levels of left-to-right IHI significantly correlated with higher AQ scores. Furthermore, individuals displaying increased left-to-right paralleled by reduced right-to-left IHI showed increased interference when presented with angry faces. This is the first study to provide a biological mechanism mediating the asymmetry between left and right frontal cortical activity, and its reflection in human aggression.

Introduction

The World Health Organization has estimated that each year over a million people lose their lives due to self-inflicted, interpersonal or collective violence. The realization that aggression threatens today's society has prompted social and biological scientists to investigate the underlying causes of this destructive behaviour.

Aggressive behavior generally refers to actions that are intended to cause physical or psychological harm to another individual. Despite the fact that aggression is able to secure or grant access to desired resources, it is often time consuming and potentially harmful (Nelson & Trainor, 2007). The origins of aggressive behavior are highly complex and in addition to studying environmental factors elucidating the neurological underpinnings of this phenomenon is of critical importance in order to attain a more complete understanding of aggressive behavior. According to one important line of research, an aggressive personality style is often associated with impulse control problems and reduced emotion regulation wherein the frontal lobes play a pivotal role (Davidson, Putnam, & Larson, 2000). Furthermore, there now is ample evidence suggesting asymmetrical involvement of the frontal hemispheres in the propensity to display aggressive behavior (for review, see Harmon-Jones, 2003). In particular, neural activity of the left frontal cortex has repeatedly been shown to correlate positively with the approach-related emotion anger and aggressive tendencies. In further support of this assumed cortical asymmetry, a recent study revealed that relative higher levels of left-sided as compared to right-sided cortical excitability underlies higher levels of approach-related motivational tendencies and lower levels of avoidance-related motivational tendencies (Schutter, de Weijer, Meuwese, Morgan, & van Honk, 2008).

These findings are in agreement with a prior repetitive transcranial magnetic stimulation (rTMS) study (d'Alfonso, van Honk, Hermans, Postma, & de Haan, 2000). In this study the lateralized role of the frontal cortex in approach- and withdrawal-related motivation was addressed by measuring the attentional bias for threatening facial expressions as a proxy for fight–flight tendencies (Dimberg & Ohman, 1996). In particular, angry facial expressions constitute an important nonverbal communication signal that enables the observer to rapidly distinguish threatening intentions (Van Honk & De Haan, 2001). In addition, angry facial expressions are argued to play an important role in establishing dominance–submission hierarchies (Ohman, 1986). For example, anxious individuals have the tendency to avoid angry facial expressions, which is interpreted as a sign of submission and harm avoidance (flight mode; MacLeod & McLaughlin, 1995; for an alternative view see Mogg & Bradley, 1998). In contrast, anger-prone individuals exhibit increased attention for angry facial expressions, unveiling approach-related motivational tendencies and intentions to dominate (fight mode; Dimberg & Ohman, 1996; van Honk, Tuiten, de Haan, van den Hout, & Stam, 2001). Results from the study by d'Alfonso and colleagues (2000) demonstrated that inhibitory rTMS to the right frontal cortex as compared to the left frontal cortex caused an increased bias toward angry faces (i.e., fight mode). This change in attentional bias was suggested to result from a shift toward left frontal cortex dominance following inhibitory low-frequency rTMS to the right frontal cortex. Further support for the left-lateralized involvement of the frontal cortex in approach-related motivation was recently provided by a study showing that increasing left but not right frontal cortex activity by voluntary contracting of the contralateral hand was associated with higher levels of experienced anger and overt aggressive behavior in a noise-blast administration paradigm (Peterson, Shackman, & Harmon-Jones, 2008).

Importantly, cortical asymmetries arise by virtue of differences in mutual inhibitory function of the left and right hemispheres (Chiarello & Maxfield, 1996a). A physiological basis for investigating frontal brain communication, balance, and asymmetries involves studying the white-matter fiber connections between the cerebral hemispheres. This bundle of fiber connections is called the corpus callosum (CC) and constitutes the main trajectory for information transfer between the cerebral hemispheres. Communication between the hemispheres is based on a cortical mechanism of excitatory CC fibers targeting inhibitory interneurons that is known as interhemispheric inhibition (IHI). IHI can be demonstrated by comparison of the motor evoked potential (MEP) of, for instance, the abductor pollicis brevis (APB) to a unilateral pulse with the MEP of the APB to a unilateral magnetic test pulse that is preceded by a contralateral magnetic conditioning pulse. When the test pulse is given ~10 ms after the conditioning stimulus, a significant reduction in MEP size of the test response is observed (Ferbert et al., 1992). The observation that IHI is absent in acallosal patients (Meyer, Roricht, & Woiciechowsky, 1998) but is preserved in patients with lesions in the descending corticospinal tract (Boroojerdi, Diefenbach, & Ferbert, 1996) suggests that IHI predominantly is a phenomenon of the CC.

In keeping with the proposed dominant left hemispheric involvement in anger and aggressive behavior (Carver & Harmon-Jones, 2009; Peterson et al., 2008), the aim of the present study was to test the hypothesis that dominant left-to-right IHI was associated with a more aggressive personality style and higher attentional bias scores toward angry facial expressions.

Method

Participants

Twenty healthy non-smoking right-handed volunteers (18 females), mean ± SD age, 21.0 ± 1.81 years, were recruited among the student population at Utrecht University, Utrecht, The Netherlands. None of the participants had a history of psychiatric or neurological conditions. Written informed consent was obtained and volunteers were paid for participation. All volunteers were naïve to the aim of the study. The study was in accordance with the standards set by the Declaration of Helsinki (Edinburgh Amendments).

Buss Perry aggression questionnaire

Aggressive personality style was assessed with the 29 item Buss Perry aggression questionnaire (AQ) (Buss & Perry, 1992; Meesters, Muris, Bosma, Schouten, & Beuving, 1996). The ordinal response scale ranged from ‘1- extremely like me’ to ‘5- extremely unlike me’. The total AQ score provides a general index of trait aggression that can be further subdivided into four categories: Physical aggression (nine items), verbal aggression (five items), anger (seven items), and hostility (eight items).

Attentional bias to emotional emotional facial expressions

Biased responding to emotional faces was determined by recording vocal response latencies to neutral and emotional faces (van Honk et al., 2001).

Participants were instructed to name the color of the face as fast as possible. Facial stimuli were taken from the Ekman and Friesen’s *Pictures of Facial Affect* and the *Karolinska directed emotional faces set* (Ekman, 1976; Lundqvist, 1998). Thirty angry, thirty happy and thirty neutral faces were presented in random order and the inter-trial interval randomly varied between 1500 and 2500 milliseconds. Each trial consisted of a 750ms presentation of a fixation point, followed by a 250 ms presentation of an angry, happy or neutral facial expression. All faces (14 cm x 9 cm) were colored either red, green or blue and projected in the centre of a 20“ computer screen (70 Hz refresh rate) against a black background. Viewing distance was 150 cm. Initiation of vocal response was detected using a microphone connected to a voice-activated relay.

Transcranial magnetic stimulation

TMS was performed using two biphasic magnetic brain stimulators (maximum output 4160 A peak / 1750 VAC peak) and an iron core coil (Neotonus, Atlanta, USA) over the over the left and right primary motor cortex (M1). The following conditions were applied: (1) single-pulse TMS to the left M1 (uMEP$_{\text{left}}$), (2) paired-pulse TMS with the conditioning pulse to the right M1 preceding the single-pulse TMS to the left M1 by 10 ms (cMEP$_{\text{left}}$), (3) single-pulse TMS to the right M1 (uMEP$_{\text{right}}$), and (4) paired-pulse TMS with the conditioning pulse to the left M1 preceding the single-pulse TMS to the left M1 by 10 ms (cMEP$_{\text{right}}$). TMS was applied at a frequency of 0.18 ± 0.02 Hz. Position and anterior-to-posterior direction of the coils were kept constant throughout the experimental session. The angle of the coil was monitored through leveling staffs mounted on the coils. Figure 1 illustrates how IHI was measured.

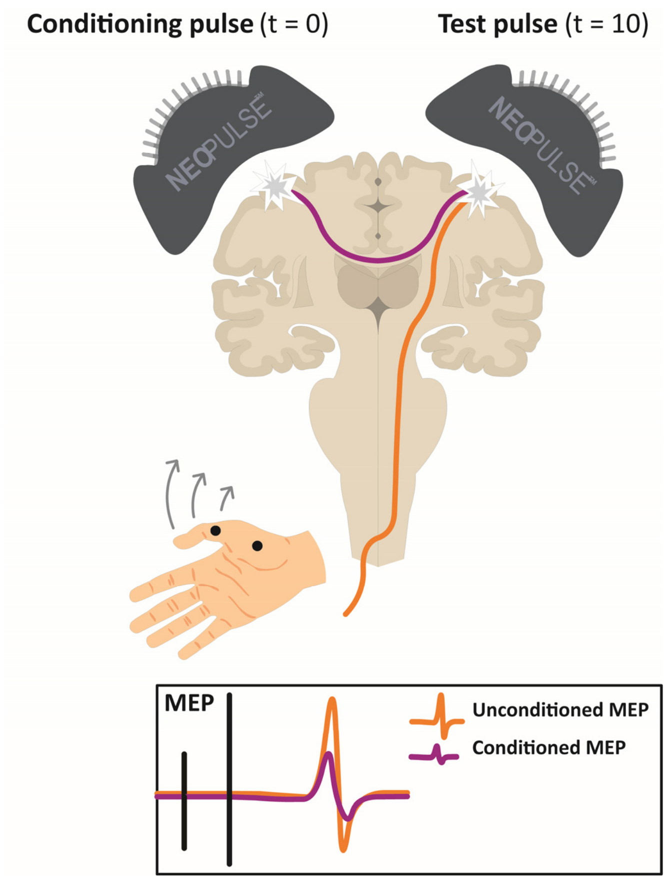

Figure 8.1. Example of the TMS paradigm measuring left-to-right IHI. The conditioning TMS pulse to the left hemisphere is followed by a TMS test pulse to the right hemisphere 10 ms later.As a result of interhemispheric projections ending on inhibitory interneurons the motor evoked potential (MEP) of the conditioned response will be smaller than the unconditioned MEP of the TMS test pulse alone.

Electromyographic recordings

Surface electromyogram (EMG) was recorded using sintered 11 x 17 mm active Ag-AgCl electrodes with the ActiveTwo system relative to the common mode sense (CMS) in a belly-tendon arrangement (BioSemi, Amsterdam, The Netherlands). The active electrodes were placed over the muscle belly of the left and right abductor pollicis brevis (APB). The reference electrodes were placed over the proximal phalanx of the left and right thumb. The ground was attached to the right wrist. The EMG signal was digitized at 16 kHz, low-pass filtered (-3 dB cut-off frequency: 3334 Hz; roll-off: 30 dB/octave), and offline high-pass filtered (-3 dB cut-off frequency: 20 Hz; roll-off: 24 dB/octave).

Procedure

Upon arrival at the laboratory participants received oral and written information on the experiment and were screened for contraindications to TMS (Keel, Smith, & Wassermann, 2001). After informed consent was obtained right handedness was assessed with the Edinburgh handedness inventory (Oldfield, 1971), mean ± SD, 44.65 ± 2.18. Next, participants completed the AQ. The experimental session was continued with the determination of resting MT (MT) for the left, mean ± SD, 51.85 ± 12.87, and right M1, mean ± SD, 48.5 ± 13.76. Participants were seated upwardly in a dentist chair and asked to relax the arms by placing them on the upper leg with the palm of the hand facing upwards. The coil was initially positioned on the scalp halfway the vertex and the external auditory meutus. By moving the coil systematically in different directions by approximately one centimeter and gradually increasing TMS intensity (inter-stimulus interval 5 s) the site for eliciting reliable thumb twitches (five out of five) was found. Next, intensity was decreased until five out of ten consecutive pulses induced a visually identifiable twitch. Finally, the coil was moved again over the scalp to search for additional scalp sites that surpass the 50% thumb movement criterion. If such a site was found, TMS intensity was further decreased according to the 50% criterion (Schutter & van Honk, 2006). Following MT determination, EMG electrodes were attached and participants were instructed to relax. Twelve uMEPs and twelve cMEPs were recorded from the left and right APB to 120% MT TMS in randomized fashion (48 trials in total). Finally, participants performed the attentional bias task. Stimulation parameters were in accordance with the International Federation of Clinical Neurophysiology safety guidelines (Wassermann, 1998).

Data analyses

Aggressive personality style was defined as the sum of the scores on the four subscales, yielding a total AQ score (Buss & Perry, 1992). The MEP was quantified as the peak-to-peak amplitude of the maximal EMG response. Left-to-right (l-r IHI) and right-to-left interhemispheric inhibition (r-l IHI) were expressed according to the formulas $[(1-(cMEP_{right} / uMEP_{right})) * 100]$ and $[(1-(cMEP_{left} / uMEP_{left})) * 100]$ respectively. Bias for angry and happy faces was calculated by subtracting the individual mean reaction times

(RT) to neutral faces from the individual mean response latencies for angry and happy faces respectively. Positive attentional bias scores stand for increased attention for emotional faces (i.e., interference), whereas negative attentional bias scores represent avoidant responses to emotional faces (i.e., facilitation) (van Honk et al., 2001)

A step-wise linear regression analysis (method: probability of *F* to enter < 0.05; probability of *F* to remove > 0.1) was performed to examine the relationship between AQ score and IHI. Two additional step-wise linear regression analyses (method: probability of F to enter < 0.05; criteria probability of F to remove > 0.1) were performed to study the interrelations between the attentional bias scores and IHI. The overall alpha level of significance was set at 0.05 (two-tailed).

Results

TMS was well tolerated by all participants and no adverse events occurred. Due to technical failure data of one participant were lost and in one participant IHI could not be reliably estimated. In Table 1 the group mean and standard error of the mean of the IHI, AQ scores and attentional bias scores are depicted.

Table 8.1. Means and standard errors of the mean (SEM) of the IHI, AQ and attentional bias scores.

	l-r IHI	r-l IHI	AQ total	Anger	Physical	Verbal	Hostility	Anger bias	Happy bias
mean	42.2	31.1	65.11	16.5	18.39	14.72	15.5	-0.19	-2.68
±	±	±	±	±	±	±	±	±	±
SEM	6.58	9.19	3.48	1.29	1.29	0.85	1.05	4.37	6.77

The linear regression analysis demonstrated that left-to-right IHI was the best predictor for AQ score, $F(1, 17) = 12.36$: $p = 0.003$ ($\beta = 0.66$: $R^2 = 0.44$). The relationship between left-to-right IHI and AQ scores is shown in Figure 2.

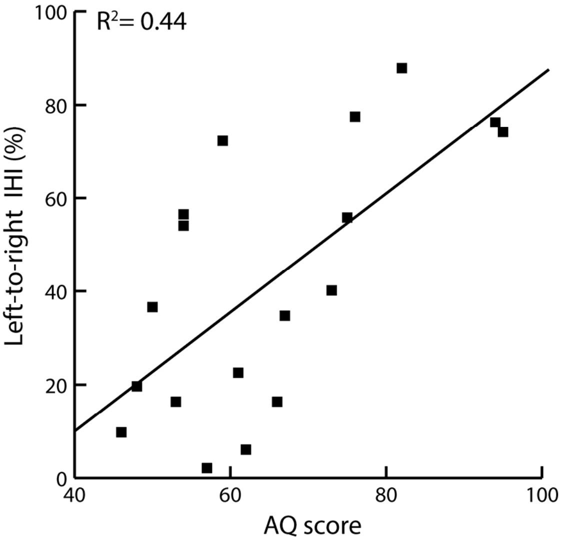

Figure 8.2. Higher levels of left-to-right interhemispheric inhibition (x-axis) are associated with a more aggressive personality style (y-axis).

Exploratory analyses revealed that l-rIHI was significantly correlated with the QA subscales anger, *r* = 0.55: p = 0.018, hostility, *r* = 0.58: p = 0.011, physical aggression, *r* = 0.49: p = 0.039, but not verbal aggression, *r* = 0.40: p = 0.101.

The second linear regression analysis showed that the attentional bias scores for angry facial expressions could be best explained by a model that included left-to right (β = 0.41) and right-to-left IHI (β = -0.66), *F*(2, 16) = 6.32: p = 0.01 (R^2 = 0.46). The attentional bias score for happy facial expressions could not be explained by IHI (p-values > 0.28). Figure 3 shows that a dominant left-to-right IHI (i.e., negative value) yields increased attention for angry faces (i.e., negative bias score).

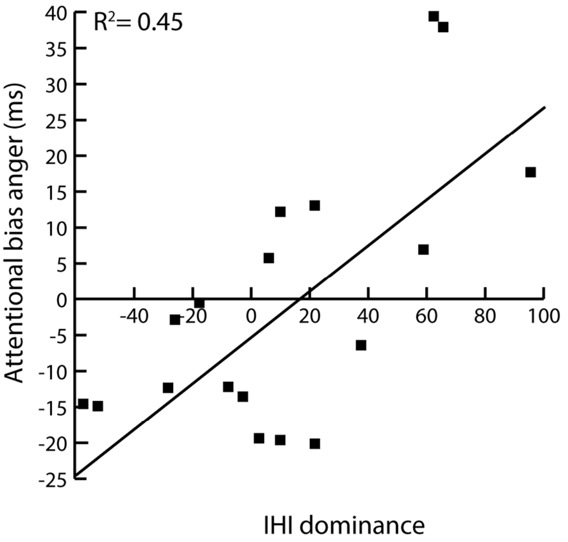

Figure 8.3. Higher left-to-right and lower right-to-left IHI is linked to a stronger attentional bias for angry facial expressions. X-axis: unstandardized predicted values of IHI: y-axis: attentional bias scores for angry facial expressions (in ms)

Finally, the AQ subscale physical aggression was significantly correlated to the attenional bias score for angry faces, r = 0.47: p = 0.049. No other significant correlations between AQ subscales and attentional bias scores were observed (all p-values > 0.59).

Discussion

The current results show that anger and aggression are positively associated with a dominant left-to-right IHI in healthy volunteers and extend the proposed left-dominant frontal asymmetry model (Harmon-Jones, 2003; van Honk & Schutter, 2006b). Moreover, our findings provide evidence for the view that an aggressive personality style and attentional bias to angry faces can be linked to a functional brain state wherein the approach-related motivational system in the left frontal cortex controls the avoidance-related motivational system in the right frontal cortex (van Honk & Schutter, 2006a). This view fits findings of the study mentioned earlier demonstrating an attentional bias towards angry facial expressions after inhibitory rTMS to the right frontal cortex as compared to inhibitory rTMS to the left frontal cortex (d'Alfonso et al., 2000). The results were interpreted in terms of slow frequency repetitive TMS induced shifts in cortical asymmetry as a result of local reductions in cortical excitability subsequently modifying callosal inhibitory function (Wassermann, Wedegaertner, Ziemann, George, & Chen, 1998). This interpretation coincides with the proposal that approach-related behaviors like aggression stem from differences in functional interhemispheric connectivity of the frontal cortex as well as with interhemispheric suppression theories (Chiarello & Maxfield, 1996b).

Notably, total AQ scores were explained by left-to-right IHI exclusively, whereas attentional bias scores for angry facial expressions were explained by both left-to-right and right-to-left IHI. A possible explanation for these findings is that the AQ is a unidimensional measurement in the sense that it assesses behavior primarily associated with approach- (e.g., fight) and not avoidance-related behavior (e.g., flight). Responses to angry facial expressions, on the other hand, are suggested to reveal a continuum of approach- and avoidance-related motivational tendencies that range from aggressive dominance to fearful submission (Dimberg & Ohman, 1996; Van Honk & Schutter, 2007). Finally, physical aggression was presently found to correlate with higher attentional bias scores for angry facial expressions, $r = 0.47$: $p = 0.049$, and IHI dominance, $r = 0.58$: $p = 0.01$. These observations do not only contribute to the internal consistency of the present findings, but also suggest that dominant left-to-right IHI and the attentional bias for angry faces provide a biological and cognitive emotional predictor for physical aggressive behavior.

In sum, our data suggest that on the cortical level an aggressive personality style and attentional bias for angry faces can be explained by differences in inhibitory connectivity between the left and right frontal cortex. It should however be noted that although the corpus callosum is the primary pathway responsible for IHI (Meyer, Roricht, Grafin von Einsiedel, Kruggel, & Weindl, 1995), the physiological mechanisms involved are still incompletely understood and contributions from descending unilateral pathways cannot be entirely ruled out. The fact that the frontal asymmetry model of approach- and avoidance-related behaviour emphasises the prefrontal cortex rather than M1 should be considered a limitation of the present study. However, there is increasing evidence from TMS studies to suggest that the physiological mechanisms by which M1 operates are to a reasonable extend similar to those of the prefrontal cortex (Daskalakis et al., 2008; Kahkonen, Komssi, Wilenius, & Ilmoniemi, 2005).

Even though left-to-right IHI, but not right-to-left IHI was associated with AQ scores (see also Table 1), our findings should be interpreted with caution because only AQ scores were used to describe aggression with other personality measures absent. Despite the selectivity of the present relationship possible influences of anxiety and/ or avoidance-related motivation which are assumed to be lateralized to the right frontal cortex cannot be completely ruled out as evidenced by the presently observed interrelations between attentional bias scores and IHI. Finally, the vast majority of participants in the present were female college students which should be considered a limitation when extending the present results to the male sex or the general population.

In conclusion, to our knowledge this is the first human study to establish a direct relationship between a physiological pattern of dominant left-sided interhemispheric inhibition of the right frontal cortex as evidenced by TMS and indices of aggression.

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The methodological bias

On the importance of being variable

Chapter 9

Starting as early as the 1920's, when Hans Berger introduced electroencephalography (EEG) to the world, technological advancements have made the imaging of ongoing activity in the human brain increasingly possible. A rich tradition of systematic investigation of human behavior has provided insights in many phenomena that have puzzled scientists for ages, including the mind-brain relationship. Neuroscientists are gradually succeeding in providing the neural correlates of phenomena that were formerly confined to phenomenological description. Traditionally, in evaluating how brain processes sub-serve behavior, a certain amount of error variance in the data is commonly regarded an inevitable nuisance. This variance is generally disregarded as averaged measures of neural and behavioral responses have proven to be sufficiently powerful to discriminate between conditions or subjects. Investigation of the variance around the means has therefore long been considered redundant.

A recently published paper by Garrett and colleagues (Garrett, Kovacevic, McIntosh, & Grady, 2011) however, is among one of the recent empirical pleas for considering signal variance as a genuine neural property in the study of brain-behavior relationships. In their paper, Garrett and colleagues (2011) provide a sophisticated display of how variability-based patterns of brain activation aid prediction of behavioral performance and age. In the study at hand, the authors compared predictive power of variability- and mean-based patterns of brain activity in the context of behavioral performance and age in a group of young adults and a group of older adults. Based on earlier studies, greater neural signal variability was hypothesized to be related to younger age as well as to better behavioral performance, and secondly, the patterns of variability- and mean based brain activation with predictive properties were expected to be largely spatially distinct. On the basis of the results presented, the authors conclude that neural signal variability is indeed strongly associated with younger age and better behavioral performance, and that the brain areas in which variability contributes to predictive power are highly distinct from areas in which mean-based measures of brain activity predict age and behavioral performance.

Remarkably, the set of regions in which greater brain variability corresponded to younger age and better performance is highly similar to the pattern of spontaneous activity of the resting-state brain, or default-mode network (DMN). The DMN is defined as the set of brain regions that shows coherent spontaneous BOLD-fluctuations during rest and a consistent pattern of decrease in activity during task performance. Similar to the observed spatial pattern in the Garrett et al. (2011) study, the DMN includes the dorsal and ventral medial prefrontal cortex, posterior cingulate cortex/ retrosplenial cortex and lateral parietal cortex. Interestingly, an association between the DMN and age as well as variability in task performance has also been established by recent studies on functional connectivity, showing reductions in DMN connectivity associated with older age and worse cognitive performance. Specifically, in younger adults, performance on a working memory task was positively correlated with functional connectivity within the DMN (Hampson, Driesen, Skudlarski, Gore, & Constable, 2006). In addition, studies in older adults reported profound age-related reductions in functional connectivity and intrinsic activity within the DMN that were associated with reduced cognitive performance (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008). These findings indicate that functional connectivity within the DMN is important for good cognitive performance and efficient processing. Crucially, coherency in spontaneous fluctuations in BOLD signal has been shown to account for variability in event-related brain responses (Fox, Snyder, Zacks, & Raichle, 2006). It is suggested that spontaneously fluctuating activity over brain regions may represent the system's continuous adjustment to anticipated events, thereby enhancing responsivity and efficiency (Ghosh, Rho, McIntosh, Kotter, & Jirsa, 2008). Therefore, the functional relevance of high brain variability particularly within regions of the DMN is in concurrence with the suggested role of this network in self-reflective activity, in terms of the ongoing preparation for future events.

The study by Garrett and colleagues (2011) does not stand on its own. Several earlier and more recent studies have exemplified the concept of variability in biological systems, and have reported on the functional implications (Garrett, Kovacevic, McIntosh, & Grady, 2012; McDonnell & Ward, 2011; McIntosh, Kovacevic, & Itier, 2008; Misic, Mills, Taylor, & McIntosh, 2010). For example, prior reports on the role of EEG variability and behavioral stability show a similar relation in which higher brain variability is related to lower behavioral variability, an association that is interpreted in terms of variability-enhanced capacity of the brain to process weak incoming signals, and thus facilitating transitions between functional states. (McIntosh et al., 2008). Furthermore, BOLD variability has proven sensitive to task demand, such that increased task fixation was associated with increased signal variability (Garrett et al., 2012). This effect was particularly pronounced in older and slower participants, replicating the earlier reported associations (Garrett, Kovacevic, McIntosh, & Grady, 2010; Garrett et al., 2011).

Adding exogenous noise to the brain has recently been shown to improve behavioral performance. For instance, mechanical Gaussian noise stimulation of the index finger improved sensorimotor performance in a behavioral task, an effect attributed to increased sensitivity of proprioceptors (Mendez-Balbuena et al., 2012). Likewise, transcranial random noise stimulation (tRNS) to the occipital cortex improved behavioral performance in a perceptual learning task (Fertonani, Pirulli, & Miniussi, 2011), and has even been shown to improve mood in treatment-resistant depression (Chan et al., 2012).

An intriguing question when considering variability in terms of brain-derived measures clearly is how variability –either spontaneous ongoing or task-induced- contributes to the brain as an efficient information processing system. Stochastic resonance might prove to be a key concept here. Stochastic resonance theory describes how noise in, for instance biological systems, can enhance the detection of even weak signals (Stein, Gossen, & Jones, 2005; Wiesenfeld & Moss, 1995) that would remain below threshold if no noise were added. Neurons are unmistakably threshold systems, and internal variability tailored around threshold values might greatly increase a neuron's sensitivity for in- and external stimuli. On a systems level, it might therefore well be that an increase in variability is accompanied by an increase in the potential of transitioning from one functional state to another, thereby facilitating behavioral efficiency (Fingelkurts, 2004). In figure 3.1.1, the concept of biological variability as a facilitator of behavioral performance is illustrated.

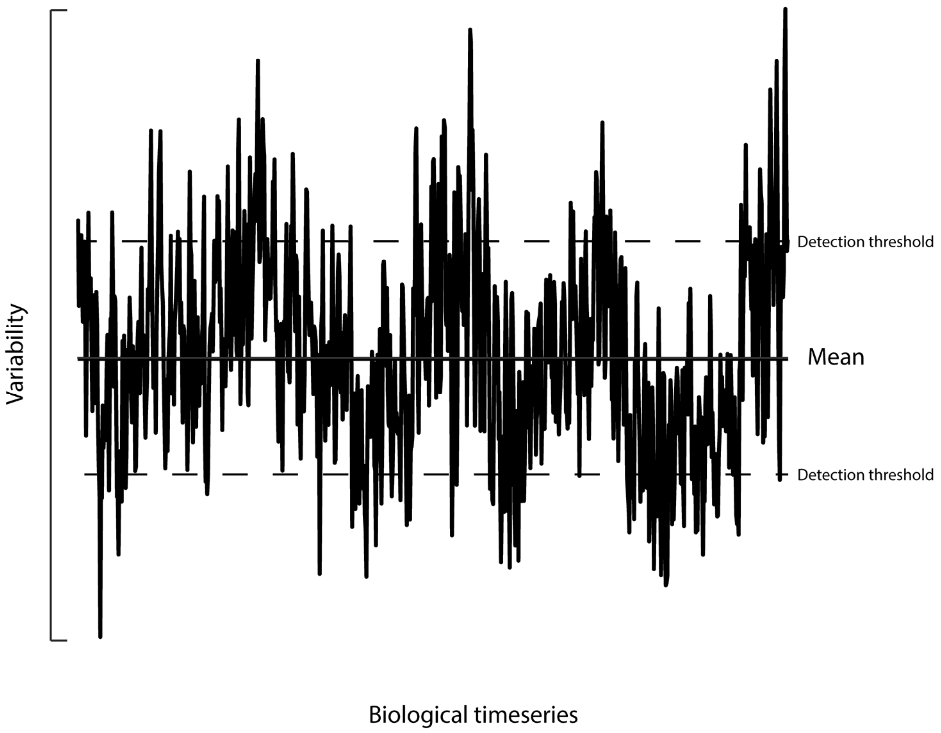

Figure 9.1. Illustration of variability in a biological timeseries and its derived mean.

Finally, considering the long history of imaging ongoing activity in the human brain and the modest role variability has played therein thus far, one might wonder what further the concept of variability can contribute to the study of brain-behavior relationships. Early studies employing single-cell recordings have shown that variability in spontaneous neuronal firing carries information in addition to the number of spikes in a certain period of time, thereby expanding the cellular information transfer capacity (for review see Stein et al., 2005). Now, studies using fMRI (Fox et al., 2006; Garrett et al., 2011) and EEG (McIntosh et al., 2008) show that brain-based variability is a predictor of behavioral performance and age, stronger even than mean-activity based predictors (Garrett et al., 2011). Recently, it was suggested that the beneficial effect on a motor learning task caused by magnetic stimulation of motor cortex might have partly been caused by a concomitant increase in motor cortex output variability (Teo, Swayne, Cheeran, Greenwood, & Rothwell, 2010). The observation of the authors that motor output variability may have driven performance enhancement, could fit the notion of increased flexibility in terms of shifting between functional states, as is necessary in acquiring new skills.

Probing brain variability as a marker for adept functioning may hold great potential for new insights in psychology and psychiatry research. Specifically, brain variability may prove to be a potential predictor of abilities such as intelligence and creativity. In the context of increased approach- as compared to avoidance-related motivational tendencies, biological signal variability could also be expected to be reflected in dominant left-to-right hemispheric variability patterns (cf. the lateralization model of motivational direction). In chapter 10, this hypothesis is tested in a sample of 60 healthy volunteers. In chapter 11, it is investigated whether the beneficiary effects of electrical stimulation of the human brain may in part arise from increases in biological variability, as has been suggested for magnetic brain stimulation (Teo et al., 2010). In sum, the recent results described above are an appeal for giving variability in brain-derived measures full consideration when studying brain-behavior relationships, and the studies reported on in the following chapters may assist to ultimately weigh the importance of being variable.

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Corticospinal state variability and hemispheric asymmetries in motivational tendencies

Chapter 10

Based on: Schutter, D.J.L.G., Hofman, D., Hoppenbrouwers, S.S, and Kenemans, J.L. (2011).
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Abstract

This transcranial magnetic stimulation (TMS) study examined interrelations between frontal asymmetrical differences in the degree of variability of cortical excitability levels and motivational tendencies. The relative standard deviation in motor evoked potentials (MEP) to single pulse TMS over the left and right primary motor cortex, and approach- and avoidance-related motivational tendencies was investigated in sixty right-handed healthy volunteers. Results showed that subjects exhibited significantly higher cortical state variability in the left as compared to the right frontal cortex and subjects displayed a dominant pattern of approach versus avoidance related motivational tendencies. Differences in left-right cortical state variability and approach-avoidance related motivation were significantly correlated and are consistent with the frontal lateralization model of motivational direction. This study demonstrates that MEP variability may provide an additional means for studying non-stationary properties of the cerebral cortex in relation to frontal asymmetries and motivational tendencies.

Introduction

State variability as opposed to inertia in physical systems has been proposed to reflect a range of metastable states that facilitates state transitions and contribute to greater internal flexibility in adapting to changing external conditions (Fingelkurts, 2004; Stein, Gossen, & Jones, 2005). Despite the fact that biological systems aim for reaching a homeostatic steady state, the non-stationary property of biological systems supposedly represents an important aspect of function (Higgins, 2002). Indeed, according to stochastic models a moderate degree of internal variability must be present in physical systems in order for these systems to operate on an optimum level. Increased signal variability observed during development for instance, has been related to lower variability in behavioural performance (McIntosh, Kovacevic, & Itier, 2008). Moreover, a recent TMS study involving primary cortex stimulation showed a positive association between motor learning performance and motor output variability (Teo, Swayne, Cheeran, Greenwood, & Rothwell, 2010). The importance of variability in biological systems is further underscored by research showing that the inability of the heart to respond during stress resulting from reduced heart rate variability increases the risk of congestive heart failure and myocardial infarction (Tapanainen et al., 2002). Furthermore, a recent resting state functional magnetic resonance imaging study demonstrated that variability in the blood oxygen level-dependent (BOLD) signal was a more powerful predictor for age than the mean BOLD signal, suggesting that signal variability is more than just noise or error variance (Garrett, Kovacevic, McIntosh, & Grady, 2010).

Reductions in the variability of non-stationary electrocortical signals as indexed by fewer rapid transition processes between different (quasi) meta-stable states have been associated with various forms of psychopathology including depressive disorder (Fingelkurts, 2010). This reduction in neural transients may be indicative for a lower degree of neural complexity and subsequently lower state variability (Tononi, Sporns, & Edelman, 1996). Together these findings suggest that state variability or physiological flexibility instead of fixed homeostatic steady states is of vital importance for a biological system to adapt to changing conditions in order to maintain its functionality (McIntosh et al., 2008).

A direct way of indexing state variability on the cortical level may be through quantifying the degree of stability in excitability levels using single-pulse transcranial magnetic stimulation (TMS). In single-pulse TMS a coil is placed over a subject's scalp which is used to create secondary electric currents in superficial parts of the cerebral cortex by generating time-varying magnetic pulses (Hallett, 2000). When current intensity reaches a critical value neurons will depolarize and generate an action potential. Macroscopic response to single pulse TMS over the primary motor cortex (M1) can be measured from the contralateral hand muscles with surface electromyographic (EMG) recordings, known as the compound motor evoked potential (MEP). This approach is used to mark individual levels of cortical excitability which reflects the sum of the inhibitory and excitatory synaptic contact points on motor neurons necessary to activate the corticospinal tract and provides a means to sample state variability of excitability levels in the cerebral cortex.

The increasing environmental challenges faced by the human species during the course of evolution called for integration of primitive motivational (e.g., fight-flight), cognitive and action systems that may have contributed to the lateralized emergence of approach- and avoidance-related motivational tendencies in the anterior parts of the cerebral cortex (Davidson, 1993; Van Honk & De Haan, 2001). Previous studies have shown that cortical excitability levels reflect functional brain states underlying motivational tendencies and behaviour (d'Alfonso, van Honk, Hermans, Postma, & de Haan, 2000a; Wassermann, Greenberg, Nguyen, & Murphy, 2001). In a recent study relative higher left-to-right hemispheric levels of M1 mean cortical excitability were found to correlate with relatively greater approach-to-avoidance related motivation (Schutter, de Weijer, Meuwese, Morgan, & van Honk, 2008). The direct relations between M1 cortical excitability and motivational tendencies extend earlier electrophysiological research that found evidence for an association between the left frontal cortex and the behavioural activation system (BAS), that is approach-related motivation, whereas the right frontal cortex was related to the behavioural inhibition system (BIS), that is avoidance-related motivation (Sutton & Davidson, 1997). Factor analytic studies have demonstrated that approach-related motivation (i.e., BAS) correlates to extraverted personality styles and reward sensitivity, while the avoidance-related motivation (i.e., BIS) is linked to introverted personality styles and punishment sensitivity (Elliot & Thrash, 2002). Together the BIS and BAS scores are taken to reflect the ratio between approach- and avoidance-related motivational tendencies. The lateralized involvement of the frontal cortex in approach- and avoidance-related motivational tendencies is also known as the frontal asymmetry model of motivational direction (Harmon-Jones, 2003). In further support of this model, studies that have applied slow inhibitory repetitive TMS (rTMS) over the right frontal cortex demonstrated shifts towards more approach-related behavior (Schutter, van Honk, d'Alfonso, Postma, & de Haan, 2001; van Honk, Schutter, d'Alfonso, Kessels, & de Haan, 2002), whereas studies that applied slow inhibitory rTMS over the left frontal cortex showed a significance increase in avoidance-related behavior (d'Alfonso, van Honk, Hermans, Postma, & de Haan, 2000b; Knoch et al., 2006). Because the brain's motor circuit constitutes an integral part of the internal motivational system and behavioral output (Frijda, 1986), it is therefore not unreasonable to assume that cortical state variability as measured from M1 reflects a physiological property that is associated with motivational tendencies. In sum, the frontal asymmetry model of motivational direction predicts that a dominant motivational predisposition will go accompanied by relatively higher resting state variability of the corresponding hemisphere as measured by the coefficient of variation (Stein et al., 2002).

The primary objective of the present study therefore was to examine whether the degree of response variability to single pulse TMS over left and right M1 reflects a physiological property of the corticospinal tract with functional significance defined in terms of approach and avoidance-related motivation. Central to the idea of non-stationary brain signals and the frontal asymmetry of motivational direction (Harmon-Jones, 2003; Sutton & Davidson, 1997), we anticipated that asymmetries in corticospinal state variability between the left and right M1 would be associated with asymmetries between approach and avoidance-related motivational tendencies.

Methods

Participants

Sixty healthy non-smoking right-handed volunteers (37 females), mean ± SD age, 22.1 ± 3.55 years, were recruited among the student population at Utrecht University in The

Netherlands. Students were recruited and tested between June 2008 and May 2010 as part of ongoing TMS experiments. None of the participants had a history of psychiatric or neurological conditions. Written informed consent was obtained and volunteers received payment for participation. All volunteers were naïve to the aim of the studies. All studies from which data were collected for the present study were in accordance with the standards set by the Declaration of Helsinki (Edinburgh Amendments) and approved by the medical ethical committee of Utrecht University.

Procedure

Prior to the experiments subjects received oral and written information on the experiment and were screened for contraindications to TMS (Keel, Smith, & Wassermann, 2001). After informed consent was obtained right handedness was assessed with the Edinburgh handedness inventory (Oldfield, 1971), mean ± SD, 44.55 ± 2.83, and the BIS/BAS questionnaire (Carver & White, 1994) to assess avoidance and approach-related motivational tendencies was administered. Next, resting motor threshold (rMT) for the left, mean ± SD, 47.13 ± 7.54, and right M1, mean ± SD, 45.58 ± 7.89, were determined (Schutter & van Honk, 2006) using biphasic magnetic brain stimulators (maximum output 4160 A peak /1750 VAC peak) and iron core coils (Neotonus, Atlanta, USA). After completion of rMT assessment, 11 x 17 mm Ag-AgCl electrodes were attached in a belly-tendon arrangement and participants were instructed to relax and keep their hands still. The active electrodes were placed over the muscle belly of the left and right abductor pollicis brevis (APB). Reference electrodes were placed over the proximal phalanx of the left and right thumb. The CMS-DRL electrodes serving as the ground were attached to the right wrist. EMG signals were digitized at 16 kHz, low-pass filtered (-3 dB cut-off frequency: 3334 Hz; roll-off: 30 dB/octave).

Twelve motor evoked potentials were recorded from the left and right APB to 120% rMT single-pulse TMS to the right and left M1 in random order at variable time intervals (frequency ≤ 0.2 Hz). Stimulation parameters were in accordance with the International Federation of Clinical Neurophysiology safety guidelines (Wassermann, 1998).

Data reduction and analysis

Average scores on the BIS and BAS scale (scoring range: 1-4) were calculated for each individual. EMG signals were offline high-pass filtered (-3 dB cut-off frequency: 20 Hz; roll-off: 48 dB/octave) and the MEP was quantified as the peak-to-peak amplitude of the maximal EMG response. In each individual cortical state variability (CSV) was defined as the coefficient of variation by computing the standard deviation of the left and right M1 MEP. The coefficient of variation was calculated for the left and right hemispheric separately according to the formula:$(SD\ MEP\ amplitude)/(average\ MEP\ amplitude)$ (Harris & Wolpert, 1998; Stein et al., 2005).

Results

TMS was well tolerated by the subjects and no adverse events occurred.

The GLM for repeated measurements testing hemispheric differences showed significantly higher CSV values for the left (mean ± SD, 0.72 ± 0.04) as compared to the right hemisphere (mean ± SD, 0.62 ± 0.04), $F(1,59) = 4.24$: p = 0.044 (two-tailed) (Figure 1a). This difference could not be explained by a difference in average MEP amplitude between the left (mean ± SD, 1.7 ± 1.52 mV) and right hemisphere (mean ± SD, 1.9 ± 1.97 mV), $F(1,59) = 0.49$: p = 0.485 (two-tailed).

The GLM for repeated measurements testing differences in motivational tendencies demonstrated significantly more approach (mean ± SEM, 3.04 ± 0.08) than avoidance-related motivation (mean ± SEM, 2.54 ± 0.07), $F(1,59) = 29.00$: $p < 0.001$ (two-tailed) (Figure 1b). The Pearson product-moment correlational analysis showed that the absolute corrected difference between left CSV and right CSV [(left CSV - right CSV) / (left CSV + right CSV)] was associated with the absolute corrected difference between the approach- and avoidance-related motivation scores [(BAS –BIS) / (BAS+ BIS)], r(58) = 0.26: p = 0.044 (two-tailed). (Figure 1c).

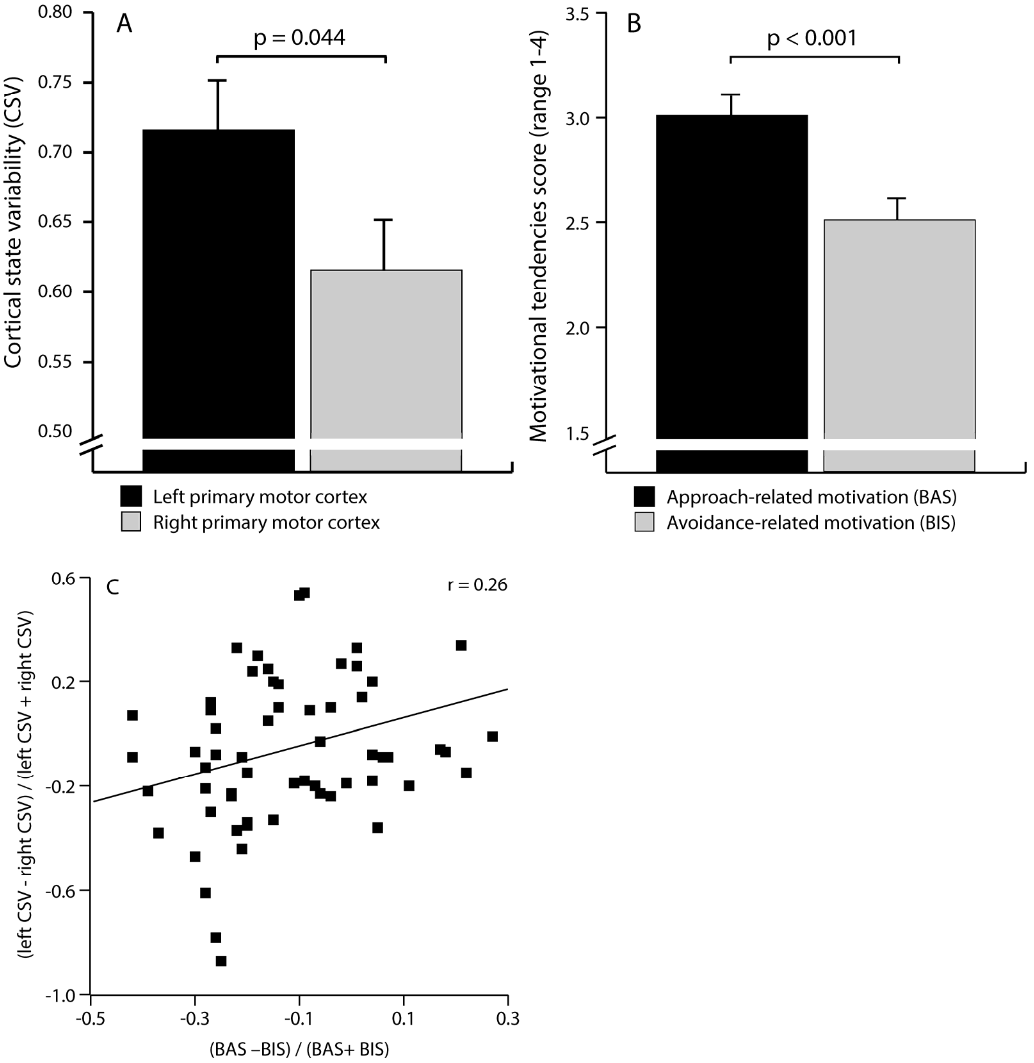

Fig. 10.1. (A) Higher cortical state variability in the left as compared to the right hemisphere; (B) significantly higher approach than avoidance related motivational tendencies; (C) higher left-to-right cortical state variability [(left CSV – right CSV)/(left CSV + right CSV)] is associated with more approach than avoidance related motivational tendencies [(BAS – BIS)/(BAS + BIS)]. Error bars represent standard error of the mean.

Discussion

The aim of the present study was to explore interrelations between cortical state variability (CSV) and indices of motivational tendencies. In accordance with the frontal asymmetry of emotion we observed that more approach as compared to avoidance related motivation is related to relative increased left-to-right sided CSV. This finding could not be explained by differences in absolute MEP amplitude suggesting that the variability of cortical excitability may represent a unique physiological property of the cerebral cortex associated with motivation and behavior in general.

In contrast to deterministic models, stochastic models assume a certain degree of variability in biological systems necessary for the ability to adapt to changing conditions. From this line of reasoning inert systems are inflexible and supposedly less able to cope with external events, an ability required for reaching an optimum level of functionality. Thus, signal variability can be more than just noise or measurement-related error variance (Garrett et al., 2010; Stein et al., 2005).

Findings showing that young adults aged 20-33 years demonstrated significant higher variability in electrocortical responses and more stable response times in a memory task as compared to children aged 8-15 years offer a developmental perspective on the functional role of biological viariability (McIntosh et al., 2008). These results support the idea that brain maturation is accompanied by the emergence of a growing number of available states and transients, arguably indicative of increasing neural complexity subserving functional/ behavioural efficiency (Friston, 1997). Increased availability of meta-stable states and transitions as indexed by higher levels of variability thus contribute to optimizing performance. Here, we propose that the increased CSV of the left hemisphere mirrors an aspect of cerebral dominance which, in line with the frontal lateralization models of emotion, may bias behavioural responses related to approach-related motivation and is related to increased behavioural flexibility (Baas, De Dreu, & Nijstad, 2008)This interpretation concurs with earlier observations of lowered variability of electrocortical signalling in depressive disorder (Fingelkurts, 2010; Lefaucheur et al., 2008) and may suggest possible CSV reductions of the left (i.e., ‘approach-related motivation’) as compared to the right frontal cortex (i.e., ‘avoidance related motivation’) in patients suffering from depressive disorder. In contrast, an opposite hemispheric pattern of CSV may increase the propensity to engage in aggressive behaviour (Hofman & Schutter, 2009).

Related to neurophysiological variability is the concept of plasticity. In general terms plasticity can be defined as the property of the nervous system to change its organizational and functional characteristics. Furthermore, cortical plasticity can be viewed as the process associated with the continuous shaping of cortical circuits and excitability levels driven by various forms of internal and external input. Thus, it may be suggested that CSV as opposed to inertia is a necessary condition for cortical plasticity. In other words, cortical circuits that do not demonstrate sufficient variability will not be responsive to various forms of manipulation including the application of non-invasive brain stimulation techniques such as paired associative stimulation (Classen, Liepert, Wise, Hallett, & Cohen, 1998; Daskalakis, Christensen, Fitzgerald, & Chen, 2008). If proven correct then CSV could a possible marker for treatment outcome. Consequently, part of the effectiveness of noninvasive brain stimulation techniques could possibly depend on increasing CSV (Fingelkurts, 2010) which may give rise to the question whether there can be too much variability in cortical excitability levels (Hofman & Schutter, 2009) Even though this is beyond the scope of the present study, it is not unlikely that the brain operates within a dynamic but restricted range of excitability levels in order to maintain both flexibility as well as a certain amount of stability (Quartarone, Siebner, & Rothwell, 2006).

It should however be noted that single cell recording studies have demonstrated that variability in inter-spike intervals should be considered an additional source of information rather than neuronal noise (Higgins, 2002; Stein et al., 2005). Analogously, fluctuations in MEP amplitude to single-pulse TMS over the primary motor cortex may provide additional information concerning changes in inhibitory and excitatory processes in the corresponding cerebral hemisphere. Although MEPs externally triggered by single-pulse TMS constitute a reliable method for indexing this variability, it does not allow for high frequency measurements of spontaneous activity used in single cell recording studies. As previous TMS studies have shown, single-pulse stimulation at low frequencies in a repetitive fashion can affect cortical physiology (Rossi, Hallett, Rossini, & Pascual-Leone, 2009). Therefore, CSV in the present study was assessed at very low (≥ 0.2 Hz) sampling frequencies. Furthermore, varying inter-stimulus intervals were introduced to minimize the possibility of underestimating signal variability. Sampling at relative fixed intervals in oscillatory systems might possibly result in sampling at approximately the same time point during a cycle. The relation between relative fixed versus true random sampling of cortical excitability in a certain time interval is therefore another important issue that deserves further discussion and attention in future studies. In spite of these limitations, this is to our knowledge the first evidence suggesting that short-term variability in MEP amplitudes to single pulse TMS may reflect a genuine functional property of the primary motor cortex.

Finally, in line with earlier reports (Garrett et al., 2010; McIntosh et al., 2008) it would be interesting to examine how CVS levels as measured with single pulse TMS behave over longer time intervals (e.g., hours-days-weeks) to obtain more information on the dynamics and stability of CSV.

In conclusion, the present TMS study is a first attempt to show that non-stationary properties of the cerebral cortex are associated with motivational tendencies, and may provide additional ways for studying the functional relevance of intra-individual variability in cortical excitability levels.

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Transcranial direct current stimulation increases resting state EEG variability in the beta frequency range: A pilot study

Chapter 11

Hofman, D., Bethlehem, R.A.I., Kenemans, J.L. and Schutter, D.J.L.G..

Abstract

Studies evaluating the physiological changes related to transcranial direct current stimulation (tDCS) have thus far focused on mean-based measures of cortical activity. Recent reports however suggest that biological signal variability may also have functional properties in the neural system. The aim of the present study was to examine the effects of tDCS on electroencephalogram (EEG) resting state signal variability while examining possible interactions with steroid hormones known to affect cortical excitability. In a double-blind cross-over design resting state EEG was recorded in healthy female volunteers who received real and sham low intensity tDCS targeting the frontal cortex on four separate occasions during the early follicular and luteal phase of the menstrual cycle. A significant increase in EEG signal variability was observed in the β frequency range following real tDCS. Although the increase in ß-band variability during the luteal phase seemed to contribute most to the main effect, no statistical interactions with menstrual phase were found. This finding suggests that studying electrophysiological variability and steroid hormones may contribute to understanding the physiological mechanisms by which tDCS establishes its effects.

Introduction

Transcranial direct current stimulation (tDCS) has in recent years regained its reputation as valuable tool for studying brain-function relationships non-invasively. Manipulation of mood and behavior have been reported in a variety of clinical and experimental settings, such as depression (Kalu, Sexton, Loo, & Ebmeier, 2012; Loo et al., 2012), working memory functioning (Fregni et al., 2005; Miniussi et al., 2008) and motor performance (Reis & Fritsch, 2011; Reis et al., 2008). Although for a range of cortical functions the beneficiary effects of tDCS have been demonstrated, the physiological mechanisms by which these effects come about remain unclear.

Thus far, studies evaluating the physiological changes related to tDCS have focused on mean-based measures of cortical activity. Using transcranial magnetic stimulation (TMS), increases of cortical excitability following anodal tDCS have been demonstrated, as well as decreases of excitability following cathodal stimulation (Nitsche & Paulus, 2000, 2001; Stagg & Nitsche, 2011). Whereas studies on tDCS related changes in mean blood oxygen level-dependent (BOLD) signal values in primary motor cortex (M1) yielded no clear effects (Antal, Polania, Schmidt-Samoa, Dechent, & Paulus, 2011; Kwon et al., 2008), electrophysiological studies have been moderately successful in identifying tDCS induced changes in ongoing as well as task-related oscillatory activity. For instance, electrophysiological changes related to tDCS have been reported in the θ (4-7 Hz) and α (8-12 Hz) band, as well as the ß (13-30 Hz) band (Jacobson, Ezra, Berger, & Lavidor, 2011; Keeser et al., 2011; Zaehle, Sandmann, Thorne, Jancke, & Herrmann, 2011).

Studies attempting to identify a neurophysiological mechanism that could explain the effects of tDCS focused on the changes in transmembrane potentials as initiators of excitability changes of neuronal cells (Stagg et al., 2009; Stagg & Nitsche, 2011). Arguably, tDCS modulates the neuronal resting membrane potential, thereby affecting neural population's firing rate at intensities well below the threshold for eliciting action potentials (Nitsche et al., 2003; Terzuolo & Bullock, 1956; Wagner, Valero-Cabre, & Pascual-Leone, 2007). A mechanism directly related to neural excitability is stochastic resonance (Wiesenfeld & Moss, 1995). Stochastic resonance theory describes how signal variability in, for example biological systems can enhance the detection of even weak signals that would remain below threshold if no noise were added (Stein, Gossen, & Jones, 2005; Wiesenfeld & Moss, 1995). Neuronal populations can be regarded threshold systems, and internal variability tailored around threshold values might greatly increase the neural population's sensitivity for external events, such as task demands and -switching. On a systems level, it might therefore well be that an increase in variability is accompanied by an increase in the potential of transitioning from one functional state to another, such as switching between tasks and maintaining task performance (McDonnell & Ward, 2011; McIntosh, Kovacevic, & Itier, 2008). Indeed, earlier reports on the role of brain-based variability and behavioral stability show a relation in which higher brain variability is related to lower behavioral variability. This association then is interpreted in terms of a variability-enhanced capacity of the brain to process weak incoming signals (McIntosh et al., 2008).

Thus, increases in sensitivity for external input can be considered a candidate mechanism supporting behavioral and affective effects induced by tDCS. In humans, natural fluctuations in neuronal excitability occur in females during the menstrual cycle (Smith, Adams, Schmidt, Rubinow, & Wassermann, 2002; Smith et al., 1999). These changes in steroid hormone levels are marked by the rise and descent of two steroid hormones: estradiol in the premenstrual (follicular) phase, followed by a longer lasting progesterone peak in the post-menstrual luteal phase (Vollman, 1977). Interestingly, the luteal phase of the cycle has on the cortical level been shown to result in reduced cortical excitability as compared to the follicular phase (Finocchi & Ferrari, 2011; Smith et al., 2002; Smith et al., 1999). This observation suggests that the relatively high levels of progesterone in the luteal phase result in increased inhibitory activity in human cortical tissue. This reduced cortical excitability is proposed to result from increased inhibitory GABA-ergic activity, which in turn has been linked to cognitive deficits (Enomoto, Tse, & Floresco, 2011; Shilyansky et al., 2010). Taken together, these studies leave progesterone a candidate steroid hormone for modulating task performance through affecting cortical activity

The present pilot study aimed to explore the potential of tDCS as a modulator of resting-state electrophysiological signal variability. In order to assess potential interactions with steroid hormone induced fluctuations of cortical excitability we implemented a four session counterbalanced within subjects design in which normally cycling females were stimulated in both the follicular and luteal phase using real and sham tDCS. We hypothesized real tDCS to result in increased frontal electrophysiological signal variability, without the need for a concomitant increase in mean signal power. Secondary to this primary hypothesis, we anticipated the luteal phase in which progesterone levels are high to potentiate the effect of real tDCS as compared to the follicular phase.

Material and Methods

Participants

Eight healthy non-smoking right-handed female volunteers, mean age ± SD, 24.5 ± 3.66, were recruited at Utrecht University campus, Utrecht, The Netherlands. None of the volunteers had a history of psychiatric or neurological conditions. All volunteers reported to have a regular menstrual cycle and were medication free. Participants were naïve to the aim of the study and were paid for participation. Written informed consent was obtained from all participants, and the study was approved by the local ethical committee.

Resting state electroencephalogram

EEG was recorded from 32 scalp locations according to the International 10-20 EEG System using Ag-AgCl-tipped electrodes (sampling rate: 256 Hz). Electro-oculogram (EOG) was recorded from bipolar montages from the sub- and supra-orbital regions of the right eye and the outer canthi of the eyes. Raw EEG recordings were made with the ActiveTwo system (the active electrode is a sensor with very low output impedance, system by BioSemi, Amsterdam, The Netherlands) relative to the common mode sense (CMS). By physically integrating the first amplifier stage with a sintered Ag-AgCl electrode, extremely low-noise recordings free of interference can be achieved, which is of critical importance to the present study since measurement noise would contaminate ‘true’ electrophysiological variability. The ground consists of the active CMS and passive driven right leg (DRL) electrode which are positioned on the scalp to form a feedback loop driving the participant’s average potential as close as possible to the analog-to-digital converter (i.e., the amplifier “zero”) reference voltage in the A/D-box.

Transcranial direct current stimulation

A battery-driven Eldith DC-stimulator Plus (NeuroConn GmbH, Ilmenau, Germany) was used for stimulation with conductive-rubber electrodes placed in wet sponges saturated with Parker Spectra 360 electrode gel (Parker Laboratories, Fairfield, USA). The anodal and cathodal electrode (3 x 5cm) were placed under the stretchable electrode cap between the F3-C3 and F4-C4 electrode sites of the International 10-20 System respectively. Current intensity was set at 350 μA and total stimulation duration was 10 minutes excluding 30s ramping up and ramping down the intensity. Maximum current density during active tDCS was 0.023 $\mu A/cm^2$ and impedance limit was set to < 20 kΩ. In the sham stimulation condition, stimulation was stopped after the 30s ramp up.

Progesterone assay

To confirm fluctuations in progesterone levels over the cycle, saliva samples were obtained ~ 30 minutes before tDCS. Saliva samples were frozen immediately after each laboratory session and stored at -25° Celsius until assay at the Department of Biopsychology, TU Dresden, Germany. After thawing, the sampling tubes used for passive drooling were centrifuged at 20,000 rpm for 5 min, resulting in mucous compounds being restricted to the lower part of the tube. Salivary progesterone concentrations were measured using commercially available hemiluminescenceimmuno-assays with high sensitivity (IBL International, Hamburg, Germany). Averaged, log-transformed progesterone levels confirmed progesterone levels to be higher in the luteal than in the follicular phase: $t = 2.05$, $p= 0.049$ (two-tailed).

Procedure

Participants received sham or active tDCS on two separate sessions during the early follicular (mean test days from beginning of cycle: real 3.5, SD 2.14 and sham 3.38, SD 1.4) and luteal (mean test days from beginning of cycle: real 18.3.5, SD 1.6 and sham 18.5, SD 1.51) phase of their menstrual cycle in a randomized fashion, see figure 1. Testing hours were kept constant throughout all four sessions. Participants were instructed not to consume coffee, tea and chocolate in the two hours prior to testing and to refrain from alcohol or drugs for at least 24 hours before each session. Upon arrival at the laboratory, participants were prepared for EEG recording and tDCS electrodes were placed over the target sites. Next, subjects were seated in a comfortable dentist chair in a dimly lit room adjacent to the control room and instructed to relax and keep movements to a minimum. A four-minute baseline resting state EEG, in which one minute of eyes open was alternated with one minute of eyes closed was recorded. The baseline resting state EEG recording was followed by 10 minutes of tDCS and the session was concluded with a second four minute resting state EEG recording within 5 minutes after tDCS had ended.

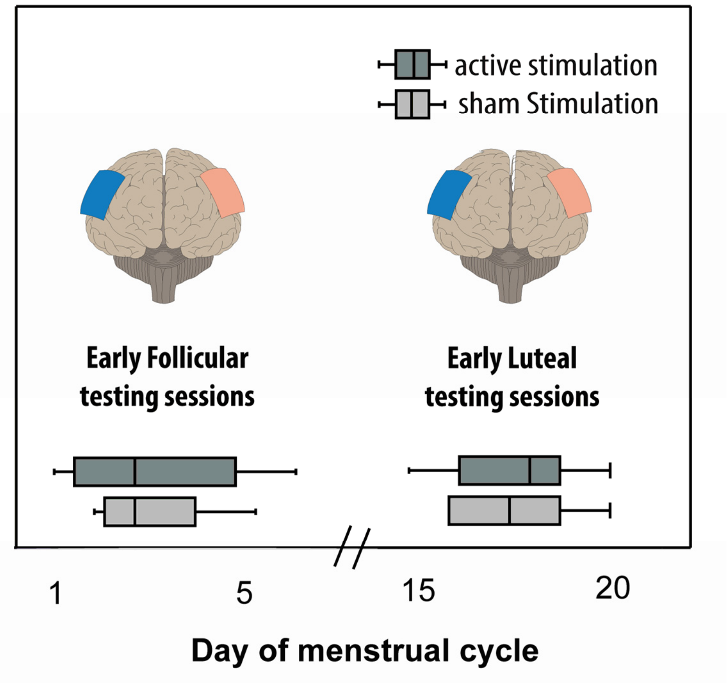

Figure 11.1. Design of the present study. Participants were tested in two phases of their menstrual cycle in a randomized, sham-controlled tDCS protocol. Grayed-out bars indicate testing periods, plotted against the days of the menstrual cycle, depicted on the x-axis.

Data reduction and analysis

Raw EEG signals were referenced to the average signal of the 32 electrodes and further chunked into 4-s epochs. To minimize interfering electromyographical activity in the EEG recordings, power and variability estimates were performed using the 120 seconds containing the EEG from the eyes-closed epochs. Epochs containing residual muscle movements and other artifacts resulting in amplitudes greater than -/+ 50 μV were rejected prior to further analysis. Artifact-free EEG was band-pass 1-30 Hz filtered (48 dB/octave) and spectral power in the δ (1-4 Hz), θ (4-8 Hz), α (8-12 Hz) and β (13-30 Hz) frequency bands was estimated by a fast Fourier transform (Hanning window length: 10%) for the C3, F3, C4 and F4 electrode, and averaged over all remaining epochs. EEG variability was computed by dividing standard deviation by its average power (Harris & Wolpert, 1998).

Greenhouse-Geisser corrected general linear models (GG-GLM) for repeated measurements were used to examine the main effects of tDCS (within-subject factor: active versus sham) and to explore interactions with phase of the menstrual cycle (within-subject factor: follicular versus luteal) on the amplitude and amplitude variability in the δ, θ, α and β frequency band of the selected electrodes (within-subject factor: C3, C4, F3, F4 electrode). Alpha level of significance was set at 0.05 (two-tailed) throughout.

Results

Stimulation was well tolerated by all participants and no adverse events occurred. All participants reported the tingling sensation under the electrodes at the start of stimulation, but none of the participants was able to reliably distinguish real from sham tDCS on the basis of self-report.

EEG mean power

Separate GG-GLMs for the δ, θ, α and β frequency band revealed neither a significant main effect of tDCS nor a tDCS x phase of the menstrual cycle interaction on resting state EEG mean power, all p-values > 0.11.

EEG variability

For the ANOVA testing the variability effects, a significant main effect of tDCS was observed on resting state EEG amplitude variability in the β frequency band solely, $F(1, 7)= 6.27$, $p= 0.04$, $\varepsilon= 1$, partial $\eta^2= 0.47$. **Figure 2** depicts the significant increase in amplitude variability in the β frequency range following real as compared to sham tDCS.

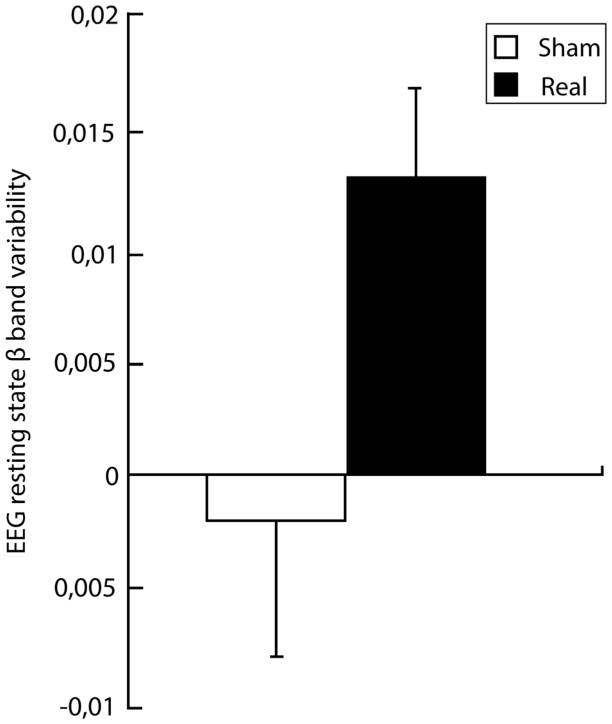

Figure 11.2. EEG resting state amplitude variability in the β frequency range increases following real as compared to sham tDCS.

The interaction between tDCS condition and phase of the menstrual cycle was not significant, $F(1, 7)= 0.30$, p= 0.60, ε= 1, partial $\eta^2= 0.04$. Although not statistically legitimated, we conducted an exploratory analysis in an attempt to inform our a priori hypothesis on the effect of low versus high progesterone on EEG variability. Testing contributions of both phases to the observed main effect revealed that the contribution to seemed to be larger in the luteal phase, $F(1, 7)= 7.18$, p= 0.03, ε= 1, partial $\eta^2= 0.51$, as compared to the early follicular phase cycle, $F(1, 7)= 2.15$, p= 0.19, ε= 1, partial $\eta^2= 0.24$. Statistical interactions with electrode location were not observed, p-values> 0.66. For the δ, θ and α frequency bands, no main effect of stimulation nor interactions were observed, all p-values> 0.14.

Discussion

Here, we aimed to explore the potential of tDCS as a modulator of electrophysiological signal variability. In a counterbalanced within subjects cross-over design we tested the effects of sham and real tDCS during the follicular and luteal phase. Results showed an increase in frontal electrophysiological ß-band signal variability, not paralleled by a possible confounding increase in mean signal power. The anticipated interaction with phase of the cycle did not reach significance, although post-hoc exploration of the main effect on β -band variability suggested the luteal phase to be the larger contributor to the increase in electrophysiological variability.

The fact that the effect was observed in the β-band of the frequency spectrum is in line with the suggestion that during rest, the brain shows distinct electrophysiological patterns, in the spatial as well as the frequency domain (Mantini, Perrucci, Del Gratta, Romani, & Corbetta, 2007; Rosanova et al., 2009). Resting state frequency of oscillatory activity has been shown to increase from occipital cortex to the frontal areas, in functional networks (Mantini et al., 2007), as well as in spontaneous oscillatory activity after perturbation (Rosanova et al., 2009). This notion coincides with recent accounts on the functional relation between the frontal cortex and EEG beta oscillations (Hofman & Schutter, 2011; Swann et al., 2009), as well as reports on the association between β synchronization and motor control (Conway et al., 1995; Halliday, Conway, Farmer, & Rosenberg, 1998; Kilner, Baker, Salenius, Hari, & Lemon, 2000; Kilner et al., 2003). Taken together, these findings suggest ß-band activity to be a candidate target rhythm for modulation of human function.

Human task performance has thus far predominantly been related to mean measures of neural activity, but systematic investigation of variance around these means has in recent years gained ground as useful supplementary approach (Deco, Jirsa, & McIntosh, 2011). Studies using electro- or magnetoencephalography (McIntosh et al., 2008; Raja Beharelle, Kovacevic, McIntosh, & Levine, 2012), functional magnetic resonance imaging (fMRI) (Garrett, Kovacevic, McIntosh, & Grady, 2010, 2011) and transcranial magnetic stimulation (TMS) (Schutter, Hofman, Hoppenbrouwers, & Kenemans, 2011; Teo, Swayne, Cheeran, Greenwood, & Rothwell, 2010) have now shown relations between increased levels of neural variability and increased behavioral and motor performance as well as motivational direction. Effects of tDCS on, for instance motor learning could therefore in part benefit from increases in neuronal variability, thereby facilitating cortical plasticity. Noise-driven enhanced capacity to switch between functional states may foster behavioral skills such as motor learning (Teo et al., 2010), or even recovery from psychiatric conditions (Chan et al., 2012).

The present low-intensity stimulation protocol did not affect overall mean power for the frequency bands investigated. It is conceivable that the current stimulation protocol was not sufficient to induce amplitude modulations under resting state conditions, but still was able to influence the cortical brain state as suggested by elevations in resting state EEG β band variability. In addition, as the estimation of mean amplitudes is done by averaging over prolonged periods of sampling, signal variability could prove a more sensitive measure to pick up initial changes in cortical activity that would remain unnoticed by mean-based measures. Although not formally permitted, explorations of our main effect suggested the luteal phase wherein progesterone is high to be the main contributor to the increase in β -band variability. This observation coincides with our a priori hypothesis that progesterone would facilitate the effect of low intensity tDCS on EEG activity through its effect on GABA-ergic activity, resulting in altered cortical excitability. The present pilot study may contribute to the growing awareness that steroid hormones may play a significant role in the effects of low intensity tDCS and other brain stimulation techniques (Huang, Wei, Chou, & Su, 2008; Schutter & van Honk, 2010).

In conclusion, considering signal variability in brain-derived measures in studying brain-behavior relationships may hold promise as a fundamental mechanism underlying behavioral and affective change. Considering naturally occurring fluctuations in steroid hormone levels may further inform the possibilities of potential therapeutic intervention.

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Epilogue

Chapter 12

The present thesis started with expressing the ambition to describe what mechanisms enable man to successfully cope with social challenge. To that end, we adopted an approach rooted in social neuroscience methods and guided by evolutionary doctrine. The main tenet in the first two parts of this thesis is that human behavior to a certain extent can be described in terms of *response biases,* the third part explores an alternative to the *methodological bias*. The studies from part 1 show that automatic response biases enable individual safeguarding as well as the establishment of social coexistence. Successful social coexistence is primarily dependent on the formation of stable social hierarchies, which are in part established through dominance contests, or even aggression. Part 2 therefore focuses on the individual biases in the expression of the motivation to dominate or aggress. Aggressive behavior may to a certain extent be adaptive, in contemporary societies individual success also depends on the amount of control one is able to exert over one's impulses. Such a functional repertoire might be reflected in the amount of intrinsic individual biological variability, a proposition investigated in part 3. The series of studies reported on in the present thesis are summarized in table 1.

In the first part, response biases that serve to protect an individual as well as its group members are described. These biases conceivably generalize to the whole of the population, and even extend into other species in line with the proposition of 'common descent' (Darwin, 1871). Therefore, this part is referred to as 'The normative bias'. First, in chapter **3**, the premise that non-verbal communication through emotional facial expressions serves an alarm function that prepares the observer(s) for responding to possible threat was tested (Blair, 2003; Preston & de Waal, 2002). To that end, fearful, happy and neutral facial expressions were presented – fearful faces defensibly associated with action preparation – shortly after which magnetic pulses to the M1 were delivered. Changes in CST excitability using the motor evoked potential (MEP) were recorded. Functional coupling of emotional processing and action tendencies as indexed through CST excitability has been established in earlier TMS studies (Schutter, de Weijer, Meuwese, Morgan, & van Honk, 2008; Wassermann, Greenberg, Nguyen, & Murphy, 2001).

Table 12.1. Aims and main findings of the empirical chapters of this thesis.

chapter	aim	main findings
3	*Investigate the notion of non-verbal communication through emotional facial expressions as an alarm function that prepares the observer for threat.*	Fearful facial expressions, but not happy or neutral facial expressions resulted in increased MEP amplitude.
4	*Investigate the mechanisms that regulate coping with fairness in the context of proximate and distal social interdependence.*	Proximate: mimicry of unfair happy faces is attenuated. Distal: increased angry mimicry of unfair actors and decreased angry mimicry of fair proposers.
6	*Investigate the explanatory power of frontal resting state β-band oscillatory activity, and add spatial specificity to the asymmetry model.*	Asymmetries over the anterior electrode locations proved to be related closest to trait aggression, while asymmetries over the central electrode locations were associated with response inhibition.
7	*Investigate the feasibility of the asymmetry in cortical – subcortical processing mode as a correlate of dominance motivation, and relate these two measures of attentional bias for angry faces, as well as it concurrent electrophysiological pattern.*	Increasing dominance motivation causes the δ/β asymmetry to shift towards greater δ prominence and reduced β presence. N170 in response to angry faces decreased with increased dominance motivation, whereas the attentional bias increased.
8	*Investigate the CC as a mechanism of allostasis in the frontal asymmetry of emotion model.*	Left-to-right IHI significantly is related to AQ scores. Increased left-to-right paralleled by reduced right-to-left IHI showed increased attentional bias for angry facial expressions.
10	*Investigate differences in the degree of variability of cortical excitability levels as a predictor of motivational tendencies.*	Modeling CSV and BIS/BAS scores in an interhemispheric asymmetry results in a significant correlation between CSV and behavioral approach.
11	*Investigate the effects of tDCS on EEG resting state signal variability while examining possible interactions with steroid hormones known to affect cortical excitability.*	A significant increase in EEG signal variability was observed in the β frequency range following real tDCS. Increases in ß-band variability during the luteal phase seemed to contribute most to the effect.

For example, in a study testing baseline CST excitability against behavioral approach and avoidance tendencies, it was shown that higher levels of left hemispheric excitability was mirrored in increased approach motivation (Schutter et al., 2008). Presenting participants with fearful facial expressions, but not happy or neutral facial expressions resulted in increased MEP amplitude. These findings provide the first direct evidence for increases in CST excitability to threat, and concur with earlier evolutionary views on the physiological resultants of fear stimuli (LeDoux, 1996; Ohman, 1986).

Positioning the observed modulation of MEP amplitude in one of three stages of social information processing shows how closely connected the conceptual levels are. For one, the presentation of a face conceivably results in activation of the FFA (Haxby, Hoffman, & Gobbini, 2000), a ‘labeled lines’, dedicated process at the perception stage of social information processing (Adolphs, 2010). A soon as 300ms after onset of the face, the emotional expression has modulated the functional resultant such that it matches the prediction made by the fearful face better; the possibility of impending threat.

Where chapter 3 demonstrated the functional significance of the fearful face, chapter **4** describes what possible mechanisms may come into play when maintaining social coherence is at stake. Probing implicit norm compliance, we manipulated fairness of confederates in an economic bargaining game. First, it was shown that mimicry of happy faces is attenuated in response unfair interaction, while mimicry of angry facial expression remains relatively unaffected. Second, after the bargaining game, when the proposers have acquired either a fair or unfair reputation, we observe increased angry mimicry of proposers with an unfair reputation and decreased angry mimicry of fair proposers. These findings provide direct empirical evidence that non-conscious mimicry is modulated by fairness, and may even suggest that mimicry can function strategically, serving short-term personal goals as well as long-term societal goals. Thus, emotional facial expressions fulfill a paramount communicatory function in human sociality, expressing affiliation- as well punishment motivation.

The interpretation of the present data from chapter 4 is directly inspired by the PAM as described by Preston & de Waal (2002). If we consider the PAM as depicted in chapter 2, figure 2.2, mimicry as used in the present study, as a measure of interdependence should be positioned in the motor domain of the PAM. Clearly, this interdependence is also manipulated in the present experiment: during interaction one still is dependent on whether the confederate shares or not, and therefore as long as the game continues, overt expression of punishment behavior could be costly. After the game, the immediate urge for consideration of one's personal loss or gain has lessened. Through automatic increases of the imitation of the angry facial expression, it could be argued that resentment from unfairness is communicated. Taken together, proximate goals can increase interdependence and thereby imitation to facilitate cooperation, but also decrease interdependence and imitation when norms are violated (Preston & de Waal, 2002). Long-term goals similarly affect interdependence, but now the cause of the modulation of imitation behavior is sought in the shared norm that makes up human societies (Preston & de Waal, 2002). Within this framework, the differential modulation of facial mimicry can be rooted in fairness-modulated interdependence, were proximate and distal goals show different modulation of facial mimicry (Hofman, Bos, Schutter, & van Honk, 2012).

The reflexive imitation of the emotional facial expressions used in the fairness experiment lends towards the functional attributes awarded to the basic category of social perception (Adolphs, 2010). The observed imitation however, as the precursor of simulation, shows distinct marks of the social cognition and regulation categories. Despite its implicit and automatic properties, it seems affected by causes or motives that are typically ascribed to social cognition or – regulatory processes. As such, the exact mechanisms by which these behaviors are brought about remain to be clarified. This again stresses the original claim made by Cacioppo & Berntson (1992) to maintain a multilevel outlook on social neuroscience issues. It also shows how, as a superordinate level of explanation, evolution theory can contribute to social neuroscience as a guideline for the implementation of theoretical as well as empirical approaches to social neuroscience.

Ever since Darwin's 'Origin of the species' and 'Descent of man', the concept of evolutionary adaptedness as an explanatory heuristic in affect and cognition has been adopted as a phenomenon shared throughout the animal universe. Also in the present thesis, the adaptive value of behaviors observed in the experimental setups (responding to fear and (un)fairness) has been stressed and positioned in an evolutionary context.

Indeed, many psychological phenomena as the ones observed in the experiments reported on can be framed in our evolutionary history. In applying an evolutionary-based explanation to an empirical finding however, some caution may be warranted. Considering the difficulty that the mental faculties as described by Darwin have left little or no mark in the remainder of our ancestors, our account of their coping with environmental challenge is confined to assumption (Richardson, 2007). For instance, evolutionary accounts typically presume that our mental functions have evolved as a result of natural selection, where it is perfectly possible that they are the result of evolution modulating some other (related or not) property (Bolhuis & Wynne, 2009). As such, an evolutionary approach to social neuroscientific questions can be used to derive valuable clues as how to interpret a certain mechanism, but would benefit heavily from the approaches and tools detailed in the prologue to actually tap into the mechanisms of study, and vice versa.

Part 2 takes the concept of biased responding to the level of the individual. In the studies reported in this part, the research focus is to a certain extent orthogonally dimensioned to the approach of part 1. Heedful of the normative bias, the three chapters 6 – 8 investigate the degree to which individual biases modulate universal mechanisms of motivation and affect. By now, several studies have come up with genetic and structural predictors for personality traits suggesting that is a characteristic that can differ much between individuals, but should show constancy over different contexts (Kanai & Rees, 2011). Rather than taking interindividual differences as a source of noise in the study of human behavior, it can also be employed as an additional level of explanation. For instance, it might well be that experimental manipulations might not lead to group-level differences, but prove to modulate behavior dependent on an individual's personality trait (Calder, Ewbank, & Passamonti, 2011).

Especially the regulatory influence exerted by the PFC in the processing of emotion and motivation renders this structure a primary candidate source of individuality in motivation and emotion (Barbas, Saha, Rempel-Clower, & Ghashghaei, 2003; Damasio, 1996; Davidson, 1998; Davidson, Putnam, & Larson, 2000; Harmon-Jones, Gable, & Peterson, 2010; LeDoux, 1996).

Studies into the nature of PFC involvement in emotion and motivation have given rise to a successful cortical centred theory on affective and social processing: The frontal asymmetry of emotion model. As a behavioral mechanism of coping with environmental stress, approach and withdrawal tendencies represent the very basic repertoire. It is observed in the simplest of species up to primates, and is argued to be present at any level of phylogeny where behavior itself is present (Davidson, 1992, 2004). Particularly with the evolvement of networks complex as the human brain, functional asymmetries may have evolved to preclude conflicts between action tendencies (Davidson, 2004; van Honk & Schutter, 2006)

The current asymmetry model of motivation states that approach-related behaviors are subserved by left-hemispheric frontal processing, whereas withdrawal or avoidance behaviors are mediated by right-hemispheric activity (Harmon-Jones, 2003; van Honk & Schutter, 2006).

C**hapter 6** first investigates a hypotheses derived from the asymmetry model, and further specifies its predictive power. In this study, we followed the approach taken in the Schutter and colleagues study (2008), and we investigated whether individual differences in trait aggression and behavioral inhibition were reflected in the same asymmetrical patterns of frontal resting state β-band oscillatory activity. In addition, instead of probing M1 excitability, we investigated the selective contributions of the prefrontal and motor cortex areas to these associations. We showed that relative dominant right frontal β-band oscillatory activity was related to heightened trait aggression and reduced response inhibition. Testing specificity of the several contributing electrode locations was able to further inform this relation. Specifically, asymmetries over the anterior electrode locations proved to be related closest to trait aggression, while asymmetries over the central electrode locations were associated with response inhibition.

Our study further extends the asymmetry model by adding local specificity. By showing that β-band activity over M1 electrode locations (C3/C4) is particularly sensitive to measures of motor inhibition, whereas β-band activity over more anteriorly situated electrode locations shows increased affinity with self-report measure of aggressive behavior, we refine the model and further embed it in social neuroscience literature. The link between asymmetrical frontal activity and aggressive behavior has long been established (Harmon-Jones & Allen, 1998), but the covariation of putatively related factors has thus far not been extensively described. Therefore, the role of β-band activity as a more powerful predictor as compared to α-band activity in terms of association as well as selectivity shows that the model is well capable of incorporating new measures and concepts (Hofman & Schutter, 2011). β-band activity as a superior predictor (compared to α-band activity) of personality and task performance might lie in its prominence in (sensori) motor areas (Engel & Fries, 2010; Jensen et al., 2005). β-band has been shown to reflect cortical inhibition (Jensen et al., 2005), and has therefore been proposed to play a role in hemispheric asymmetries. This notion is illustrated by studies showing that pre-stimulus β-band surges predict successful inhibition of behavioral responses (Ruiz, Strubing, Jabusch, & Altenmuller, 2010). In addition, human M1 has been identified as an output target of inhibitory influence in the network of behavioral motor control. Studies employing TMS in Go-no-Go tasks have shown rises in GABA-mediated intracortical inhibition in no-go trials, suggesting that voluntary inhibition of behavior is ultimately exerted at the M1 level (Coxon, Stinear, & Byblow, 2006; Sohn, Wiltz, & Hallett, 2002).

In **chapter 7**, we conceptually build on chapter 6 and exploit the interpretation of β-band oscillatory activity as an inhibitory rhythm. As chapter 6 showed, β-activity modeled in a cortical interhemisperic asymmetry can be used as a predictor of aggressive behavior and impulse control. In chapter 7, we employed β-activity as an index of cortical control over subcortical drive, as expressed in low-frequency oscillatory activity in the δ-band. Computing the ratio between the two frequencies thus yields an asymmetry in cortical – subcortical processing mode, which in turn was used as a correlate of dominance motivation. We showed that with increasing dominance motivation, the δ/β asymmetry in oscillatory activity shifts towards greater δ prominence and reduced β presence, a pattern arguably reflecting a state of relative subcortical dominance over cortical activity. In addition, N170 in response to faces decreased with increased dominance motivation. In the context of incentive processing, the asymmetry in δ/β activity has been proposed a proxy for indexing asymmetrical subcortical and cortical processing. β-band oscillatory activity has been shown to originate from cortical mechanisms, in which inhibitory GABAergic interneurons play a central role (Traub, Bibbig, LeBeau, Buhl, & Whittington, 2004; Uhlhaas & Singer, 2006). Recent accounts of high-frequency oscillations have suggested that particularly β-band activity might reflect the inhibitory properties of GABAergic interneurons. On a functional level, β-oscillations have been linked to the maintenance of the current cognitive or motor state (Engel & Fries, 2010), thereby providing a mechanism for the control of intrinsic motivation. In contrast, δ -Band activity is suggested to stem from limbic and subcortical generators, such as the brainstem, ventral tegmental area (VTA), nucleus accumbens (NAcc) and thalamus, and has been interpreted to reflect the drive for reward (Knyazev, 2007, 2012; Steriade, McCormick, & Sejnowski, 1993; Uhlhaas, Roux, Rodriguez, Rotarska-Jagiela, & Singer, 2010). Studying the asymmetry in δ/β therefore might further add to the asymmetry model of emotion and motivation as it is able to incorporate aspects of the balance between cortical and subcortical structures, as stressed in normative theories of emotion regulation (Damasio, 1996; LeDoux, 1996; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008).

Together these findings suggest that dominance motivation is related to the behavioral response to signs of aggression. This relation is reflected in the resting state asymmetry in δ/β activity, and in the present study is complemented by a reduced N170 in response to facial expressions. The face-sensitive N170 is generally taken to be the earliest electrophysiological component reflecting the processing of faces (presumably reflecting the 'core system', chapter 2, figure 2.1). The here observed modulation of an early 'labeled lines' component of social perception (Adolphs, 2010) directly suggests that the information processing categories of social cognition and – regulation can modulate early perceptual processes. Therefore, the modulatory influence of individual biases stemming from cognition or regulatory processes may point towards tight integration of emotional category and facial feature processing. Recent studies focusing on the interplay between affective significance and perceptual processing indeed shown that even at very early stages, saliency of the stimulus affects perceptual processing (Luo et al., 2010; Pourtois, Spinelli, Seeck, & Vuilleumier, 2010). These results are in line with the earlier discussed dual-path model as formulated by LeDoux (1996), in which the fast, subcortical route via the amygdala is able to affect cortical processing. A recent study by Lim and colleagues further extends this model by showing that the amygdala indeed shapes the perceptual experience of affectively significant stimuli, and importantly, that this amygdala influence is mediated by frontal activity (Lim, Padmala, & Pessoa, 2009). Through mediation of amygdala influence on visual cortical responses, the prefrontal cortex may therefore be the structure reflecting individual biases in social-affective behavior. Finally, the causal role of the PFC in regulatory control over affect-induced response patterns was tested in a study manipulating PFC activity. Employing repetitive TMS to the left PFC, thereby reducing its activity, it was shown that disruption of activity in this region was reflected in increases in behavioral errors during trials that required emotional control (Volman, Roelofs, Koch, Verhagen, & Toni, 2011).

The last chapter of part 2 aimed to provide an adaptive mechanism for the approach and withdrawal systems described in chapters 5 and 6. As noted, the left PFC is predominantly implicated in the processing of approach-related behavior, whereas the right PFC is mainly related to withdrawal-related behavior (chapter 5). Faced with challenge however, an organism should be able to adjust dominant motivational stance according to situational demand. Such ‘allostasis’, or ‘stability through change’ (McEwen, 1998) has been proposed a critical mechanism in maintaining an organism’s homeostasis. In humans, the CC is the main trajectory for information transfer between the cerebral hemispheres, and therefore **chapter 8** aimed to relate functional integrity of the CC to basic motivational stance. Through TMS of the bilateral motor cortices, functional interhemispheric connectivity between the left and right cerebral hemisphere was indexed (Ferbert et al., 1992). Functional interhemispheric connectivity was quantified through interhemispheric inhibition (IHI) using TMS, which was related to AQ scores (Buss & Perry, 1992), and attentional biases for angry facial expressions. In line with our expectations, we showed that left-to-right IHI significantly correlated with higher AQ scores. This pattern reflects that with increasing left hemispheric dominance over its right homologue, trait aggression increases. Furthermore, we showed that individuals displaying increased left-to-right paralleled by reduced right-to-left IHI showed increased interference when presented with angry faces. By showing that interhemispheric information transfer is related to motivational stance, we show the feasibility of the CC as a mechanism of allostasis. Although scarce, studies investigating the role of the CC in affect confirm its involvement in a variety of socio-affective skills. For instance, agenesis of the

CC has been shown to result in deficiencies in social cognitive abilities such as theory of mind (Symington, Paul, Symington, Ono, & Brown, 2010). Aberrant patterns of interhemispheric connectivity have also been found in borderline personality disorder patients with alexithymic traits, a condition marked by deficits in the ability to process emotions (Lang et al., 2011).

The three studies described in part two paint a picture in which the PFC takes in a central place. Modeled in an interhemispheric balance, an aggressive personality style is related to left PFC dominance over the right PFC (chapters 6, 8). Left hemispheric dominance is further characterized by increased attentional biases for angry facial expressions, a mark of dominance behavior arguably driving aggressive trait (Van Honk & Schutter, 2007). Directly testing the notion that dominance motivation is expressed in attentional vigilance for angry facial expressions confirmed this relationship, and through the assessment of the electrophysiological component reflecting the processing of the face, we suggested a mechanism by which such attentional capture could occur. Finally, the study described in chapter 7 adds a new dynamic to the asymmetry model: the asymmetry in cortical and cortical processing as expressed in the ratio between δ- and β-oscillatory activity. This proposition is in line with the triple imbalance model as proposed by van Honk and colleagues in which it is stated that imbalances at several levels of cortical communication predispose to aggressive behavior (van Honk, Harmon-Jones, Morgan, & Schutter, 2010).

Together, the studies from part 2 illustrate how individuality is reflected in systems that bear the mark of human development. Although nearly every human being will present with the biological and functional mechanisms described above, the extent to which they are expressed in behavior might vary greatly between individuals. As such, evolution can be taken to set the stage for the human behavioral repertoire, but the play is still performed by individual actors. The mechanisms by which such individuality may be instantiated are presented in figure 12.1 as a research heuristic.

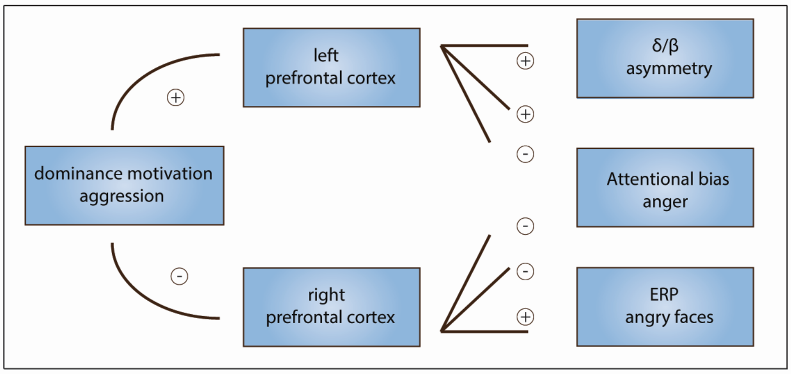

Figure 12.1. Dominance motivation and aggression are reflected in dominant left-hemispheric activity. Further, increased dominance motivation and aggression is marked by increased δ/β asymmetries, attentional biases but decreased ERPs to angry facial expressions.

Where in the parts one and two behavioral and brain biases in coping with our environment were discussed, part 3 focuses on the methods and conventions that describe these biases. For psychologists who aim to describe the behavioral and cortical properties of human function, variability is commonly merely a nuisance. The most obvious way of dealing with variability in psychology is simply repeating stimulus presentation and report averaged responses – with an index of variability as an attribute of measurement error. This *methodological bias* has resulted in a under appreciation of the relationship between behavioral variability and brain variability. Since early acknowledgements of the notion that variability in brain-derived measures is a property of the system (Arieli, Sterkin, Grinvald, & Aertsen, 1996), studies further illuminating the role of biological variability in cognitive neuroscience have only sparsely been appearing. The recent years however have seen the tide turning: several reports have begun to shed light on the functional properties of biological variability, and its beneficial effects have even inspired a recent review to rename the phenomenon of stochastic resonance in neural systems to ‘stochastic facilitation’ (McDonnell & Ward, 2011). It has been proposed that brain variability, comparable to the waxing and waning of EEG waves or attentional lapses during sustained mental effort, reflects an organizational principle of continuous exploration of functional representations that together make up the brain’s dynamic repertoire (Deco, Jirsa, & McIntosh, 2011; Fingelkurts, 2004; Ghosh, Rho, McIntosh, Kotter, & Jirsa, 2008). The notion of a dynamic repertoire that is maintained by the continuous exploration of functional possibilities motivated **chapter 10**. In this TMS study, we examined interrelations between frontal asymmetrical differences in the degree of variability of cortical excitability levels and motivational tendencies. Motivational tendencies in the present study were described by the balance in behavioral approach and inhibition as measured with the BIS/BAS scales (Carver & White, 1994). The relation between cortical state variability (CSV) in motor evoked potentials (MEP) to single pulse TMS over the left and right primary motor cortex, and approach- and avoidance-related motivational tendencies was investigated in sixty right-handed healthy volunteers. We showed that modeling CSV and BIS/BAS scores in an interhemispheric asymmetry results in a significant correlation between the two, a relation that is consistent with the frontal lateralization model of motivational direction. This study demonstrates that MEP variability may provide an additional means for studying non-stationary properties of the cerebral cortex in relation to frontal asymmetries and motivational tendencies. Moreover, the positive relation between dominant left-hemispheric CSV and dominant behavioral approach suggests that the behavioral tendency to explore the environment (BAS-fun seeking), persistence to obtain goals (BAS-drive) and the sensitivity to reward (BAS-reward responsiveness) indeed is reflected in increased CSV in the hemisphere arguably subserving such patterns of behavioral approach. As such, neurophysiological variability is conceptually closely related to plasticity. Cortical plasticity can be regarded a process associated with the continuous shaping of cortical circuits and excitability levels driven by various forms of internal and external input (chapter 10). Thus, it could be that cortical variability is a necessary condition for cortical plasticity. In other words, cortical circuits that do not demonstrate sufficient variability will not be responsive to various forms of manipulation. This proposition was substantiated empirically by a recent study showing that theta burst stimulation (a magnetic stimulation paradigm able to potently induce cortical plasticity) to the human M1 enhanced motor learning, in which the authors claim that the observed facilitation was likely due to increased motor output variability (Teo, Swayne, Cheeran, Greenwood, & Rothwell, 2010). Therefore, the notion of beneficial effects of brain stimulation techniques being at least partly dependent on modulation of brain variability is a research topic that may hold great promise.

In **chapter 11** we investigated this possibility. Particularly, we examined the effects of tDCS on EEG resting state signal variability while examining possible interactions with steroid hormones known to affect cortical excitability. In a double-blind cross-over design resting state EEG was recorded in healthy female volunteers who received real and sham low intensity tDCS targeting the frontal cortex on four separate occasions during the early follicular and luteal phase of the menstrual cycle. A significant increase in EEG signal variability was observed in the β frequency range following real tDCS. Although the increase in ß-band variability during the luteal phase seemed to contribute most to the main effect, no statistical interactions with menstrual phase were found. This finding suggests that studying electrophysiological variability and steroid hormones may contribute to understanding the physiological mechanisms by which tDCS establishes its behavioral effects. The fact that the effect was observed in the β-band of the frequency spectrum is in line with the suggestion that during rest, the frequency of oscillatory activity increases from occipital cortex to the frontal areas, in functional networks (Mantini, Perrucci, Del Gratta, Romani, & Corbetta, 2007), as well as in spontaneous oscillatory activity after perturbation (Rosanova et al., 2009). In addition, we observed that progesterone facilitated the effect of low intensity tDCS on EEG activity. The mechanism by which this modulatory influence is brought about is unclear, but the commonplace explanation would refer to its effect on GABA-ergic activity, resulting in altered cortical excitability (Finocchi & Ferrari, 2011; Smith et al., 1999). Despite its limitations, the results presented in chapter 11 may contribute to the growing awareness that steroid hormones play a significant role in modulating cortical functioning (Huang, Wei, Chou, & Su, 2008; Schutter & van Honk, 2010).

The first hints of the extent to which exogenously adding noise to a biological system is able to facilitate behavioral performance, or alleviate pathology, are now starting to appear. As noted above, magnetic stimulation of M1 has been suggested to facilitate motor learning through the induction of additional noise, increasing brain variability (Teo et al., 2010). On a further note, peripherally inducing noise in the sensorimotor system proved to result in creased stability in sensorimotor performance, interpreted to be instigated by noise-induced increases in sensorimotor receptor sensitivity (Mendez-Balbuena et al., 2012). Finally, transcranial random noise stimulation (tRNS) has also been shown to be able to significantly improve mood in major depressive disorder, even beyond the effects of tDCS (Chan et al., 2012). These observations render noise stimulation a candidate technique for the alleviation of psychopathology, next to established stimulation protocols such as high and low frequency rTMS and tDCS (Terney, Chaieb, Moliadze, Antal, & Paulus, 2008).

Considering brain measures of biological variability in the broader context of the present thesis unmistakably indicates its importance in facilitating behavioral adaptation to ever changing environmental demands. A certain amount of plasticity in the cortical systems subserving behavior is a form of adaptedness required to efficiently and timely coping with environmental challenge. The motivation to actively explore an individual’s surroundings arguably adds to an individual’s functional repertoire through the accumulation of new knowledge and skills. Inevitably, variation between, and variability in, members of a species is necessary for mechanisms of evolution to discern between individuals at all, and therefore the study of variability in biological systems deserves the attention that has recently been accumulating on the topic.

Concluding remarks

The studies reported on in the present thesis hopefully illustrate the importance of keeping a multilevel outlook on human social behavior. Despite an impressive accrual of empirical knowledge since the advent of neuroimaging methods, the necessity of multidisciplinary approaches has become ever clearer. Man is equipped with a brain that holds the experience of many predecessors – and within these boundaries, we give rise to a remarkable individuality. To disentangle the contributions of the normative and individual biases present in our patterns of behavior is a challenge social neuroscience will be occupied with for many more years.

Together, our studies suggest several new avenues in the study of human social behavior. For example, the extent to which imitation indeed serves as a strategic means in non-verbal communication still needs to be investigated, as no behavioral measure of such strategic motivation was incorporated in the present experiment. The frontal asymmetry of emotion model could benefit from incorporating spatial specificity in its prediction of behavior. We showed that more central regions of PFC were more predictive of motor inhibition, but the extent to what such specificity extends is unclear, and for future studies to determine. Also, as this spatial specificity could depend on the functional characteristics of the frequency band of study, taking into account interactions between oscillatory frequency and topographical location could further specify the model. Moreover, the consideration of EEG ratios in asymmetrical configurations could possibly further identify whether the predictive power of the asymmetry model lies in cerebral activity per se, or is dependent on specific (ratios between) frequency bands. We showed that variability in biological systems can also be regarded a functional property of an organism. As such, manipulation of biological variability might be a possibility to intervene with psychopathology. If variability, be it in a certain brain network, indeed is indicative of the brain's potential to employ a certain repertoire in coping with upcoming events, enhancing this potential might be worthwhile pursuing.

In closing, all of this would not have been possible if mankind would resemble the man created by Robert Musil in his infamous novel. As noted, man can be taken to have qualities however, and we have gladly taken advantage of that fact.

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Nederlandse samenvatting

Ons brein heeft mede door de ervaring van onze voorgangers zijn huidige vorm gekregen. Een dergelijke 'continuïteit van de geest', zoals Charles Darwin voorstelt in zijn ‘The Descent of Man’, beschrijft hoe, vergelijkbaar met fysieke kenmerken van de mens, gemeenschappelijke afstamming inzicht kan geven in onze mentale vermogens. Zij zijn het resultaat van evolutie door natuurlijke en seksuele selectie, en bieden inzicht in welke eigenschappen en gedragingen succesvol zijn geweest in de ontwikkeling van de menselijke soort. De mens heeft aangetoond dat zij om kan gaan met dreiging, zij heeft sociale structuren ontwikkeld die zowel sterke als zwakkere soortgenoten herbergen, en heeft gedurende dat alles voldoende variatie in zijn individuele leden behouden om als soort om te gaan met toekomstige uitdagingen.

Dit proefschrift beoogt te beschrijven welke mechanismen de mens in staat te stelt succesvol met in het bijzonder sociale uitdaging om te gaan. De focus in de eerste twee delen van dit proefschrift ligt op het evenwicht tussen de bescherming van het individuele belang versus het in stand houden van stabiele sociale structuren. Het eerste deel beschrijft in termen van normatieve gedragspatronen, dat wil zeggen patronen waarvan verondersteld wordt dat zij bij ieder individu aanwezig zijn, hoe min of meer automatische gedragsneigingen het individu kunnen beschermen, maar ook het samenleven in sociale groepen mogelijk maken. Succesvol samenleven is primair afhankelijk van stabiele sociale hiërarchieën, die voor een deel gevormd worden door dominantie over anderen, en soms zelfs door agressie. Deel twee richt zich daarom op verschillen in de mate waarin individuen dominant of agressief gedrag laten zien. In hedendaagse samenlevingen hangt individueel succes ook af van de mate waarin men in staat is om eigen gedragsimpulsen te controleren, en zich dus aan te passen aan specifieke situaties. Een dergelijke functioneel gedragsrepertoire is afhankelijk van een flexibel biologisch systeem, een eigenschap die wellicht wordt weerspiegeld in de hoeveelheid intrinsieke biologische variabiliteit. Deze stelling is onderzocht in deel drie, door juist variatie rondom gemiddelde waarden van activiteit in het menselijk brein te gebruiken als een voorspeller van gedrag.

In hoofdstuk 3 is getest of non-verbale communicatie door middel van emotionele gezichtsuitdrukkingen als een alarmfunctie voor dreigend onheil kan dienen. Om dit te kunnen doen werden angstige, blije en neutrale gezichtsuitdrukkingen getoond aan een groep gezonde proefpersonen. De rationale achter de emotionele gezichtsuitdrukkingen is dat angstige gezichten automatisch zouden leiden tot actiepreparatie in het brein van de proefpersonen. Deze actiepreparatie is te meten door kort na het tonen van de gezichten met magnetische pulsen de primaire motorcortex (M1) te stimuleren met behulp van transcraniële magnetische stimulatie (TMS). Dit resulteert in spieractiviteit van bijvoorbeeld de duim, activiteit die te kwantificeren is in zogenaamde motor evoked potentials (MEPs): de registratie van de grootte van de beweging van de duim veroorzaakt door de magnetische stimulatie van M1. De amplitude van een MEP kan op deze wijze inzicht geven in de prikkelbaarheid van het gestimuleerde gebied, waarbij een verhoogde actiepreparatie zich manifesteert in een verhoogde prikkelbaarheid van de corticospinale baan, wat terug te zien is in een verhoogde MEP amplitude. Het tonen van angstige gezichtsuitdrukkingen aan de proefpersonen leidde tot een verhoogde MEP amplitude, een effect dat niet werd waargenomen bij de neutrale of blije gezichtsuitdrukkingen. Deze bevinding is het eerste directe bewijs voor toename in corticale prikkelbaarheid bij het waarnemen van angst bij anderen, een automatische reactie die individuen beter voorbereidt op het omgaan met plotselinge dreiging.

Waar hoofdstuk 3 een functie van het angstige gezicht voor het individu laat zien als het gaat om dreiging, is hoofdstuk 3 vooral gericht op de mechanismen die mogelijk een rol spelen bij het in stand houden van sociale structuren. Door *eerlijk gedrag* als een impliciete sociale norm te manipuleren in een economisch uitwisselingsspel, waren we in staat automatische reacties op eerlijk en oneerlijk gedrag tijdens en na het spel te meten. Als maat voor reacties op oneerlijk gedrag is gemeten in hoeverre proefpersonen de emotionele gezichtsuitdrukkingen imiteerden. Over het algemeen wordt aangenomen dat imitatie van gezichtsuitdrukkingen er automatisch voor zorgt dat er een sociale band ontstaat tussen mensen; door bijvoorbeeld ook een beetje droevig te gaan kijken naar een verdrietig persoon laat je zien dat je de ander begrijpt. In ons uitwisselingsspel op de computer lieten we zien dat imitatie van blije uitdrukkingen van oneerlijke spelers ten opzichte van een voormeting afneemt, terwijl imitatie van boze uitdrukkingen van oneerlijke spelers nauwelijks verandert. Bij eerlijke spelers zagen we geen veranderingen ten opzichte van de voormeting. Na het uitwisselingsspel, waarin de computerspelers zich ofwel een eerlijke ofwel een oneerlijke reputatie verworven, zien we een toename van de imitatie van boze uitdrukkingen van spelers met een oneerlijke reputatie, en juist verminderde imitatie van boze uitdrukkingen van eerlijke spelers. Bij de blije uitdrukkingen werden geen verschillen gevonden ten opzichte van de voormeting. Deze resultaten laten zien dat onbewuste imitatie van gezichtsuitdrukkingen wordt beïnvloed door eerlijkheid, en suggereren dat deze vorm van imitatie een strategische functie heeft. Zo wordt er tijdens het uitwisselingsspel, wanneer er nog geld te verdienen valt, geen risico gelopen en blijkt door het uitblijven van de imitatie van de blije uitdrukking van oneerlijke spelers passief dat men zich niet gedraagt volgens de eerlijkheidsnorm. Als het spel is afgelopen, wordt de boze uitdrukking van de oneerlijke speler beantwoord met meer boze imitatie, terwijl de eerlijke speler wordt beantwoord met verminderde boze imitatie. Mogelijk wordt hier een automatisch en onbewust mechanisme zichtbaar, dat er aan bijdraagt dat complexe sociale structuren als de onze in stand gehouden worden door te stimuleren dat ieder individu zich aan ongeschreven sociale normen houdt.

Deel één beschrijft enkele mechanismen die de mens als soort mogelijk hebben geholpen om te gaan met dreiging en het leven in complexe sociale structuren. Deel twee onderzoekt de mate waarin individuele eigenschappen deze universele gedragsmechanismen beïnvloeden. Studies hebben inmiddels aangetoond dat er genetische en structurele voorspellers voor persoonlijkheidskenmerken zijn, wat suggereert dat individuen veel van elkaar kunnen verschillen, maar dat die verschillen in meer of mindere mate constant zijn in een verscheidenheid aan sociale contexten. In de mens is met name de frontale cortex (FC) in verband gebracht met de regulatie van emoties en motivatie, en is dus een bron van individualiteit in gedrag. Studies naar de aard van de FC betrokkenheid bij emotie en motivatie hebben geleid tot een succesvolle theorie over affectieve en sociale verwerking: het frontale asymmetrie model van emotie. Het asymmetrie model van emotie stelt dat de linker FC voornamelijk betrokken is bij benadergedrag (inclusief boosheid), terwijl de rechter FC voornamelijk betrokken is bij vermijdingsgedrag (inclusief angst). Deze fundamentele gedragingen worden teruggevonden in de eenvoudigste diersoorten tot in primaten en mensen, en vormen de functionele basis voor het omgaan met dreiging en het najagen van beloning.

In hoofdstuk 6 is met behulp van het elektro-encefalogram (EEG) een hypothese direct afgeleid van het asymmetrie model onderzocht. EEG is de registratie van elektrische hersenpotentialen onder sensoren die worden aangebracht op de hoofdhuid. Het menselijk EEG weerspiegelt post-synaptische potentialen van grote aantallen (meestal 10 miljoen tot 1 miljard cellen per sensor) piramidale cellen in de cerebrale cortex. In het EEG zijn verschillende frequenties aanwezig, elk met zijn eigen functionele kenmerken. Zo is bijvoorbeeld activiteit in de β-band (12-30 Hz) in verband gebracht met de actieve onderdrukking van afwijkingen van het huidig gedrag. In deze studie onderzochten we of de mate waarin men agressief gedrag vertoont en problemen heeft zijn/haar impulsen te controleren werd weerspiegeld in asymmetrische patronen van frontale β-band activiteit van het brein in rusttoestand. Daar bovenop onderzochten we de selectieve bijdragen van de prefrontale en motorische cortex gebieden aan het voorspellen van agressie en respons inhibitie. In hoofdstuk 6. werd aangetoond dat dominantie van de rechter frontale cortex in termen van β-band activiteit gerelateerd was aan verhoogde agressie en verminderde respons inhibitie. Daarbij lieten we zien dat de asymmetrie in de voorste elektrode locaties voornamelijk gerelateerd was aan agressie, terwijl asymmetrie op de middelste elektrode locaties voorspellend was voor respons inhibitie.

Uit hoofdstuk 6 bleek frontale asymmetrische β-activiteit een voorspeller van agressief gedrag en respons inhibitie te zijn. In hoofdstuk 7 hebben we β-activiteit gebruikt als een indicator van corticale controle over subcorticaal gegenereerde impulsen, gemeten in laagfrequente EEG activiteit in de δ-band (1-4 Hz). Activiteit in de δ-band is in eerdere studies naar voren geschoven als een correlaat van de neiging om dominant gedrag te vertonen, en de verhouding tussen de δ en β activiteit weerspiegelt mogelijk de mate waarin de cortex in staat is subcorticale neigingen te reguleren. Ook hebben we nu de gedragsreactie op boze uitdrukkingen gemeten. Door mensen te vragen de kleur van een gezicht te benoemen zonder daarbij aandacht te besteden aan de uitdrukking van het gezicht, kan vastgesteld worden in hoeverre zij afgeleid worden door een emotioneel gezicht ten opzichte van een neutraal gezicht: soms doet men daar langer over, soms korter. Daarbij hebben we een extra EEG maat gebruikt om de reactie op boze gezichtsuitdrukkingen te registreren: de *event-related potential* (ERP). Een ERP laat zien welk effect de aanbieding van een stimulus in een bepaalde taak heeft, en geeft daardoor informatie over het onderliggende verwerkingsproces. We toonden aan dat naarmate men een dominantere persoonlijkheid heeft, de δ / β verhouding opschuift naar meer δ- en verminderde β-bijdrage aan de ratio. Daarnaast bleek dat dominante individuen langer deden over het benoemen van de kleur van boze gezichten, wat duidt op verhoogde aandacht voor elementen in de omgeving die de dominante positie van het individu kunnen bedreigen. Als laatste bleek dat de ERP voorafgaand aan het benoemen van de kleur van het gezicht liet zien dat de gedetailleerde verwerking van gezichten minder werd naarmate dominantie toenam.

Het laatste hoofdstuk van deel twee richt zich op het mechanisme dat aanpassingen van benader- en vermijdgedrag in verschillende situaties mogelijk zou kunnen maken. Wanneer organismen geconfronteerd worden met veranderende omgevingseisen moeten zij in staat zijn te schakelen tussen benader- en vermijdgedrag, om optimaal aan te sluiten bij de nieuwe sociale orde. Bij de mens vormt het corpus callosum (CC) de belangrijkste structuur in het brein voor informatieoverdracht tussen de hersenhelften, en daarom test hoofdstuk 8 de functionele integriteit van het CC als voorspeller van agressie en dominantie. De mate van communicatie tussen de linker en rechter hemisfeer door het CC werd gekwantificeerd door middel van interhemisferische inhibitie (IHI) met behulp van TMS. Zoals we verwachtten was links naar rechts IHI significant gecorreleerd met hogere agressie. Dit suggereert dat met toenemende links hemisferische dominantie over het rechter homologe gebied, de waarschijnlijkheid van agressief gedrag toeneemt. Verder toonden we aan dat wanneer we het patroon van rechts op links IHI ook meenemen, de gedragsreactie op boze uitdrukkingen ook te voorspellen valt. Samengenomen laten deze bevindingen zien dat het menselijk CC inderdaad gerelateerd is sociaal-emotioneel gedrag. Gezien het feit dat het CC de belangrijkste structuur is voor informatie-uitwisseling tussen de beide hemisferen vormt deze witte stof baan een belangrijke kandidaat-structuur is om schakelingen tussen benader- en vermijdgedrag mee te verklaren.

De studies in deel twee van het proefschrift illustreren hoe individualiteit tot uitdrukking komt in het menselijk brein, dat toch de gedeelde geschiedenis van de menselijke ontwikkeling draagt. Ieder mens zal de biologische en functionele mechanismen zoals hierboven beschreven laten zien, maar de mate waarin zij worden uitgedrukt in gedrag kan sterk variëren tussen individuen. Als zodanig kan evolutie beschouwd worden als een kader in het interpreteren van menselijk gedrag, waarbinnen variatie tussen individuen een belangrijke factor is wanneer het gaat om het beschrijven en voorspellen van dit gedrag.

Waar in de delen een en twee gedrags- en hersenen patronen betrokken bij het omgaan met omgevingseisen werden besproken, richt deel drie zich op de methoden en conventies die deze patronen normaal gesproken beschrijven. Vaak wordt aangenomen dat het beschrijven van gedrag lijdt onder variabiliteit in het presteren van bijvoorbeeld proefpersonen: het introduceert ruis rondom een gemiddelde taakprestatie. De meest voor de hand liggende manier van omgaan met variabiliteit in de psychologie is het simpelweg herhalen van de stimulus presentatie en het rapporten van de gemiddelde prestatie – eventueel met een indicatie van de variabiliteit als een attribuut van de meetfout. Deze methodologische conventie heeft er toe geleid dat de relatie tussen gedragsvariabiliteit en hersenvariabiliteit nauwelijks onderzocht is.

De studies die wel gedaan zijn suggereren dat variabiliteit in hersenactiviteit een organisatorisch principe is dat de continue exploratie van responsmogelijkheden voorbereid: het brein is continue bezig met het genereren van voorspellingen over de toekomst. Deze stelling is onderzocht in hoofdstuk 10. Gebruik makend van het frontale asymmetrie model, onderzochten we de relaties tussen variabiliteit in corticale prikkelbaarheid (vergelijkbaar met de toepassing in hoofdstuk 3) en benader- en vermijdgedrag. We toonden aan dat corticale variabiliteit in de linker FC samenhangt met meer benadergedrag, zoals voorspeld zou worden aan de hand van het asymmetriemodel.

Dit duidt er op dat ook basale gedragspatronen afhankelijk zijn van biologische flexibiliteit, iets wat deels afhankelijk is van variabiliteit in hersenactiviteit.

Neurofysiologische variabiliteit is dus conceptueel nauw verwant aan corticale, en misschien ook functionele plasticiteit. Corticale plasticiteit kan worden beschouwd als de voortdurende aanpassing van corticale circuits en prikkelbaarheid niveaus door verschillende vormen van interne en externe input. Gezien het feit dat magnetische en elektrische stimulatie van het brein vele gedragseffecten teweeg gebracht hebben, zou het mogelijk zijn dat deze effecten tenminste deels veroorzaakt worden door de manipulatie van hersenvariabiliteit.

In hoofdstuk 11 onderzochten we deze mogelijkheid. In het EEG onderzochten we de effecten van elektrische stimulatie van het brein (transcraniële gelijkstroom stimulatie, tDCS) in vrouwen, zodat we de invloed van hormonen waarvan bekend is dat ze hersenfunctie beïnvloeden ook konden beoordelen. In een dubbelblinde cross-over studie werd EEG geregistreerd bij gezonde vrouwelijke vrijwilligers die echte en nep tDCS van de frontale cortex ondergaan hadden. Dit vond plaats in zowel de vroege folliculaire en als de luteale fase van de menstruele cyclus. We vonden een significante toename in variabiliteit in het β-band van het EEG signaal na echte tDCS, en niet na nepstimulatie. Hoewel de stijging van de β -band variabiliteit tijdens de luteale fase het meest leek bij te dragen aan het tDCS effect, werden er geen statistisch significante interacties met menstruele fase gevonden. Deze bevinding suggereert dat het bestuderen van elektrofysiologische variabiliteit kan bijdragen aan het begrijpen van de fysiologische mechanismen die vorm geven aan tDCS geïnduceerde gedragseffecten, en dat inachtneming van relevante steroïde hormonen kan bijdragen aan het verder verklaren van dergelijke effecten.

Samen tonen de studies 10 en 11 aan dat biologische variabiliteit inderdaad een rol kan spelen in het faciliteren van gedragsveranderingen. Een zekere mate van plasticiteit, mogelijk gemaakt door variabiliteit in corticale systemen die betrokken zijn bij de regulatie en executie van gedrag, draagt wellicht bij aan het optimaliseren van het gedragsrepertoire.

De studies in dit proefschrift illustreren het belang van het verklaren van menselijk sociaal gedrag op meerdere niveaus. De mens is uitgerust met een brein dat gevormd is door enerzijds de evolutie als soort, en anderzijds blijk geeft van de variatie die behouden is gebleven tijdens die ontwikkeling, wat er uiteindelijk toe leidt dat we continue gestalte geven aan een opmerkelijke individualiteit. Het ontwarren van de bijdragen van respectievelijk normatieve en individuele mechanismen aan ons gedrag is een uitdaging die de sociale (neuro) wetenschappen nog jaren bezig zal houden.

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'*You get what you give*' is me meegegeven aan het begin van dit promotietraject, en dat is een mooi motto. Ik heb inmiddels geleerd bij wie het te heiligen: een besef waar ik in de volgende pagina's graag rekenschap van geef.

Eerst en vooral: Dennis. Je hebt me het vertrouwen gegeven je VIDI project uit te voeren, en hebt me daarbij alle ruimte gelaten om nieuwe initiatieven te ontplooien: voorliggend proefschrift is daar de fysieke weerslag van. De vele uren van discussies, verkenningen van nieuwe experimentele richtingen of samen in het lab een nieuwe opstelling bouwen waren de dingen die de afgelopen jaren zeer de moeite waard maakten. Je fascinatie met - en liefde voor de wetenschap is inmiddels legendarisch – die hoef ik niet meer te benoemen. We hebben elkaar door de jaren heen steeds beter leren kennen, en zullen dat in de jaren die gaan komen hopelijk blijven doen. Dank.

Leon, dank voor het feit dat je bereid bent op te treden als mijn promotor. Daarbij, je hebt een erg leuke leerstoelgroep, in zijn huidige maar zeker ook in zijn voorgaande samenstelling: Floris, Stijn, hopelijk gaat het jullie zo goed als ik verwacht dat het jullie gaat – wellicht treffen we elkaar in de toekomst weer eens in een nieuwe omgeving! Der Ivo, Sie kompensieren die Abfahrt der oben genannten Männer ausgezeichnet, hoffentlich bleiben Sie noch eine Weile im (für Sie) Ausland, wenn auch nur für die schmutzigen Mimik, die ihnen zeigt wenn ich dich versehentlich anschaue. Bauchspeicheldrüse. Joke, Alexander, Elise, Iris, Manon: onze labmeetings zijn nuttig, sommige meer dan andere, maar altijd leuk, dank daarvoor. Een bijzondere vermelding verdient Jack, inmiddels met zijn eigen leer- en bureaustoel. Ondanks de stormachtige ontwikkeling die je carrière de afgelopen jaren heeft doorgemaakt, ben je altijd zo lekker gewoon gebleven…iets waar we ieder bezoek weer de vruchten van plukken! Estrella, ik geloof dat het eerder uitgesproken is, maar ook dan: als één mijn onvolprezen kamergenoten (pick one) weer tegen je aan begint te bazelen is het toch bewonderenswaardig dat je niet gewoon na een zin of 5 hoofdschuddend wegloopt…het blijven bijzondere types. David, ik heb het geluk dat jij dezelfde dingen interessant vind als ik, hopelijk kunnen we die gedeelde interesse vorm blijven geven.

En dan mijn oorspronkelijke kamergenoten van 16.18. Als je ze zo op de foto ziet, denk je: 'Dat had je beter kunnen treffen'. En dat is natuurlijk ook helemaal waar. Echt mooie jongens zijn het niet, maar toch had ik ze voor geen goud willen missen. Sylco, we zijn dit samen gestart, en nu hebben we het inderdaad ook nog eens samen afgemaakt. Het heeft ons op plekken gebracht, en soms ook niet. Sorry van de foto, ik kon het niet laten. Ik hoop dat ik een klankbord voor jou heb kunnen zijn zoals jij dat voor mij was. We blijven elkaar zien, dank voor alles! Peter, de wetenschap heeft ons langs Grote Titels geleid, en verre oorden doen verkennen. Hoewel: zo ver was een en ander nu ook weer niet. Wel hebben we contact kunnen leggen met collega-wetenschappers, door altijd bedachtzaam te spreken over theorie en praktijk, of het nu in Barcelona in de metro was of in Zürich in het Universiteitscentrum. Gelukkig hebben we de foto's van de rondleiding nog. Los daarvan: laten we nog maar wat experimentjes gaan doen!

De afdeling waarbinnen het altijd prettig toeven is: de Psychologische Functieleer. Frans (jammer dat je goeddeels weg bent), Albert, Susan: jullie geven de afdeling een smoel binnen en buiten het van Unnik. Eveline, binnen onze afdeling geef jij gestalte aan het enige dat echt constant is: het secretariaat, en wel op een heel prettige manier. Alle overige PF collega's: dank voor de afgelopen jaren, ik voeg er graag nog vele aan toe. In het bijzonder wil ik verder Chris Dijkerman bedanken, die me de kans geeft om onderzoek te blijven doen, en de leden van zijn onderzoeksgroep voor de aangename kennismaking: Rudmer, Nathan, Haike, Helen, Maartje, Manasa, Anouk, Alyanne en Miranda. Maria 'heb je al netwerken?!?' Boersma: het is een kleine wereld, en onlangs is de padlengte tussen onze plekken significant afgenomen, daar heb ik al veel plezier van gehad! De afgelopen jaren hebben verschillende studenten bijgedragen aan het lopend en nieuw onderzoek. In het bijzonder wil ik Alexander Backus (dank voor je breintjes!), Eddie Brummelman (ik ben blij dat je de wetenschap in bent gegaan), Richard Bethlehem en Lilli van Wielink danken, jullie hebben erg mooi werk geleverd.

Some things just aren’t to be made by man, and therefore we have Siarhei. Thanks for everything thus far, let’s kick some Limburg hill ass this April!

Veronica en Ans, jullie zijn het ijkpunt voor een succesvol secretariaat geworden. Dat is geboekstaafd in alle voorgaande proefschriften waarvan jullie de wording hebben meegemaakt, en ik voeg het mijne daar graag aan toe. Dank voor alles, gelukkig zien we elkaar nog af en toe.

Zonder vooropleiding was dit alles niet mogelijk geweest, en het Onderwijsinstituut Psychologie is een bijzonder waardevolle leerschool gebleken, en niet alleen door het onderwijs dat zij verzorgde. Maarten, je bent een voorbeeld geworden en gebleven, dank voor je vertrouwen en, niet onbelangrijk, humor. Kamergenoot van het eerste uur, Mirande, en baas van het tweede uur, Frank Jan: dank voor het vertrouwen en – belangrijker – het vele plezier dat ik heb gehad. Leuk dat ik weer wat voor jullie kan doen. Nel, Gonny, Roel en Piet, rotsen in de branding van het medewerkers- en onderwijssecretariaat, leuk dat we elkaar zo nu en dan nog zien. Ria….hoe het precies komt dat we zoveel plezier hadden weet haast niemand, maar het werkte wel goed. Als een en ander niet kon zoals het moest, dan moest het maar zoals het kon, wat vaak een minstens zo mooi resultaat opleverde. Of het nu ging om een stapel pennen, een zak met bellen of zeg, een doosje, je weet overal moeiteloos mee om te gaan. Nu die verrekte data nog.

Erik en Hiske: leuk dat we elkaar ook na de SGS zijn blijven zien, graag tot binnenkort! Sterkhouders sinds 1989 (en 1990): Ronald, Freek, Erik, Olaf, en Lammert. Zonder jullie was het niet half zo leuk geweest. We hebben vanaf klas 1 lief en leed gedeeld, iets wat de voedingsbodem is geworden voor iedere grap die een gesprek op een willekeurig verjaardagsfeestje doorkruist. Gelukkig zijn we in staat ons repertoire continue uit te breiden, ik hoop dat jullie daar net zoveel plezier aan beleven als ik dat doe. Freek, we zijn lang geleden samen begonnen met het worden van wie we nu zijn – een heel eind gekomen, niet? Ol, jij bent de verpersoonlijking van het realiseren van dromen en doelen. Ik ken niemand die zo to-the-point heeft weten te verwezenlijken wat hij nastreefde, respect. Erik, leuk dat we elkaar weer wat vaker zien nu jullie dichterbij wonen, als ik eens iets kan doen.... Lam, je bent een bijzonder mens. Einstein zou je opgevoerd hebben als bewijs dat tijd relatief is, en voor alle momenten dat je er wel was: leuk. Samen met Eefje draai je een mooi gezin in een mooi huis, moge dat lang zo blijven. Ron, vanaf het fietsen naar school (zit daar nu een roze olifant?) tot het beheer van de nalatenschap van Tinus Millen – ik ben blij en trots dat ik het met jou kan en kon doen. Hopelijk gaan we er mee door tot het einde der tijden. Ik zou zeggen: SCHIET!

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Pap en mam, jullie hebben me vanaf het allereerste begin gestimuleerd eruit te halen wat erin zit, en belangrijker, te doen wat goed voelt. Dat heeft soms geleid tot wat merkwaardige hobbels in de weg, maar misschien is dat juist wat het afleggen ervan de moeite waard maakt. Ik had geen betere ouders kunnen wensen. Dank jullie wel. Zonder voor een ander te willen spreken, denk ik toch niet dat ik alleen sta in bovenstaande. Collin, Tom en Suzanne, volgens mij hebben we pas geleden laten zien wat we aankunnen met z'n allen. Ik ben benieuwd wat er allemaal nog met ons zal gebeuren, het zal allicht weer de aanleiding zijn voor een of andere pop zo rond de kerstdagen!

Lien, we zijn inmiddels al een aardige tijd samen, maar het voelt nog altijd als gisteren dat we elkaar ontmoetten. We hebben bepaald niet stilgezeten de afgelopen tijd, maar nog steeds zijn we nog lang niet klaar. Ik kan je onmogelijk vertellen hoe gelukkig ik met je ben.

Kom, laten we gaan kijken wat de toekomst brengt, en samen heel oud worden.

Publications and personal statement

Peer-reviewed journal articles

Schutter, D.J. *&* **Hofman, D***. (under review)*. Sex steroids and interhemispheric connectivity in the female brain.

Hofman, D., Terburg, D., van Wielink, L. & Schutter, D.J. *(in revision).* Coalescence of dominance motivation and responding to facial anger in resting-state and event-related electrophysiology.

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Abstracts

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Dennis Hofman was born April 30TH, 1977 in Laag Soeren, in the municipality of Rheden. In 1996 he obtained his high school diploma from the Stedelijk Gymnasium Apeldoorn. The same year he started his undergraduate studies of Psychology at Utrecht University, from which he graduated in 2007. Early 2008 he started his graduate studies into the nature of human social behavior, which resulted in the present thesis. He is currently a post-doctoral researcher at the Utrecht based Touch, action and perception lab headed by prof. Chris Dijkerman.

Dennis Hofman werd geboren op 30 april 1977 in Laag Soeren, in de gemeente Rheden. In 1996 behaalde hij zijn middelbare school diploma aan het Stedelijk Gymnasium Apeldoorn. In hetzelfde jaar begon hij zijn studie Psychologie aan de Universiteit Utrecht, waar hij in 2007 afstudeerde. Begin 2008 is hij begonnen met zijn onderzoek naar sociaal gedrag van mensen, wat resulteerde in dit proefschrift. Hij is momenteel postdoctoraal onderzoeker in het Utrechtse actie en perceptie lab onder leiding van Prof. Chris Dijkerman.