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In the Eye of the Storm

Connectivity studies on antisocial behavior and psychopathy

In het oog van de storm: Connectiviteits-studies over antisociaal gedrag en psychopathie
(met een samenvatting in het Nederlands)

Proefschrift

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Door

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Contents

The Ugly Woman Bandit

Not even 20 years of age, he robs 13 banks, convenience stores and gas stations. It was a game, figuring out how to get away with the most money and the least chance of getting caught. Of course, he did get arrested and was sentenced to 13 years. He escapes prison and is off police radar for years, before he gets pulled over for running a red light. After finishing his sentence, as a parolee, he works as a chauffeur at a hospital and is asked to deliver roughly $50,000 in cash to a bank. "My pleasure," he says and calls his buddy, "Wanna go to the World Championship Soccer?" After spending everything, he comes back to Toronto where he, within a year, robs 16 banks amounting to nearly $40,000. For the fun of it, he disguises himself as a woman before robbing a bank. Next day, he makes newspaper headlines being dubbed 'The Ugly Woman Bandit,' which really bothered him as his girlfriend had spent two hours on his make-up. After 26 armed robberies in 3 consecutive days he is finally arrested and sentenced to 24 years. In jail, he comes up with the idea to send a letter (on the original and genuine paper used by Correctional Services of Canada) to the judge on behalf of his parole officer, stating that his behavior had been impeccable and that he should be considered for early release. Obviously, his plan fails. When asked whether he really thought it would have worked, he replies "No, but it would have been brilliant if it had."

This is the first true psychopath I ever encountered. He is a friendly, well-spoken and personable guy. He is now 55, has spent most of his life imprisoned and has no ties to anyone. Within 2 hours he smilingly cons me out of $15 worth of parking tickets and scams the guy running the cafeteria out of a soda pop.

PART 1

'Here the reader and the author must take leave of each other. Before I retire from his sight, I shall only add, if I have not advanced, agreeably to my wishes, the interests of medicine by this work, I hope my labours in the cause of humanity will not be alike unsuccessful ; and that the sufferings of our fellow creatures, from the causes that have been mentioned, may find sympathy in the bosoms, and relief from the kindness, of every person who shall think it worth while to read this history of them.'

Benjamin Rush
1812

§1 General Introduction

Aggression and antisocial behavior are public health problems and, as such, weigh heavily on society and its members. In extreme forms however, aggressive antisociality is considered a mental health problem. Although precise statistics are not available, it is estimated that in America alone crime is trillion dollar-a-year business (1) with psychopaths accounting for a disproportionate number of crimes. Kent Kiehl has estimated that psychopathy costs the American society up to $460 billion a year (1). In The Netherlands on forensic psychiatric care alone, €683 million is spent each year (2). Antisocial behavior can occur as the resultant of many entities including alcohol abuse, traumatic experiences, anxiety or personality traits such as impulsivity and hostility. Similarly, having a certain personality structure, for instance a psychopathic personality, will put one at great risk for destructive aggressive behavior. Presently, leads are beginning to emerge that point toward a neurophysiological basis of aggressive and antisocial behavior. Although neurophysiological data on aggressive and antisocial behavior are available, given its profoundly disruptive nature it is still far too little- particularly in the case of the psychopath's antisociality which is unsurpassed in terms of horror and intensity. The neural basis of antisocial behavior includes various entities that interact, with none being solely responsible for the end products of aggression and antisocial behavior. Through the complex interplay between key brain structures such as the amygdala, orbitofrontal cortex and the mesolimbic reward system, the communication between these brain structures, neurotransmitters, peptides and hormones antisocial behavior can rise fast and manifest ruthlessly.

Before venturing further into the neural correlates of aggression and antisocial behavior a clear definition should first be given. However, this is not an easy undertaking as aggression and antisocial behavior can come in many forms. In general, antisocial behavior encompasses all behaviors that defy the social order and can include theft, robbery, fraud, aggression and murder. With regards to aggression, some crucial elements are thought to be necessary, one of which is the intention to harm another living being (3). This *intention* may not always be evident and can sometimes be easily denied by the perpetrator. Others have therefore stressed that the *act* of inflicting harm upon others is key (3), which is more of a behavioristic viewpoint. One possible definition of the concept of aggression might

then be 'the delivery of any form of definite and observable harm-giving behavior towards any target' (3). Furthermore, there are different types of aggression with the most common distinction being that between reactive and instrumental aggression. Reactive aggression has also been denoted with the terms *hostile, impulsive, affective, hot* and *affective defense aggression*. Instrumental aggression is sometimes referred to as *premeditated, cold, proactive* and *predatory attack*. Reactive aggression is thought of as being impulsive and motivated by anger, usually in response to some external provocation and it is characterized by intentionally hurting another person. It can also be a means of defending oneself against imminent threats or rivals for food or access to mating partners. Instrumental aggression by contrast, does not relate to the enemy or victim per se but serves a different goal, for instance monetary gain. Instrumental aggression is purposeful and goal-oriented (3) and is virtually only found in psychopaths. While reactive aggression generates physiological over-arousal, instrumental aggression is associated with little autonomic responsivity.

In this thesis I will examine pathological brain connectivity associated with antisocial behavior (e.g., aggression) and psychopathy and will attempt to coalesce these snapshots into a coherent portrait of the antisocial brain.

§1.1 A genealogy of psychopathy

As antisocial behavior, including aggression, is found in high degrees in psychopaths, the section below will briefly describe the evolution of the clinical construct of psychopathy. It is said that if you spend an hour in a room with someone, and afterwards you feel somewhat sad or depressed, there is a good chance that person is depressed. Implicitly, I had assumed I would be intimidated, nervous or flat-out frightened in my encounters with psychopaths. Instead, I felt nothing and I believe my feelings reflected the affectively deserted inner world of the psychopath. The true psychopath is immune to depression or delusions, he is devoid of anxiety or fear, shame or guilt, happiness, love and sadness- he only has a bleak understanding of us and he will consider most of our daily endeavours inane. Yet he understands what we want and he will predatorily play his cards, unencumbered by the grievances he inflicts. In this regard, psychopathy is a perfect storm of brain dysfunction: it combines the most profound affective and behavioral disruption with very little personal discomfort. Any emotion the psychopath may experience is short-lived and superficial and this lack of emotionality allows them to account for nearly half of all serious crime, including homicide, aggravated sexual assault and unlawful confinement. The psychopath blusters through life and sees the world twirling around him, yet he is incapable of being affected by it- he remains in the eye of the storm, where it is calm.

One of the first notions of the concept of *psychopathy* emerged approximately two centuries ago. A French psychiatrist, Philippe Pinel (1801), described patients with a *manie sans delire* (insanity without delirium) who appeared normal in their reasoning powers and understanding of the world but were unable to regulate and control their behavior, subjecting them to 'instinctive and abstract fury' (cited in Hervé & Yuille, (4)). Until that time, distortion of reasoning and intellect was seen as the main problem in mental disorders and relative intactness of the mind was therefore not considered insanity (5). Pinel then may have been one of the first in the history of psychiatry to propose that a disorder confined to the 'faculties of affect' could also be considered a *manie*, even without lesions in the faculties of intellect (*sans delire*) (5). In 1812, Benjamin Rush described a group of patients that showed signs of conduct disorder during childhood and perpetrated crimes from an early age without any sign of repentance. While Pinel emphasized the psychiatric inability of these patients to regulate and inhibit their behavior, Rush took a

different approach. He argued that these patients suffered from a "derangement of the moral faculties" (6) and since morality was traditionally founded in a sense of deity, these psychopathy-like patients were principally godless (7) (interestingly, a moral perspective on the pathophysiology of psychopathy is still contemporary). Similarly, Prichard (1835) talked off *moral insanity* but also designated the disorder to be primarily affective in nature: "There is likewise a form of mental derangement in which the intellectual faculties appear to have sustained little or no injury, while the disorder is manifested, principally or alone, in the state of the feelings, tempers or habits." (cited in Hervé & Yuille, p33). In his psychiatry text book Kraepelin (1904) described the 'psychopathic personalities' of which a sub-group was called *swindlers*. Swindlers were glib and ingratiating but, again, primarily morally insane. Partridge (1928) introduced the term 'sociopathic personality' as he believed that the characteristic pathological symptom of psychopaths is that they are unable to adjust to the demands society puts on its members (8) (Later, Lykken used the term 'sociopath' to describe people that may have been law-abiding citizens had they been raised by able parents and 'sociopathy' should therefore be considered an acquired form of psychopathy (8)). Partridge talked of individuals that were emotionally instable, expressed themselves only through anger and, to a degree, felt alienated. Schneider (1934) depicted the 'self-seeking' psychopath- a pleasant and likeable person but profoundly egotistical and incapable of regular affective experience. One can see that from the very start certain features such as unfeelingness, deception and disinhibition were perceived by the founding fathers of psychopathy research as the core characteristics of psychopathy. These and other clinicians paved the way for Hervey Cleckley.

Until Cleckley's book *The Mask of Sanity* theorists had not come to a uniform description of the clinical construct of psychopathy. Rather, it had become more of a container concept for devious and morally reprehensible behavior, and the various roads to this antisociality were not adequately designated (4). Cleckley narrowed the clinical construct of psychopathy delineating it as a constellation of 16 criteria, commonly known as the Cleckley Checklist (9). This list consisted of criteria such as superficial charm and good intelligence, absence of delusions or irrational thinking, lack of remorse or shame, an impersonal sex life, low incidence of suicide and persistent unreliable behavior (9). To Cleckley, at the core of psychopathy lay a 'semantic aphasia' – psychopaths fluently produce grammatically correct sentences but the true significance of their words completely

eludes them. Cleckley metaphorized the inner life of the psychopath to be so desolate that he has little to convey, as if the language he uses cannot really symbolize anything with any emotional connotation. In fact, Cleckley goes on to compare the persona of the psychopath to the monkey that, given infinity, will write Shakespeare's works on a typewriter: the psychopath will use his rational powers to mimic a sane and affable human being while, underneath the veneer, the end product is merely a cold and mechanical copy. Cleckley famously wrote "Although not deeply vicious, he carries disaster lightly in each hand". Perhaps one could read in this sentence some sort of sympathy that Cleckley felt for his psychopathic patients- he doesn't mean to be the way he is. In any case, it certainly does show that Cleckley developed the clinical construct of psychopathy in a psychiatric institution in which the antisocial behavior of the psychopath appeared inaptly motivated, rather than penetratingly pernicious. This conceptualization has changed over the years.
The Hare Psychopathy Checklist (PCL-R) standardized the field of psychopathy research. From this point on, when talking about a psychopath, we all refer to the same construct and as such, the PCL-R has become the gold standard in psychopathy research. The PCL-R consists of 20 items that can be scored 0, 1 or 2 depending on the degree to which a certain trait is present. A cut-off of 30 is used to diagnose psychopathy in North America while cut-offs of 25 have been employed in other (e.g., European) countries. The PCL-R has a high correlation (r= .83) with the Cleckley Checklist. Like the Cleckley Checklist, the PCL-R specifies personality features such as the lack of remorse or guilt, shallowness, glibness and superficial charm but also includes other criteria such as 'early behavioral problems'. Factor analysis of the PCL-R shows that at least two factors underlie psychopathy. The first factor designates the core of the psychopathic personality and includes traits such as callousness, shallow affect, grandiosity, manipulativeness and superficial charm which have been summarized with the terms 'aggressive narcissism' or 'emotional detachment.' Factor 2 covers the behavioral aspects consisting of stimulation-seeking, parasitical behavior, the inability to form realistic plans for the future and revocation of condition release which has been simplified with the term 'antisocial lifestyle.' Further factor analyses showed that Factor 1 can be subdivided into an Interpersonal and Affective component while Factor 2 is composed of Lifestyle and Antisociality facets (See Figure 1).

In recent years a debate on the equalization of the PCL-R with the clinical construct of psychopathy has come to dominate the theoretical side of psychopathy research. The

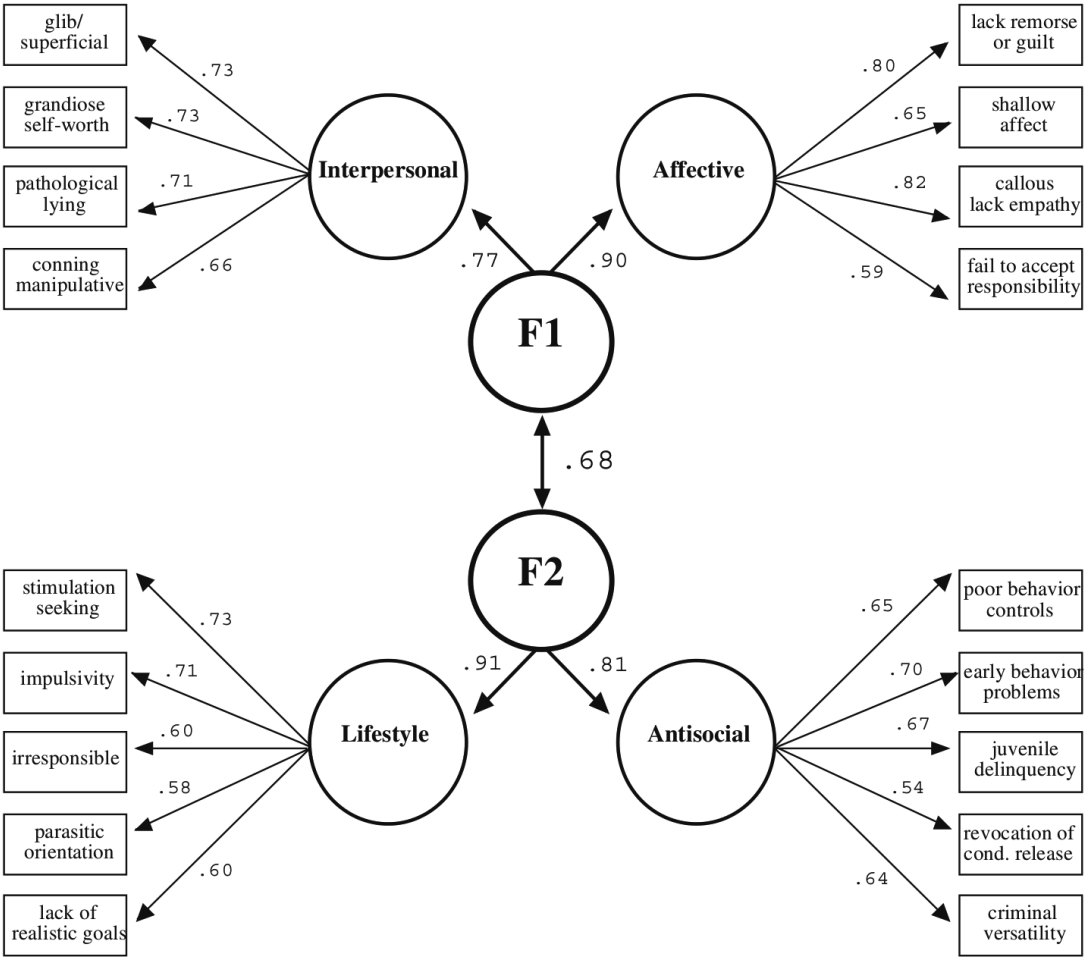


Figure 1. Adopted from Hare and Neumann (2008). This Figure depicts how factor analysis of the PCL-R yields two main factors (the first being the personality style and the second being the antisocial lifestyle) that can be further divided in an interpersonal, an affective, an antisocial and a lifestyle component. Two items are not in this list as they are unrelated to either factor: i) *many short-term marital relationships* and ii) *promiscuous sexual behavior*.

alleged *construct drift* from the Cleckley psychopath has been stressed most prominently by Skeem and Cooke (10). One of their key criticisms relates to the inclusion of criminal behavior in the definition of the PCL-R. Items such 'Criminal Versatility,' 'Revocation of Conditional Release,' and 'Juvenile Delinquency' weigh heavily on the total score on the PCL-R, exemplifying that Hare developed the PCL-R in prison with incarcerated (male) offenders. However, these items do not necessarily relate to the personality structure that enables antisocial behavior and may only be a distant sign of certain personality traits (e.g., impulsiveness, hostility). It may even be the case that someone with a severe psychopathic personality, but without too much criminal behavior, does not reach the cut-off of 30. Also, criminal behavior is a legal definition of unwanted behavior influenced by the culture and society in which one lives and does not reflect personality traits per se. By contrast, one could contend that the legal system partly reflects the lawful anchoring of interpersonal norms and is intended to streamline societies. In line, Hare argued that having psychopathic traits will put one at great risk of manipulative and deceptive behavior, reactive and instrumental aggression, the violation of interpersonal norms and, by inference, the persistent defiance of societies' laws (11). Acknowledging this, Skeem and Cooke state that criminal behavior should be considered a corollary of psychopathy rather than a defining feature (10, 12).

The last development in the psychopathy construct came from the hands of Christopher Patrick who conceptualized psychopathy as consisting of three phenotypic domains: *boldness, meanness, and disinhibition* (7). *Boldness* is defined as the "capacity to remain calm and focused in situations involving pressure or threat, an ability to recover quickly from stressful events, high self-assurance and social efficacy, and a tolerance for unfamiliarity and danger." *Disinhibition* is defined as "a general propensity toward impulse control problems, lack of planfulness and foresight, impaired regulation of affect and urges, insistence on immediate gratification and deficient behavioral restraint." *Meanness* is defined as "deficient empathy, disdain for and lack of close attachments with others, rebelliousness, excitement seeking, exploitativeness, and empowerment through cruelty." These three phenotypic domains are modulated by *difficult temperament* and *low fear*. Importantly, Patrick approaches psychopathy as a dimensional construct allowing for different severities with a different configuration of boldness, meanness and disinhibition: some psychopaths may be fearless and extremely bold and may function well as Special Forces in the military. Others may suffer from the same fearlessness but, combined with

strong disinhibition, will get into incessant contact with the law. Of all three factors, disinhibition is likely to be found in high degrees in patients with antisocial personality disorder (ASPD). Meanness and boldness will also be found but, given the rather behavioral definition of ASPD, will be found in more varying degrees. As the Diagnostic Statistical Manual IV *text revision* (DSM-IV-TR) does not acknowledge psychopathy as a personality disorder, there is often confusion between psychopathy and ASPD. It is therefore important to distinguish between the two- the difference will be discussed in further detail in Box 1.

§1.2 Disrupted brain networks in antisocial behavior and psychopathy

In this section, I will highlight specific pathways in the brain that may lead to antisocial behaviour and psychopathy. Antisocial behavior is often the result of impulsive, stimulation-seeking and, in general, disinhibited behavior. In this light, it could be considered to point toward aberrant functioning of the dopaminergic reward system. This system has indeed been implicated in psychopathy (13-15) and aggression (16). Dopamine antagonistic drugs like haloperidol have antiaggressive effects (16) and have been the first choice for aggressive patients (16, 17). As psychopaths are impulsive, need stimulation and are highly sexually promiscuous, a theoretical decomposition of the clinical construct of psychopathy also suggests dysfunction in the mesolimbic reward pathway (§1.2.3). Second, psychopathy is a personality disorder with strong dysregulation of affect and, as such, abnormal working of brain structures that are highly involved in emotion would be expected. Indeed, the amygdala, ventromedial prefrontal cortex (vmPFC) and the white matter tract connects amygdala to PFC, the uncinate fasciculus, have repeatedly been implicated in the affective deficits of psychopathy (18-21). In psychopathy, amygdalo-vmPFC connectivity may be *hypo*functioning which may enable instrumental aggression. By contrast, it will be argued (§1.2.2) that *hyper*functioning of this network may be involved in reactive aggression as it is found in individuals with high degrees of antisocial behavior. Moreover, preliminary evidence suggests that interhemispheric connectivity may be affected in aggressive behavior and potentially in psychopaths and I will address this issue in further detail below (§1.2.1). Fourth, the function of the dorsolateral prefrontal cortex (DLPFC) in the regulation of impulses and emotions will be addressed (§1.2.4). It will be argued that disruption of this brain area could result in the disinhibitory behavior that is found in ASPD and psychopathy. Last, I will contend that the last decennium has heralded the cerebellum as an important contributor to affect, cognition and, at a higher level, psychiatric disorders. When its function is disrupted, a syndrome of inappropriate and disinhibited behavior may arise out of its complexities (§1.2.5).

§1.2.1 Interhemispheric connectivity

Interhemispheric connectivity is an important process that underlies various cognitive and emotional functions. On the system's level, frontal functional interhemispheric

Box 1. Psychopathy and Antisocial Personality Disorder

Personality is defined as a long term pattern of characteristic behaviors, feelings and thoughts. These entities do not directly show personality traits but, by definition, are inferred from behavior. In the case of the psychopath, these traits are likely to be expressed through aggressive and criminal behavior, which are easier to measure than more subjective traits like 'grandiosity,' 'callousness' or 'shallow affect.' These subjective traits also rely more on the clinician that is assessing them. In short, when in 1987 the DSM-III was created, this was the rationale for the definition of the antisocial personality disorder and it resulted in clinically reliable assessments. Unfortunately, traits such as egocentricity and callousness define the very core of the psychopathic personality and the trade of the objective and noninferential criteria with these subjective traits resulted in the situation in which up to 80% of prison inmates meet criteria for ASPD whereas only 20-25% can be considered psychopathic. Fortuitously, the DSM-V rectified this somewhat by incorporating the more subjective traits. In addition, Patrick's concept of disinhibition has been included indicating a shift toward the conceptualization of this personality disorder as is done in the psychopathy literature. In Table 1 the old and the new criteria for the definition of ASPD can be found.

DSM-IV

Antisocial Personality Disorder

A) There is a pervasive pattern of disregard for and violation of the rights of others occurring since age 15 years, as indicated by three or more of the following:

1. **failure to conform to social norms with respect to lawful behaviors as indicated by repeatedly performing acts that are grounds for arrest;**
2. **deception, as indicated by repeatedly lying, use of aliases, or conning others for personal profit or pleasure;**
3. **impulsiveness or failure to plan ahead;**
4. **irritability and aggressiveness, as indicated by repeated physical fights or assaults;**
5. **reckless disregard for safety of self or others;**
6. **consistent irresponsibility, as indicated by repeated failure to sustain consistent work behavior or honor financial obligations;**
7. **lack of remorse, as indicated by being indifferent to or rationalizing having hurt, mistreated, or stolen from another;**

B) The individual is at least age 18 years.
C) There is evidence of conduct disorder with onset before age 15 years.
D) The occurrence of antisocial behavior is not exclusively during the course of schizophrenia or a manic episode.

DSM-V

Antisocial Personality Disorder

A) Significant impairments in personality functioning manifested by:

1. Impairments in self functioning (a or b):

- **Identity: Ego-centrism; self-esteem derived from personal gain, power, or pleasure.**
- **Self-direction: Goal-setting based on personal gratification; absence of prosocial internal standards associated with failure to conform to lawful or culturally normative ethical behavior.**

AND

2. Impairments in interpersonal functioning (a or b):

- **Empathy: Lack of concern for feelings, needs, or suffering of others; lack of remorse after hurting or mistreating another.**
- **Intimacy: Incapacity for mutually intimate relationships**

B) Pathological personality traits in the following domains:

1. Antagonism, characterized by:

- **Manipulativeness: Frequent use of subterfuge to influence or control others; use of seduction, charm, glibness, or ingratiation to achieve one's ends.**
- **Deceitfulness: Dishonesty and fraudulence; misrepresentation of self; embellishment or fabrication when relating events.**
- **Callousness: Lack of concern for feelings or problems of others; lack of guilt or remorse about the negative or harmful effects of one's actions on others; aggression; sadism.**
- **Hostility: Persistent or frequent angry feelings; anger or irritability in response to minor slights and insults; mean, nasty, or vengeful behavior.**

2. Disinhibition, characterized by:

- **Irresponsibility: Disregard for – and failure to honor – financial and other obligations or commitments; lack of respect for – and lack of follow through on – agreements and promises.**
- **Impulsivity: Acting on the spur of the moment in response to immediate stimuli; acting on a momentary basis without a plan or consideration of outcomes; difficulty establishing and following plans.**
- **Risk taking: Engagement in dangerous, risky, and potentially self-damaging activities, unnecessarily and without regard for consequences; boredom proneness and thoughtless initiation of activities to counter boredom; lack of concern for one's limitations and denial of the reality of personal danger.**

C) The impairments in personality functioning and the individual's personality trait expression are relatively stable across time and consistent across situations.

D) The impairments in personality functioning and the individual's personality trait expression are not better understood as normative for the individual's developmental stage or socio-cultural environment.

E) Individual's personality trait expression are not solely due to the direct physiological effects of a substance (e.g., a drug of abuse, medication) or a general medical condition (e.g., severe head trauma).

Table 1. Here, the differences between the criteria for ASPD in the DSM-IV-TR and DSM-V are outlined. A clear shift towards the construct that has been delineated in the psychopathy literature is visible, i.e., the inclusion of disinhibition and more emphasis on personality traits such as callousness and hostility. DSM-IV Antisocial Personality Disorder

connectivity has often been overlooked as a mechanism by which the frontal cortex is involved in cognition and emotion. Frontal functional interhemispheric connectivity refers to signal transfer between the left and right frontal cortex, which mainly occurs through the corpus callosum (22). Deficits in frontal functional interhemispheric connectivity have been demonstrated in disorders characterized by behavioural dysregulation including attention deficit/hyperactivity disorder (ADHD) (23) and schizophrenia (24). The frontal lateralization theory of emotion poses that the right prefrontal cortex is associated with avoidance behavior whereas the left prefrontal cortex is more commonly related to approach behavior (25, 26). Avoidance behavior is focused on eluding (potential) punishment mirrored by approach behavior which is driven to attain (possible) rewards (25, 27). With regards to aggression, it has been postulated that an asymmetry in the frontal cortices underlies these behaviors. That is, relatively higher left-sided frontal activity may induce more reward dependency and more aggression. By contrast, higher right-sided frontal activity has been associated with behavioral withdrawal, depression and anxiety (26). Anger is an emotion that has high approach motivation, is often the precursor for offensive aggression (28) and is indeed lateralized to the left prefrontal cortex (28). Therefore, it appears that asymmetries in interhemispheric connectivity constitute an efficient heuristic model to investigate aggressive behavior in healthy and psychiatric individuals.

Some of the first empirical research in psychopathy examined interhemispheric connectivity, albeit indirectly: Cleckley noted that a semantic aphasia may lie at the core of psychopathy (9) and this was one of the reasons early psychopathy research investigated language processing. As language is strongly lateralized, these researchers used lateralized processing tasks such as the verbal dichotic listening task (29, 30). On this task healthy individuals typically show a right ear advantage which is accounted for by left hemisphere superiority in language processing (31). These studies showed a remarkable reduction of lateralization in language processing in psychopaths (29, 30, 32). Further studies corroborated this by demonstrating that psychopaths demonstrate reduced lateralization of other functions as well. For instance, psychopaths show less lateralized performance on facial affect recognition tasks (33) and on tasks designed to measure the decoding of emotional stimuli (34). Further lateralization deficits have been found in motor dominance (i.e., higher proportion of ambidextrousness) (35) and divided attention tasks (36). Although the underlying pathophysiology is unclear, reduced lateralization could suggest

two things. First, there may be a neurodevelopmental component to the reduction in hemispheric specialization. Lateralization of function and hemispheric specialization are important mechanisms through which the brain frees up space: by allowing one particular function to recruit a specified set of neuronal populations, other brain areas can confine to other functions (37). This process starts early in life and impairments in it may cause subtle cognitive and affective deficits. Second, impaired lateralization in psychopaths may be elicited through deficits in interhemispheric connectivity (30). The corpus callosum is an important white matter tract connecting the cerebral hemispheres and plays a vital role in the exchange and integration of information between the hemispheres (22). Given the behavioral evidence for lateralization deficits, and empirical data gathered through magnetic resonance imaging (MRI), it is likely that interhemispheric connectivity across the corpus callosum is affected in psychopaths (18, 38). However, data on functional interhemispheric connectivity deficits is lacking and, therefore, transcranial magnetic stimulation (TMS) and electroencephalography (EEG) will be introduced as a means to study interhemispheric connectivity. In addition, this proxy of interhemispheric connectivity will be related to personality features as measured per the NEO Five Factor Inventory (NEO-FFI). The advantage of using TMS and EEG to assess interhemispheric connectivity is that it is possible to elucidate possible directional deficits in interhemispheric connectivity. That is, it is possible that right-to-left interhemispheric connectivity is more strongly affected that left-to-right interhemispheric connectivity.

§1.2.2 Amygdala-ventromedial Prefrontal Cortex

Connectivity between the amygdala and ventromedial areas of the prefrontal cortex network is involved in psychopathy but has also been implicated in reactive aggression, albeit in different manners. In humans and other mammals, the threat detection system involves a network of the amygdala, periaqueductal gray, hypothalamus and prefrontal cortex. In general, this system allows three responses to threat. When a threat is distant and does not pose an immediate danger this circuit will induce the organism to freeze. At higher levels of threat stimulation, when escape is possible, the organism will attempt to do so. At even higher levels the organism will react with aggression. Indeed, whereas in psychopathy amygdalo-prefrontal connectivity appears hypoactive (19-21, 39), individuals with high levels of reactive aggression (e.g., patients with antisocial personality

disorder or borderline personality disorder) show hyperactivity of this network (40). In these individuals prefrontal areas such as the OFC function sub-optimally (40) which is evidenced by reduced prefrontal blood flow in violent offenders (41). Furthermore, OFC lesions have been associated with increased levels of reactive aggression (42). In short, the idea is that deficient functioning of prefrontal areas results in poor modulation of the subcortical areas that mediate the threat detection system and, subsequently, higher chances of displaying reactive aggression.

Psychopaths show a remarkable affective emptiness, shortened with the term callous-unemotional (CU) traits. CU traits have been suggested to relate to (para)limbic dysfunction (43) in general, and the amygdala in particular. This reduced empathy and emotional responding is particularly worrisome in adolescents with high levels of impulsivity and disruptive behavior as these CU traits negatively impact treatment outcome (44). The amygdala is strongly involved in emotion, the processing of emotionally laden information and the learning of conventional and moral rules (20). Recently, Yang and colleagues (45) showed that psychopaths present with smaller amygdala volumes bilaterally and deformations in the basolateral, lateral, cortical and central nuclei of the amygdala. In line with the proposed model of amygdala dysfunction in psychopathy, the extent of amygdala dysfunction predicts the score on the PCL-R (46) with the strongest correlations being those with the affective component of the PCL-R (factor 1). Moreover, on the behavioral level, amygdala dysfunction has implications for psychopathic behavior, namely for aversive conditioning and passive avoidance learning (39). Aversive conditioning involves a stimulus that is coupled with aversive outcomes which induce the individual to avoid certain situational factors (47), for instance antisocial behavior. Passive avoidance learning is defined as the learning of latent contingencies that involve punishment, i.e., if there is no manifested relationship between a certain act and a subsequent penalty, psychopaths have severe difficulty in discerning this connection which, in turn, may explain why psychopaths fail to learn from punishment. Furthermore, fearful facial expressions are social signs for impending danger but also signal to peers that the behavior exhibited by someone could be considered dangerous or unwanted and. In children and adolescents with CU traits, fearful facial expressions induce less amygdala activation (44). Indeed, enhanced amygdala responses are seen in reactive aggression but diminutive amygdala reactivity is associated with instrumental aggression (48), which one only finds

in psychopathy. Together these findings suggest an important role for the amygdala in reinforcement learning and the learning of adequate social behavior (20). When they are dysfunctional, as they are in psychopathy, they may result in poor socialization and the persistent moral transgressions that characterize this disorder.

Importantly, the amygdala is connected with cortical regions that control and modulate subcortical functioning (49) and are crucially important in social-emotional decision making. Through the uncinate fasciculus the amygdala communicates with the ventromedial prefrontal cortex (vmPFC) and this communication is known to be deficient in psychopathic offenders (18, 19) and boys with psychopathic traits (50). In line with Blair's suggestions, the vmPFC will be considered to include "Brodmann's areas 10 and 11 and the inferior regions of the rostral anterior cingulate cortex and subgenual cingulate cortex (BA 32 and 24)" (39). Whereas the amygdala is involved in reinforcement learning, the vmPFC encodes reinforcement outcome information (39). That is, the vmPFC actively represents the value of expected rewards which enables the individual to select between certain stimuli, although the vmPFC is not directly involved in the selection itself (39) (this is often attributed to more lateral prefrontal areas such as the DLPFC). In line, lesions of the vmPFC decrease the likelihood that individuals will avoid emotionally aversive outcomes because they are unable to weigh different stimuli or outcomes against each other (51). In fact, aversive conditioning is usually assumed to be motivated by fear (52) and, surely, psychopaths show no significant activation of the amygdala-OFC network that is recruited in healthy controls during fear conditioning (53). Using a passive avoidance task, Finger and colleagues (50) showed that youths with conduct disorder and strong psychopathic traits show significantly less activation of the amygdala and OFC. Last, the vmPFC is important in response reversal and psychopaths are unable to modulate a response set once it has been activated (54). As noted earlier, the vmPFC represents the value of an expected reward but when certain behaviors become less contingent on positive outcomes, a dysfunctioning vmPFC may result in rigid continuation of the dominant behavior. When taken together, these findings suggest strong involvement of the amygdala and its connections with the vmPFC in antisocial behavior (where this network may be hyperactive) and psychopathy (where it may be hypoactive).

§1.2.3 Mesolimbic reward pathway

The mesolimbic reward pathway activates us to pursue potential rewards and it is activated when we achieve attainment of our goal. The mesolimbic reward pathway consists of important core structures including the ventral tegmental area (VTA)/ substantia nigra, nucleus accumbens, striatum, thalamus and medial prefrontal cortex. The striatum can be subdivided into the ventral and dorsal striatum. The ventral striatum, largely consisting of the nucleus accumbens, receives input from the VTA whereas the dorsal striatum (the medial part of the caudate nucleus and lateral part of the putamen) is innervated by the substantia nigra. From the striatum, neurons travel through the pallidum (internal and external globus pallidus) to the thalamus from where neurotransmission is relayed to the frontal cortex. This particular network has been implicated in reward drive, pleasure, impulsivity and addictive behavior. Therefore, it would be anticipated that violent offenders and psychopaths suffer from aberrant functioning of precisely this pathway. In healthy controls, impulsive and antisocial traits are associated with stronger dopaminergic reactivity of the mesolimbic reward system (55). In low-anxiety rats, hyperactivity of the reward system is related to high and abnormal (e.g., attacks to vulnerable parts of the body) aggression (56). Therefore, these data suggest strong involvement of the mesolimbic reward system in impulsive and aggressive behavior in healthy individuals, and perhaps also in psychopathic individuals.

Psychopaths are stimulation-seeking, make rash decisions, are quick to respond with anger and show a notable fondness of drugs but direct empirical evidence showing that psychopaths do indeed suffer from structural or functional dysfunction in the mesolimbic reward pathway is limited (13, 57, 58). One study implicated gray matter damage to the reward pathway in psychopathy and suggested this damage may be relatively independent of drug abuse (13). That is, prefrontal areas that have repeatedly been implicated in psychopathy, such as the OFC, are much more susceptible to the detrimental effects caused by long term drug abuse and are therefore more difficult to relate to drug related atrophy vis a vis psychopathy. In violent offenders with psychopathic traits, high dopamine turnover (as indicated by homovanillic acid levels in cerebrospinal fluid) is predictive of those psychopathic traits (15). Taken together, aberrant functioning of the mesolimbic reward system may underlie novelty-seeking, impulsive and aggressive behavior in antisocial and psychopathic groups.

§1.2.4 Dorsolateral prefrontal cortex

The DLPFC is one of the prefrontal brain areas that is most commonly implicated in higher order cognitive functioning. It is involved in working memory (59), executive functioning (60) and the inhibition and regulation of impulses and emotion (61). Particularly in psychopathic offenders that come into constant contact with the law, aptly named unsuccessful psychopaths, the DLPFC may be affected (61). It has been suggested that the intricate interplay between the vmPFC and the DLPFC underlies adaptive behavior, aimed at evasion of potential punishment. As noted above, the vmPFC represents reward expectancy and is strongly involved in learning from punishment (62). Based on vmPFC mediated information the DLPFC comes into play when disadvantageous actions need to be discerned from advantageous actions (62). Throughout this thesis it will be argued that psychopathy is associated with difficulties in the discrimination between advantageous and disadvantageous choices. More specifically, when a particular response has been activated psychopaths tend to persevere this initial response (63), pointing to both vmPFC and DLPFC dysfunction. Although the interplay between vmPFC and DLPFC appears lateralized to the right prefrontal cortex in males (64), the left DLPFC is likely to be involved as well (61). As will be described (§3.3), psychopathic offenders show a pattern of impulsive and reckless behavior and are typically not concerned with the consequences of their actions. In line with the concept of *disinhibition* in psychopathy (7), psychopathic offenders may have deficits in the DLPFC and therefore, functionality of the left DLPFC will be indexed through TMS and EEG (§3.3). We chose to index the left DLPFC because a meta-analysis indicated it is the left DLPFC that is affected, rather than the right DLPFC (61)

§1.2.5 Cerebellar contributions

The cerebellum is highly involved in the fine-tuning of motor activity and this is undeniably one of its major tasks: a cerebellar disorder will largely manifest with ataxia (65). However, researchers have battled for the recognition that it does more than merely contribute to motoric behavior (66-70) and given its extensive connections with virtually all brain areas, this option should be taken seriously. Indeed, damage to the cerebellum may result in executive, visual-spatial and linguistic disabilities, the syndrome of which has been captured with the term Cerebellar Cognitive Affective Syndrome (CCAS). Particularly when the vermis or the posterior cerebellum is affected, this syndrome may

entail blunting of affect, a general disinhibition of behavior and subtle cognitive defects (71-75). For instance, working memory tasks recruit neuronal activation of a cortico-cerebellar network that involves the cerebellum and ventrolateral and dorsolateral areas of the prefrontal cortex (76). After cerebellar lesions working memory performance is worse and cortical areas are affected leading to the recruitment of additional brain areas to compensate for reduced cerebellar functioning (76). Also, emotion categorization tasks elicit topographically distinct but also overlapping activation patterns in the cerebellum (77). Damage to the cerebellum may therefore affect cognition and emotion which may result in disinhibited and potentially aggressive behavior.

In conclusion, the neural underpinnings of antisocial behavior and psychopathy will be approached through assessment of the functionality of the above described brain processes: interhemispheric connectivity between the (pre)frontal cortices, cortical inhibition (explained in §1.3) in the DLPFC, amygdalo-vmPFC and striato-thalamo-frontal connectivity and the contributions of the cerebellum will be explored. Below you will find the research measures that will be used in this exploration.

§1.3 Techniques to measure brain functionality

In terms of research techniques the centre of gravity of this thesis will be the use of transcranial magnetic stimulation (TMS). Most of the above described brain processes (e.g., interhemispheric connectivity) can be tested directly with TMS. Before the outline of this thesis is presented (§1.4), the various TMS paradigms that will be employed will be briefly explained. In addition, as one chapter employs diffusion tensor imaging (dti), this technique will also be introduced.

TMS is a research tool that has survived the test of time and has earned its place among other research techniques such as functional MRI. In essence, TMS is an external manipulation of the brain, i.e., it depolarizes neurons. The difficulty has always been how to measure the effects of this brain manipulation but slowly more and more ways are emerging that enable researchers to index the effects of TMS on the brain. Single pulse paradigms, paired pulse paradigms, repetitive TMS, functional MRI (fMRI) and EEG, all of which give valuable information on how the brain responds to magnetic stimulation. Below, the TMS techniques that will be used in this thesis will be explained in further detail. All definitions are derived from *Transcranial Magnetic Stimulation in Clinical Psychiatry* by George and Belmaker (78).

Motor evoked potential

A TMS pulse has a duration of about 1ms and when it is applied to the hand representation of the motor cortex, it is followed by a motor evoked potential (MEP), about 24ms later. The MEP varies in size as a function of stimulus intensity but is also influenced by variability in the corticospinal pathway (79). (See Table 2A)

Cortical inhibition

Cortical inhibition (CI) reflects the neurophysiological process through which ipsilateral inhibitory interneurons selectively tune down activity of cortical output neurons. Inhibitory interneurons can be found in layer 2/3 of the cortex and they receive transcallosal excitatory afferents. Below, the various techniques to index CI will be detailed.

Cortical silent period

The cortical silent period (CSP) is defined as 'the interruption of voluntary tonic

electromyographic activity in the target muscle contralateral to the stimulated motor cortex.' The early part of CSP appears to reflect the inhibition of spinal motoneurons (first 50-75ms) whereas in the later part supraspinal structures such as motor cortical GABAB receptor contribute (78, 80). Depending on stimulus intensity, CSP may reflect more GABAA than GABAB receptor mediated inhibition: GABAA receptors are recruited at lower intensities whereas GABAB comes into play at higher intensities (80). (See Table 2B and §3.1)

Long-interval intracortical inhibition

Long-interval intracortical inhibition (LICI) is tested by a paired pulse paradigm and is defined as 'the inhibition of a test MEP by a suprathreshold conditioning pulse delivered through the same stimulating coil.' The interstimulus interval should be between 50 and 200ms (78, 80). LICI engages primarily GABAB receptor mediated inhibitory neurotransmission which has repeatedly been demonstrated (81, 82). Contrasting GABAA receptors, GABAB receptors are G-protein-coupled receptors that work slower and for a longer period of time. Unlike short-interval intracortical inhibition, LICI can be measured from non-motor areas such as the DLPFC (83-86). LICI assessed from hand muscles correlates with suppression of EEG signal over the motor cortex. It was also shown that LICI over the motor cortex correlates with LICI measured from the DLPFC suggesting that this particular paired pulse paradigm consistently assesses similar neurophysiological processes throughout the cortex (85). It should be added that the limited spatial resolution of TMS does not allow for a very precise distinction between DLPFC and motor-cortex stimulation. (See Table 2C and §3.3)

Short-interval intracortical inhibition

Short-interval intracortical inhibition (SICI) is defined as 'inhibition of a test MEP by a subthreshold conditioning pulse delivered through the same stimulating coil.' The ISI should be between 1 and 5ms. SICI is also measured in a paired pulse paradigm but, unlike LICI, it involves a subthreshold conditioning stimulus which will target a low threshold inhibitory cortical circuit (See Table 2D and §3.1). It is thought that SICI revolves mainly around the GABAA receptor but is also regulated by neurotransmitters such as dopamine (78, 80). The idea of strong involvement of the GABAA receptor fits with data suggesting the GABAA receptor is a ligand-gated ion channel (referred to as an ionotropic receptor)

that acts relatively fast.

Intracortical facilitation

Intracortical facilitation (ICF) is defined as '*facilitation* of a test MEP by a subthreshold conditioning pulse delivered through the same stimulating coil.' The ISI should be between 7 and 20ms. ICF probably involves a complex interplay of facilitation and weaker inhibition in which facilitation prevails. As ICF is measured with the same parameters used for SICI it is assumed that the inhibition stems from the tail of inhibitory activity of GABAA receptors. The facilitatory component may be accounted for by N-methyl D-aspartate (NMDA) receptors although non-NMDA receptors may also contribute (80). (See Table 2E and §3.1)

Interhemispheric inhibition

Interhemispheric inhibition (IHI) is defined as 'the inhibitory effect of conditioning TMS over one motor cortex on the amplitude of the test MEP elicited with TMS over the other motor cortex.' IHI is measured with a paired pulse TMS paradigm in which a conditioning stimulus is administered over the ipsilateral M1 followed by a test stimulus over the contralateral M1 (87, 88). IHI can be observed when the interstimulus interval is set at 10ms or 40ms with 10ms being the more commonly used latency. A complex polysynaptic pathway is likely to be involved in IHI but more heuristic models propose that neuronal populations that mediate LICI, also mediate IHI in the contralateral hemisphere. Excitatory fibers that cross the corpus callosum are activated by the conditioning pulse and they innervate inhibitory interneurons in the contralateral cortex. Neurophysiologically, IHI would mainly tap into gamma-amino butyric acid (GABA)-B receptor functioning (See Table 2F and §3.1).

Interhemispheric signal propagation

If you throw a rock in a pond, the water will ripple until slowly the waves fade away. If magnetic stimulation of the brain would follow this pattern, the effects of one single TMS pulse would linger for seconds and the brain would not be able to function. Instead, a TMS pulse depolarizes neurons and through a chained cascade this activation will spread, but activity will inevitably be inhibited, usually within a fifth of a second. Therefore, following the path of neuronal activation after a TMS pulse will yield valuable information on the pathway but also on the subsequent inhibition of TMS-induced activation. Interhemispheric

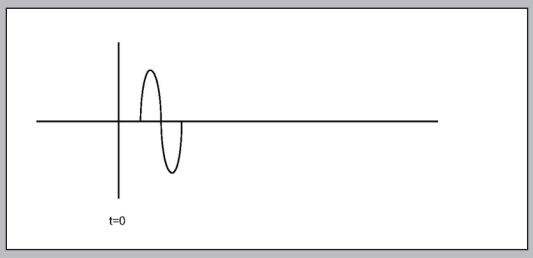
signal propagation (ISP) is a new and elegant measure of interhemispheric connectivity which is indexed through the employment of TMS and EEG (89, 90). Simply put, a pulse is administered to one hemisphere and with EEG the response of the brain is measured on the hemisphere of stimulation and on the homotopical area of the contralateral hemisphere. The ratio of the contralateral evoked potential to the cortical evoked potential of the stimulated hemisphere is subsequently calculated. As would be expected, ISP is dependent on the microstructural integrity of the corpus callosum, as measured through diffusion tensor imaging (dti) (89). The contralateral activity is between 50% and 70% of the ipsilateral activity, dependent on the cortical regions from which it is measured (e.g., motor cortex vs prefronal) (89, 90). (See §3.1)

Repetitive transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation (rTMS) involves the repeated administration of magnetic pulses to the brain with the intention to modify brain activity. A distinction has been made between low frequency (i.e. <1Hz) and high frequency (i.e., >1Hz) rTMS. For high frequency rTMS parameters of 5 to 20Hz are typically used and they tend to increase cortical excitability (91). In addition, high frequency rTMS decreases cortical inhibition (91). By contrast, low frequency rTMS decreases cortical excitability as evidenced by a decrease in MEP size after rTMS, although these effects are relatively small and are highly influenced by stimulation intensity. Whether low frequency rTMS decreases or increases cortical inhibition is unclear, it may not have strong effects on cortical inhibition at all (91). On the system's level, high frequency rTMS appears to boost the function that is specifically related to the stimulated area. Low frequency typically limits functionality (See §4.2)

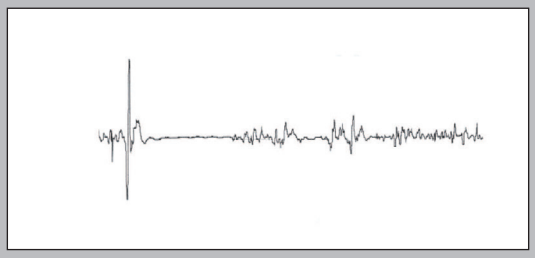
Diffusion tensor imaging

Diffusion tensor imaging (DTI) is a MRI technique that assesses the microstructural integrity of white matter, i.e., the myelination of axons. With DTI the characteristics of the diffusion of water molecules throughout the brain are measured. Diffusion of water molecules is restricted by various entities in the brain, such as cell membranes or the axons of neurons In cerebrospinal fluid water molecules diffuse in all directions whereas in for instance white matter tracts water diffusion is largely limited to one principal direction. Fractional anisotropy (FA) is the measure with which this diffusion is often quantified and it would



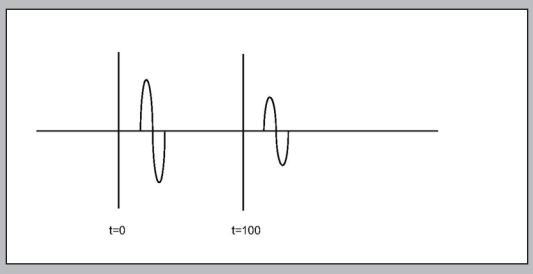
A. Single Pulse

In this figure, the vertical line represents the TMS pulse which is followed by a deflection in baseline EMG activity, known as the motor evoked potential (MEP). The MEP is measured peak to peak and occurs about 24ms after the TMS pulse.



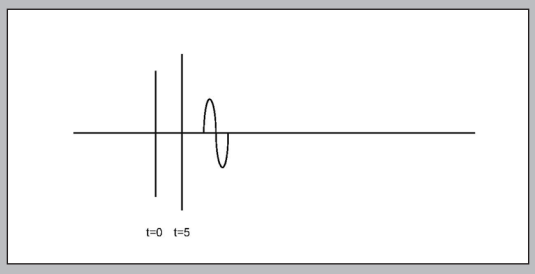
B. Cortical Silent Period

When a TMS pulse is administered during moderate muscle contractions there is an absence of EMG activity after the MEP, shown here as a flattened line. The CSP can last up to 200ms but is on average between 130 and 150ms.



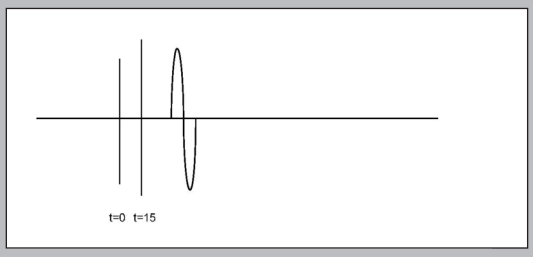
C. Long-interval intracortical inhibition

When two suprathreshold TMS pulses are administered with an interstimulus interval of for instance 100ms, the MEP is attenuated by about 50%.



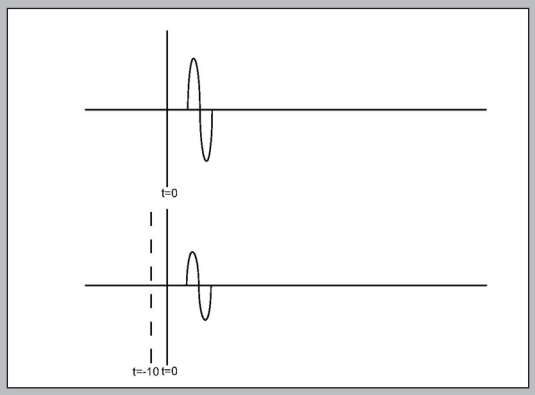
D. Short-interval intracortical inhibition

The first pulse at t=0 is subthreshold (e.g., 80% of MT) and precedes the test stimulus by 1-5ms resulting in a reduction in MEP magnitude.



E. Intracortical facilitation

Similar to SICI the conditioning pulse at t=0 is subthreshold but as the ISI is longer (between 10 and 20ms) an increase in the MEP is observed.



F. Interhemispheric inhibition

The dotted line represents a suprathreshold conditioning pulse over the contalateral hemisphere which, if it precedes the test stimulus by ~10ms, results in an attenuation of the MEP.

Table 2. Here, the various TMS measures of intracortical and interhemispheric inhibition are depicted graphically. Vertical lines represent TMS pulse with the shorter one being subthreshold and the longer ones being suprathreshold.

have an approximate value of 0 in cerebrospinal fluid and up to 1 in major white matter tracts (92). This makes it the perfect technique to assess the integrity of white matter tracts in the brain allowing for voxel-wise comparison between psychiatric and control groups. Previous studies in psychopathic and antisocial groups have shown decreased integrity of the uncinate fasciculus (which connects the amygdala to the OFC).

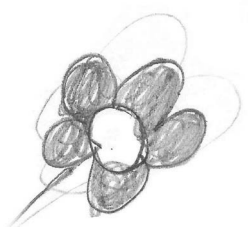
§1.4 Outline of the thesis

This thesis consists of three sections. Section 1 is a proof of principle in which the functional contributions and mechanisms of interhemispheric connectivity will be addressed. The first chapter of Part 1 (§2.1) will examine the relationship between interhemispheric connectivity and personality features as measured per NEO-PI-R. In §2.2, the influence of alcohol on interhemispheric connectivity will be examined. This is of particular importance as more than 50% of all violent crimes are associated with alcohol (93) and up to 86% of all murders (94). The last chapter of part 1 (§2.3) is a methodological intermezzo in which we will examine the functional mechanisms associated with ISP by relating it to a second TMS measure of interhemispheric connectivity, IHI.

The second part is the core of this thesis and it consists of 3 chapters in which TMS, EEG and DTI will be used to evaluate the integrity of brain networks in psychopathic offenders. In §3.1 we will examine whether psychopaths suffer from interhemispheric connectivity deficits by measuring their ISP and comparing it to that of healthy controls. Also, cortical inhibition and facilitation will be measured in the left and right motor cortex. In §3.2, an essential component of brain networks, white matter, will be assessed in psychopaths through diffusion tensor imaging (DTI). Using a tract based spatial statistics (TBSS) approach we explore white matter integrity throughout the brain in psychopathic offenders and compare them to healthy controls. Based on what was described in the previous pages an amygdalo-prefrontal network might be affected in addition to the mesolimbic reward pathway. §3.3 will test for the first time whether psychopathic offenders have inhibitory abnormalities in the DLPFC as compared to non-psychopathic individuals. To this end, we will use TMS in combination with EEG and assess LICI in the motor cortex and DLPFC. In addition, we will index working memory performance as it has been previously shown that psychopathic offenders may have impairments in this cognitive function.

Part 3 endeavours into possible contributors to antisocial behavior. Here, in §4.1, we present the cerebellum as a key brain structure that is affected in many neuropsychiatric disorders including schizophrenia and autism. We will consider evidence for potential cerebellar involvement in disinhibited behavior. In §4.2, a rTMS manipulation of the cerebellum will be introduced to see whether alterations of cerebellar activity induce affective changes. To measure affective changes we use an affective pictorial Stroop task.

PART 2



§2.1

Personality goes a long way: an interhemispheric connectivity study

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Frontiers in Neuropsychiatric Imaging and Stimulation

Part 2

Abstract

Throughout the development of psychology the delineation of personality has played a central role. Together with the NEO-PI-R, a questionnaire derived from the Five Factor Model of Personality, and recent advances in research technology it is now possible to investigate the relationship between personality features and neurophysiological brain processes. The NEO-FFI, the short version of the NEO-PI-R, reliably measures five main personality traits: Neuroticism, Extraversion, Openness to experience, Agreeableness and Conscientiousness. As behaviour and some psychiatric disorders have been related to interhemispheric connectivity, the present study used the combination of transcranial magnetic stimulation (TMS) and electroencephalography (EEG) to measure frontal interhemispheric connectivity and its association with personality as indexed by the NEO-FFI. Results demonstrated that prefrontal interhemispheric connectivity between the left and right dorsolateral prefrontal cortex (DLPFC) correlates with Agreeableness in healthy subjects. This is the first study to relate personality features to interhemispheric connectivity through TMS-EEG and suggests that Agreeableness relates to the effectiveness of prefrontal communication between hemispheres.

Introduction

Personality can be defined as the dynamic organization of psychophysical systems that create the person's characteristic patterns of thoughts, feelings and behaviour (95). Similar to IQ, personality is a robust predictor of life outcome as it reliably predicts divorce, mortality and occupational attainment (96). One of the major advances in personality research has been the development of the NEO-PI-R, a questionnaire derived from the Five Factor Model (FFM) of personality that has become a prevalent assessment tool for personality (97, 98). The NEO-PI-R, and its short version the NEO Five Factor Inventory (NEO-FFI) consists of the five factors: Neuroticism, Extraversion, Openness to experience, Agreeableness and Conscientiousness.

Personalities develop until late adolescence and are influenced by parental care, contact with peers and the predominant culture. Although most measures of personality remain relatively stable in adulthood aspects of personality may change in later life (99). In the last decade, advances in both research technology and the development of reliable indexes of personality have uncovered relationships between personality and certain brain processes. For instance, Tauscher and colleagues (100) reported an inverse relationship between prefrontal serotonin receptor binding potential and anxiety, a constituent of the neuroticism scale. In addition, neuroticism has been associated with frontolimbic serotonin receptor binding, a correlation that was mainly driven by the subfactors vulnerability and anxiety (101). Arguably, the association of serotonin receptor functioning with vulnerability and anxiety that can predispose to major depressive disorder (MDD) may explain the efficacy of selective serotonin reuptake inhibitors (SSRI) (100, 101). In a transcranial magnetic stimulation (TMS) study, neuroticism was found to positively correlate with cortical inhibition over the motor cortex (102). TMS is a relatively new research tool that allows for non-invasive investigation of brain areas and the communication between brain areas. Originally confined to the motor cortex, TMS has recently been combined with electro-encephalography (EEG) enabling measurement of cortical inhibition from non-motor areas such as the dorsolateral prefrontal cortex (DLPFC) (85). Importantly, cortical inhibition measured in the DLPFC has been associated with working memory performance (86). Through the combination of TMS and EEG, the connectivity between hemispheres can also be assayed in cortical regions more relevant to human affect, cognition and behaviour such as the prefrontal cortex. Recently, we reported that TMS-induced interhemispheric

signal propagation (ISP) correlates with the microstructural integrity of fiber bundles that constitute the corpus callosum showing that a higher integrity of the callosal fibers is associated with lower ISP (89). ISP is defined as the ratio of right to left cortical evoked activity (89). Specifically, ISP induced by single pulse TMS over the motor cortex significantly correlated with fractional anisotropy (FA) of callosal motor fibers but not with FA of the genu. FA represents the extent to which parts of the cytoskeleton including axons and cell bodies restrict the diffusion of water molecules (103). Conversely, ISP induced by prefrontal single pulse TMS was significantly correlated with FA of the genu but not with callosal motor fibers suggesting that interhemispheric connectivity as measured with TMS-EEG is mediated by interhemispheric callosal pathways (89).

Functionally, interhemispheric connectivity represents a neurophysiological mechanism that allows the hemispheres to interact enabling hemispheric lateralization and specialization of functions such as language (104). However, affect has also been shown to relate to hemispheric lateralization (105, 106) while human aggressive behaviour has been associated with asymmetric interhemispheric connectivity (107). In addition, deficits in interhemispheric connectivity have been argued to give rise to certain psychiatric disorders such as attention deficit hyperactivity disorder (ADHD) (23) and MDD (108). Taken together, these studies suggest that interhemispheric connectivity may underlie various cognitive, affective and behavioural functions that together constitute a personality style. In the present study, therefore, we sought to investigate the relationship between prefrontal interhemispheric connectivity as measured with TMS and EEG and the construct of personality as indexed by the NEO-FFI.

Methods

Participants

Ten right-handed healthy subjects (mean age = 37.8 ± 7.8, range = 27- 48 years; 4 males, 6 females) were recruited via advertisements or self-referral, and psychopathology was ruled out through the personality assessment screener (PAS; Psychological Assessment Resources, Inc). Exclusion criteria included a self-reported medical illness or a history of drug or alcohol abuse. Handedness was confirmed using the Edinburgh Handedness Inventory (109). We also administered a TMS safety screening and demographic questionnaire. Subjects had no history of seizure, brain surgery or stroke, and had never experienced

external head trauma. The average weight and height across subjects were 146.9 ± 35.3 lbs (range = 102 - 210 lbs) and 5'7" ± 5" (range = 5'1" - 6'4"), respectively. Subjects had 16 ± 2 years of education, and the mean handedness score (laterality quotient) was 89 ± 15 (range = +56 to +100) across subjects. Finally, NEO-FFI was administered in all subjects. The protocol was approved by the Research Ethics Board of the Centre for Addiction and Mental Health and all subjects gave their written informed consent in accordance with the declaration of Helsinki.

Transcranial Magnetic Stimulation

Single monophasic TMS pulses were administered to the left motor cortex and left DLPFC using a 7 cm figure-of-eight coil, and a Magstim 200 stimulator (Magstim Company Ltd., UK). In motor cortex, the TMS coil was placed at the optimal position for eliciting motor evoked potentials (MEPs) from the right abductor pollicis brevis (APB) muscle, which typically corresponded to a region between FC3 and C3 electrodes on the 10-20 EEG system (110). Localization of the DLPFC was achieved through neuronavigation techniques using the MINIBIRD system (Ascension Technologies, USA) and MRIcro/reg software using a T1-weight MRI scan obtained for each subject with 7 fiducial markers in place. Stimulation was directed at the junction of the middle and anterior one-third of the middle frontal gyrus (Talairach Co-ordinates (x, y, z)=(-50, 30, 36)) corresponding with posterior regions of Brodmann Area (BA) 9 which overlap with the superior section of BA46,as previously described (111). The optimal position was marked on the EEG cap to ensure identical placement of the coil, and the handle of the coil pointed backward, perpendicular to the presumed direction of the central sulcus, approximately 45º to the mid-sagittal line.

The TMS intensity was determined at the beginning of each experiment. For each subject, resting motor threshold (RMT) was defined as the minimum stimulus intensity that elicits a MEP of more than 50 μV in five of ten trials (112). This corresponded to 39.1% ± 6.1% of stimulator output. The suprathreshold intensity was set to elicit an average MEP of 1 mV peak-to-peak amplitude upon delivery of 20 pulses over the motor cortex; this corresponded to 63.1% ± 12.1%. A total of one hundred suprathreshold stimuli, with an interstimulus interval of 5 seconds, were delivered to each cortical region (i.e., motor cortex and DLPFC).

Electromyography

To capture EMG, two disposable disc electrodes were placed over the right APB in a tendon-belly arrangement. MEPs were band-pass filtered (2 Hz to 5 kHz), digitized at 5 kHz, and collected through commercially available software Signal (Cambridge Electronics Design, UK).

Electroencephalography

To evaluate TMS-induced cortical evoked potentials, EEG was acquired through Synamps2 EEG system (Compumedics, Charlotte, USA) using a 64-channel EEG cap. In order to monitor eye movement artifacts, four additional electrodes were placed on the outer side of each eye, and above and below the left eye. All electrodes were referenced to an electrode placed on the vertex posterior to the Cz electrode. EEG signals were recorded with filters at DC to 100 Hz at 20 kHz sampling rate, which was shown to minimize the TMS related artifacts (85). The EEG recordings were analyzed as previously described (84, 85), that is, for each subject and recording site, artifact free post-stimulus cortical evoked potentials were extracted and averaged.

TMS-Induced ISP

To quantify the propagation of TMS induced cortical evoked activity, the average cortical evoked potentials were band pass filtered (1-50Hz) and TMS-induced ISP was calculated through Equation A (Voineskos et al., 2010). To evaluate TMS-induced ISP in the motor cortex, C3 (left hemisphere) and C4 (right hemisphere) electrodes were used, which are the electrodes closest to the optimal site of APB activation through TMS. In the DLPFC, the recording electrodes of interest were AF3 (left hemisphere) and AF4 (right hemisphere), which optimally represent the overlap of BA9 and 46. In the left hemisphere, the area under the rectified curve was obtained between 50-150 ms post-stimulus. The onset (50ms) represents the earliest artifact free data that was reliably recorded post-stimulus. The offset (150ms) represents the mean duration of GABAB receptor mediated inhibitory neurotransmission that is recorded neurophysiologically (113) and is related to callosal inhibitory mechanisms (114). An average interhemispheric transfer time of 10 ms was chosen to account for the time it takes for the signal to propagate from the site of the stimulation to the contralateral hemisphere (88). Therefore, in the right hemisphere, the

area under the rectified curve was obtained between 60-160 ms post stimulus.

Equation A $$\% ISP = \left[\frac{\text{Area under rectified curve } (Right\ Cortex)}{\text{Area under rectified curve } (Left\ Cortex)} \right] \times 100$$

Statistical Analysis

Two tailed paired t-tests were used to examine the difference between the cortical evoked potentials in the left and right hemispheres for both motor cortex and DLPFC. Pearson correlation coefficients were used to assess the relationship between the five personality domains of NEO-R with TMS-induced ISP in motor cortex and DLPFC. Non-parametric Spearman correlation coefficients were also calculated give the small sample size and the non-continuous NEO-FFI factors. To account for multiple comparisons, a Bonferonni corrected alpha = 0.01 was applied. All statistical analyses were performed using SPSS 15.0 (SPSS Inc. Chicago, Illinois, USA).

Results

TMS-Induced ISP

DLPFC

Consistent with previous findings (89), the activation of the right DLPFC was significantly lower compared to the cortical evoked activity in left DLPFC (right: 581.8 ± 334.1 μv.ms, left: 974.8 ± 487.6 μv.ms; t=2.9, df=9, p=0.018) (Figure 1A). The mean TMS-induced ISP, measured through Equation A, was 66.6% ± 37.2 % across subjects. The activation of ipsi- and contralateral hemisphere is also demonstrated in the topographic illustration of the averaged cortical evoked responses measured at various latencies (Figure 2A).

Motor Cortex

Consistent with previous findings (89), the activation of the right motor cortex was significantly lower compared to the cortical evoked activity in left motor cortex (right: 284.3 ± 131.8 μv.ms, left: 717.9 ± 453.2 μv.ms; t=3.8, df=9, p=0.004) (Figure 1B). The mean TMS-induced ISP, measured through Equation A, was 48.2% ± 21.4% Similar to DLPFC, the activation of both left and right hemispheres is shown in the topographic illustration of cortical evoked potentials (Figure 2B)

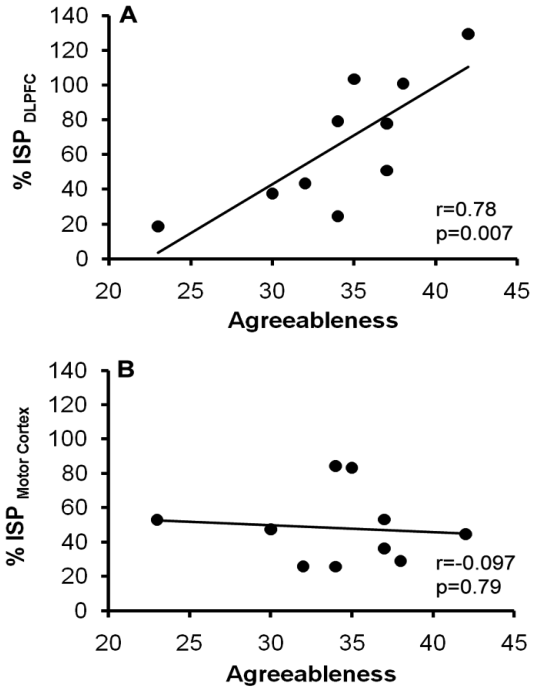


Figure 1. The relationship between interhemispheric signal propagation and Agreeableness. Data obtained from 10 healthy subjects. The x-axes represent the score on Agreeableness, a domain of the NEO-FFI. The y-axes illustrate the TMS-induced ISP from the left DLPFC to the right DLPFC. (A), and from the left motor cortex to the right motor cortex (B), obtained through equation A.

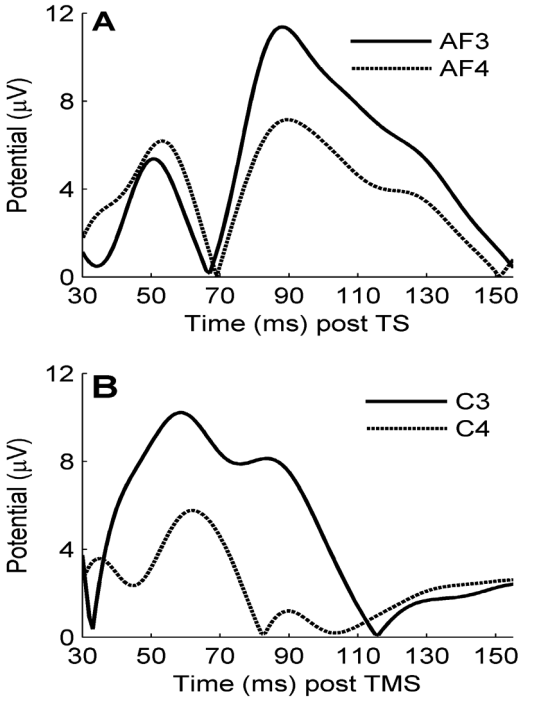


Figure 2. Cortical evoked potentials in ipsi- and contralateral hemispheres following the application of TMS to the left DLPFC and left motor cortex. The waveforms represent mean rectified cortical potentials following the delivery of single pulse of TMS to the left DLPFC (A) and the left motor cortex (B). In both figures, x-axis represents the time after the delivery of the TMS, and the y-axis represents the cortical evoked potentials (μV). These figures illustrate that application of single pulse TMS to the left hemisphere (solid waveforms) results in cortical evoked potentials in the contralateral hemisphere (dashed waveforms) that are of lower amplitude than the cortical evoked potential in the ipsilateral hemisphere.

The Relationship between NEO-FFI and TMS Induced ISP

We found a significant relationship between TMS-induced ISP in DLPFC, and Agreeableness (r=0.78, p=0.007) (Figure 3A). This relationship was specific to DLPFC as no relationship was found between agreeableness and the TMS-induced ISP in the motor cortex (r=-0.097, p=0.79) (Figure 3B). Tested non-parametrically, ISP measured from the DLPFC correlated significantly with Agreeableness (rho=0.80, p=0.006) whereas ISP measured from the motor cortex was also not significant (rho=-0.085, p=0.815). In addition, Bonferroni corrected for multiple comparisons, no relationship was found between the remaining domains of NEO-FFI and TMS induced ISP in the motor cortex or DLPFC, all p's > 0.01.

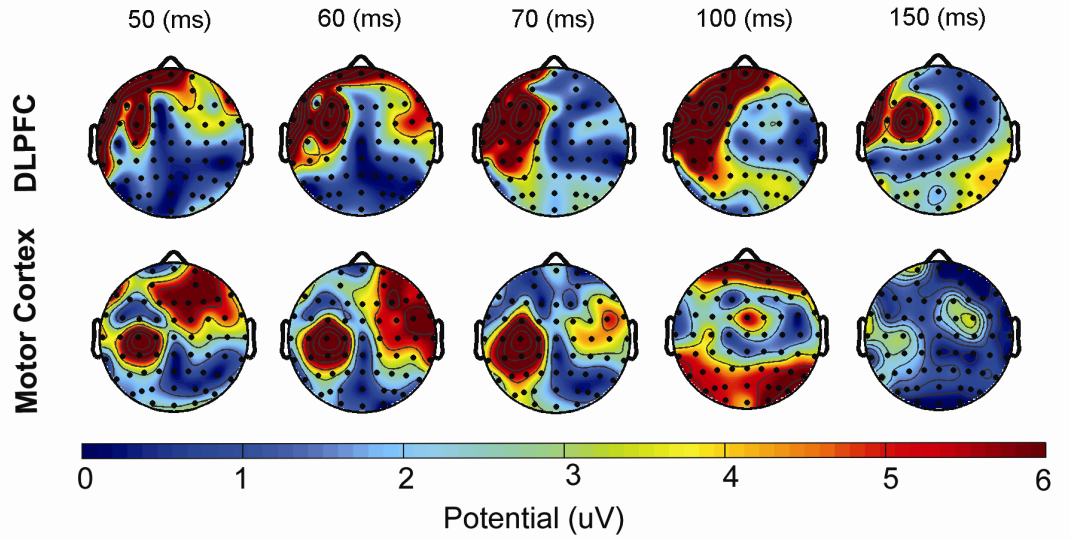


Figure 3. Topographic plots illustrate the mean amplitude of cortical evoked activity in response to application of TMS single pulse to the left DLPFC (top panel) and left motor cortex (bottom panel) at 50, 60, 70, 100 and 150 ms following the TMS delivery averaged across all ten subjects. These plots suggest that application of TMS to the left hemisphere results in activation of regions on the contralateral hemisphere but the activity is lower than that of the ipsilateral hemisphere. Topographic head plots were obtained by EEGLAB toolbox (115)

Discussion

This represents the first study to relate personality traits to neurophysiological indices of interhemispheric brain communication. Specifically, we aimed to elucidate the relationship between personality and prefrontal interhemispheric connectivity and demonstrate here that of the five main personality traits it was Agreeableness that related to TMS-induced ISP

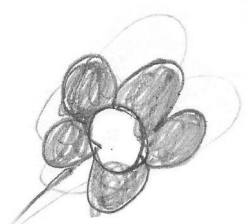
over the DLPFC. Importantly, this association was not found for connectivity between the motor cortices and therefore appears specific to prefrontal interhemispheric connectivity. As noted earlier, TMS-induced ISP over the DLPFC correlates with the microstructural integrity of the anterior part of the corpus callosum, the genu. These data, therefore, suggest that Agreeableness relates to the integrity of prefrontal interhemispheric connectivity that was previously shown to be mediated by the fibres in the genu of the corpus callosum. Complementary to dti, TMS-induced ISP provides information about the effective connectivity between certain brain areas. In addition, brain responses to TMS pulses measured with EEG can be divided into frequency bands providing information about the type of brain activity.

Agreeableness reflects the extent to which a person exhibits friendly, considerate and prosocial behavior aimed at cooperation and social harmony (116, 117). As a superordinate trait, Agreeableness covers various cognitive and emotional abilities such as empathy (118, 119) and perspective-taking (120). Previous studies have shown that Agreeableness correlates with volumes of brain areas such as the superior temporal sulcus and the (posterior part of) the cingulate cortex that process information about the intentions and mental states of others (117). In addition, Nettle and Liddle (120) established a positive relationship between Agreeableness and perspective-taking. Interestingly, involved in an extensive social cognition network subserving social behavior (121-123), the left DLPFC is associated with the processing of social information and the subsequent enabling of the prosocial behavior that is intrinsic to Agreeableness. In fact, perspective-taking, the cognitive ability to take on the perspective of another person, is dependent upon left DLPFC glutamatergic projections (124) which are also involved in interhemispheric connectivity (114). Specifically, Montag and colleagues (124) observed a negative correlation between glutamate levels and perspective-taking in the left DLPFC and hypothesized that the role of the DLPFC in social behaviour may lie in the suppression of egoistic motivations and self-perspective (124). In line, the Behavioural Inhibition System (BIS) and Behavioural Activation System (BAS) have also been associated with the NEO-PI-R (125). In this study, Agreeableness was shown to correlate positively with BIS and negatively with a subfactor of BAS (125). Corroborating the hypothesis of Montag and colleagues (124), Smits and De Boeck (125) argue that these correlations also express the suppression of egoistic reward-driven motivations leading to more favourable behaviour. The present study suggests that

the left DLPFC is indeed related with prosocial behaviour but adds to this understanding by demonstrating that this relationship involves communication with the contralateral homologous region. In addition, it is not unlikely that this relationship subserves the process of perspective-taking which has been shown to be positively associated with Agreeableness (120).

Psychiatric diseases in which interhemispheric connectivity is affected may be interpreted as demonstrating that interhemispheric transfer underlies certain psychiatric symptoms some of which may also be present in personality disorders. Indeed, deficits in interhemispheric connectivity have been associated with psychiatric disorders such as ADHD (23) and MDD (108). In fact, in ADHD deficits in interhemispheric connectivity are restored by methylphenidate treatment (23). Also, personality disorders have been shown to relate to deviant scores on the NEO-PI-R. For instance, in psychopathy, Agreeableness has been shown to be significantly lower (126) and the gold standard for the diagnosis of psychopathy, the Revised Psychopathy Checklist (PCL-R) (46), correlates negatively with Agreeableness (116), demonstrating that a high degree of psychopathy is associated with little agreeableness. At present, given that our data suggest that low ISP signifies low Agreeableness, (89) it could be predicted that the higher degrees of psychopathy relate to a lower ISP index, although such findings need to be demonstrated directly.

The present study has some limitations. First, although the currently observed correlation was strongly significant, it should be replicated in a larger sample. In addition, the proposed hypothesis of perspective-taking and prefrontal interhemispheric connectivity may also be verified in a larger sample. Second, only left-to-right ISP was tested and as hemispheric asymmetries in relation to certain personality features have been reported (105, 107), future studies may also look into right-to-left ISP. Third, we currently only indexed prefrontal interhemispheric connectivity at suprathreshold stimulus intensity levels and consequently, subthreshold stimulation should also be assayed in future testing. Despite these limitations, this study represents one of the first efforts to directly evaluate the neurophysiological relationship between connectivity in the DLPFC with personality and suggests that Agreeableness relates to the effectiveness of prefrontal communication between hemispheres.

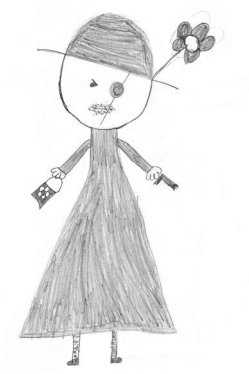


§2.2

Alcohol breaks down interhemispheric inhibition in females but not in males

Sylco S. Hoppenbrouwers, Dennis Hofman & Dennis J.L.G. Schutter

Psychopharmacology



Abstract

Alcohol has renowned behavioural disinhibitory properties which are suggested to involve reductions in frontal lobe functioning as a result of diminished interhemispheric connectivity. To examine sex differences in frontal interhemispheric connectivity in response to alcohol twelve female and ten male healthy volunteers received a single administration of 0.5‰ alcohol in a placebo-controlled counterbalanced crossover design. Paired pulse transcranial magnetic stimulation (TMS) was applied to measure interhemispheric inhibition (IHI) between the left and right primary motor cortex (M1). Results showed significant reductions in IHI after alcohol administration in female participants exclusively. These findings provide the first evidence that moderate doses of alcohol differentially affect frontal interhemispheric connectivity in males and females. The present data may shed new light on the physiological mechanisms underlying sex differences in the susceptibility to alcohol.

Introduction

In the last decades alcohol consumption steadily increased culminating in 3.2 million yearly deaths either as a direct or indirect result of alcohol worldwide (127). Moderate doses of alcohol (≤ 0.5‰) can produce feelings of relaxation and release of response inhibition, whereas higher doses of alcohol (1-1.5‰) cause impairments in motor coordination and vision. Extremely high alcohol levels (≥ 2.5‰) ultimately lead to coma and death (128). Interestingly, the effects of alcohol seem to be more pronounced in females than in males (129-132). Sex differences in response to alcohol intake can in part be explained by differences in the percentage of body fat (133) and the availability of the enzyme alcohol dehydrogenase which breaks down alcohol (134). However, other research suggests that females differ from males on the innate physiological susceptibility to the central effects of alcohol (135-138). For instance, chronic misuse of alcohol leaves female alcoholics with more brain damage than their male counterparts (132, 135). Interestingly however, moderate drinking habits also affect the female brain more strongly than the male brain (138). In addition to the general effects on the central and peripheral nervous system, alcohol typically affects frontal cortical functions such as response inhibition and cognitive regulation (139, 140). In fact, even though alcohol diffuses through all biological membranes and is distributed throughout the body, the anterior cortical regions of the brain have been shown to be especially vulnerable to the acute (141) and chronic (142) effects of alcohol. Low doses of alcohol already reduce excitability of the frontal cortex as evidenced by transcranial magnetic stimulation (TMS) and electroencephalography (EEG) (143-145). This reduction in frontal cortical excitability has been argued to relate to binding of alcohol to gamma-amino butyric acid (GABA)-a receptors in addition to alcohol-related inhibition of N-methyl D-aspartate (NMDA) currents (143). However, the precise mechanisms that underlie the behavioural effects of alcohol and possible sex differences remain unclear. One possible mechanism may involve (transient) frontal lobe impairments arguably due to reductions in effective frontal interhemispheric connectivity (Kähkönen et al., 2001). Frontal interhemispheric connectivity refers to callosal signal transfer between the left and right frontal cortex (22). This signal transfer can be measured with paired pulse TMS wherein the connectivity between the left and right primary motor cortex (M1) is operationalized by applying a conditioning pulse to ipsilateral M1 followed by a test pulse to contralateral M1 10ms later (Ferbert et al., 1992). Compared to the motor evoked

potential (MEP) elicited by the test pulse alone, the conditioning pulse inhibits the MEP of the test pulse by about 50% (114). This so-called interhemisperic inhibition (IHI) reflects an important physiological mechanism by which the frontal lobes interact and contribute to behaviour by providing a non-invasive way to study frontal interhemispheric connectivity (107).

The aim of the present placebo controlled counterbalanced cross-over design was to examine sex differences in frontal interhemispheric connectivity in response to alcohol intake as indexed by IHI. We hypothesized that alcohol will reduce IHI in both males and females. In addition, it is expected that reductions in IHI will be more pronounced in females than in males.

Methods

Participants

Twenty-two healthy volunteers (ten males), mean ± SD, 22.5 ± 0.85 years of age, participated in this study. All participants were right handed, non-smoking and free of any psychiatric or neurological disorders and had more than 12 years of education. All female participants used oral contraceptives. Subjects had no history of alcohol abuse or dependence as measured with the Alcohol Use Disorder Identification Test (AUDIT) (146). Written informed consent was obtained and volunteers were paid for participation. The study was approved by the medical ethical committee of the University Medical Centre Utrecht and in accordance with the Declaration of Helsinki. All participants were naïve to the aim of the study.

Alcohol administration and monitoring

The amount of alcohol which would induce a blood alcohol concentration (BAC) of 0.5‰ was estimated with Widmark's formula:

$$\text{BAC (‰)} = \frac{\text{grams of pure alcohol}}{m * r * (1/1.055)} - 0.085$$

where m is body weight and r refers to the distribution ratio which for men is on average 0.68 and for women 0.55 (147). The alcoholic solution (300 ml) consisted of alcohol mixed

with orange juice and a few drops of peppermint oil to mask the alcohol. Placebo (300 ml) consisted of orange juice and peppermint oil. Participants' BAC was measured every 5 minutes using an AlcoMate CORE AL-600 Pro Alcohol Breath Analyzer (AK Solutions USA LLC, Palisades Park, USA). Measurements were started when BAC approximated 0.5‰. Importantly, IHI was measured at the start of the downward limb of the BAC curve because at this point BAC values are suggested to be relatively stable (148).

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 left and right primary motor cortex (M1). Bilateral paired pulse TMS was applied to measure transcallosal inhibition (IHI). In this paradigm, the motor evoked potential (MEP) following the single test pulse (unconditioned MEP, or uMEP) to M1 is compared to the MEP evoked by the test pulse that is preceded by a conditioning pulse to the contralateral M1 10ms earlier (conditioned MEP, or cMEP) (88). The mean percentage reduction between the unconditioned and conditioned MEP was calculated. Stimulation intensity was set at 120% of the individual motor threshold (MT). To minimize anticipation effects TMS was applied at a frequency of 0.18-0.2 Hz. The following conditions were applied in random counterbalanced order: (1) a single test pulse to the left M1 (uMEPleft), (2) a conditioning pulse to the right M1 followed by a test pulse to the left M1 (cMEPleft), (3) a single test pulse to the right M1 (uMEPright), (4) a conditioning pulse to the left M1 followed by a test pulse to the right M1 (cMEPright) (88).

Electromyographic recordings

The electromyogram (EMG) was recorded using sintered 11 × 17mm 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 MEP was recorded from the left and right abductor pollicis 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. EMG signal was digitized at 16kHz, low-pass filtered (-3dB cutoff frequency: 3334 Hz; roll-off: 30dB/octave) and offline high-pass filtered (-3dB cutoff frequency: 20 Hz; roll-off: 48dB/octave).

Procedure

In the present crossover design participants received either a single dose of alcohol or placebo on one of the two occasions in a randomized counterbalanced order. Prior to the testing sessions and on a separate day, participants were invited upon the laboratory. A safety-screening list was administered to check for contra-indications to TMS (149) and health was checked with a standard interview. In addition, safety issues and experimental procedures were explained to the subject and written informed consent was obtained. Alcohol abuse and alcohol dependence were indexed with the AUDIT (150) and participants with AUDIT-scores of 0 or >8 were excluded. Right handedness was assessed with the Edinburgh handedness inventory (109). Resting MT was determined using the standardized motor threshold estimation procedure (151) (see Table 1 for details).

Participants were instructed to refrain from consuming alcoholic beverages 24 hours prior to the testing session, not to consume coffee, tea or chocolate 5 hours before testing and to use their last meal at least 2 hours prior to the testing session. To control for circadian rhythms both testing sessions were conducted at the same time of the day. Each testing session was separated by at least 24 hours. Moreover, to minimize the effects of additional hormonal influences female participants were not tested during the stopping week.

Each experimental session started with a BAC measurement to ascertain sobriety after which participants consumed the alcoholic solution or placebo. Participants had 2 minutes to drink the solution while keeping their nose closed with their hand. The time between administration and paired-pulse TMS was approximately 30 minutes. During this period EMG electrodes were attached to the left and right APB and the optimal target sites for TMS were determined. IHI was measured when the BAC curve approximated 0.5‰ on the descending limb of the BAC curve (148). At the end of the final session participants were debriefed and paid for participation. Both testing sessions took approximately one hour to complete.

Data reduction and analysis

MEP amplitude was quantified as the peak-to-peak amplitude of the maximal EMG response. Left-to-right (l-rIHI) and right-to-left transcallosal inhibition (r-llHI) were expressed according to the formulas [(1- (cMEPright / uMEPright)) * 100] and [(1-(cMEPleft

/ uMEPleft)) * 100] respectively.

A General Linear Model (GLM) for repeated measurements with Drug (alcohol versus placebo) and IHI (left-to-right versus right-to-left) as within subjects factor and Sex (female and male) as a between subjects factor was run to examine the alcohol-related effects and possible sex differences on IHI. To rule out possible alcohol-related effects of single pulse TMS on IHI, an additional GLM for repeated measurements with Drug (alcohol versus placebo) and Side (left versus right hemisphere) as within subjects factors and Sex (female versus male) as a between subjects factor was performed. Finally, to exclude effects of baseline EMG activity on IHI a 2x2 GLM for repeated measurements with Drug (alcohol versus placebo) and EMG (left versus right hand) as within subjects factor and Sex (female versus male) as within subjects factor was conducted. The alpha level of significance was set at 0.05 (two-tailed).

Results

BAC values did not differ between males, mean ± SD, 0.69 ± 0.04, and females, mean ± SD, 0.603 ± 0.05, ($p= 0.17$). Our hypothesis that alcohol would reduce IHI in both males and females was not confirmed, $F(1,21)= 2,752$, $p= 0.113$. In contrast, a significant Drug x Sex interaction, $F(1,21)= 4.95$; $p= 0.038$, was observed. Post-hoc analyses demonstrated that alcohol significantly reduced IHI in females, $F(1,11)= 12.52$; $p= 0.005$; $\eta p2= 0.53$, but not in males, $F(1,9)= 0.10$; $p= 0.76$ (Figure 1).

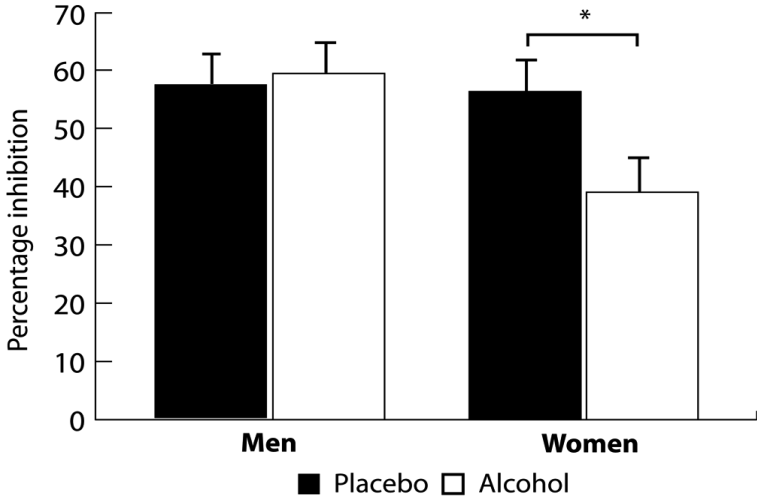


Figure 1. Mean and standard error of the mean of frontal interhemispheric inhibition in the placebo and alcohol condition.

Table 1.

	Males (mean ± SEM)	**Females** (mean ± SEM)	**p**
Age (in years)	23.3 ± 1.4	21.9 ± 1.1	0.43
AUDIT	6.4 ± 0.6	5.8 ± 0.6	0.53
MT left hemisphere	47.5 ± 2.8	49 ± 2.0	0.66
MT right hemisphere	45.2 ± 2.7	47.8 ± 2.2	0.47
Handedness	45.5 ± 0.7	46.3 ± 0.7	0.44

Table 1. Main demographics and characteristics of the participants. MT: motor threshold

The observed sex difference in IHI after alcohol could not be explained by reductions in single pulse TMS as demonstrated by a non-significant Drug * Sex interaction, $F(1,21)= 1.024$; $p= 0.324$. However, a main effect of alcohol on single pulse TMS, $F(1,21)= 4,517$; $p= 0.046$; $\eta p2= 0.184$, was observed, replicating prior studies that found alcohol-related reductions in cortical excitability ((143, 145). Finally, the sex related effect of alcohol on IHI could not be explained by differences in baseline EMG activity as shown by the non-significant Drug * Sex interaction, $F(1,21) = 0.278$; $p= 0.604$. No main effects of alcohol on baseline EMG was observed, $F(1,21)= 0.270$; $p= 0.609$. BAC values did not differ between males, mean ± SD, 0.69 ± 0.04, and females, mean ± SD, 0.603 ± 0.05, ($p= 0.17$).

Table 2.

	IHI		**Single Pulse**		**EMG**	
	males	females	males	females	males	females
Placebo (mean ± SEM)	57,1 ±5.9	56,3 ±7.2	1843.2 ±235,6	1880.8 ±653.8	4769 ±704.9	8574,7 ±2403.2
Alcohol (mean ± SEM)	59.4 ±7.2	40.7 ±8.1	1573.2 ±336	1119.8 ±396.7	6351.9 ±1118.2	8563.9 ±1256.4

Table 2. A reduction of roughly 16% in IHI is observed in females while this is not so in males. However, with regards to cortical excitability (as expressed by single pulse TMS) is reduces in both men and women. (IHI: interhemispheric inhibition, expressed in percentage inhibition of single pulse TMS. EMG: electromyogram, expressed in microvolt. SEM: standard error of the mean. Single pulse TMS is expressed in microvolt.)

Discussion

The aim of the present study was to examine alcohol-related sex differences in frontal interhemispheric connectivity and found reductions in frontal interhemispheric connectivity to a moderate dose of alcohol in healthy female but not male subjects. To the best of our knowledge this is the first study to demonstrate evidence for sex differences in frontal interhemispheric connectivity in response to alcohol that cannot be explained by effects of alcohol on baseline EMG activity or single pulse TMS. The global reduction in cortical excitability as evidenced by a decrease in MEP size in both sexes replicates earlier findings by Ziemann and colleagues (145) and Kähkönen and colleagues (143). This reduction in frontal cortical excitability has been explained in terms of increased binding of alcohol to gamma-amino butyric acid (GABA)-a receptors and alcohol-related inhibition of N-methyl D-aspartate (NMDA) currents (143). In measuring IHI with paired-pulse TMS, the conditioning pulse administered over the motor cortex is thought to activate glutamatergic excitatory callosal fibers terminating on local GABAergic interneurons of the contralateral motor cortex (114). Excitation of these GABAergic inhibitory interneurons results in inhibition of the pyramidal motor neurons which causes a reduction in the MEP size. Consequently, a decrease in frontal interhemispheric connectivity may relate to the influence of alcohol on either NMDA-glutamate receptor functioning or GABAergic inhibitory interneurons. Previous TMS research has demonstrated that alcohol mainly influences GABAergic functioning leaving glutamatergic excitatory transmission relatively unaffected (145, 152). In contrast, alcohol has also been shown to attenuate glutamate/NMDA receptor functioning (141, 153-155) leaving open the possibility that alcohol may have disrupted the excitatory callosal pathway that terminates on inhibitory interneurons. This would result in less excitation of inhibitory interneurons, subsequently leading to a relatively increased MEP size. However, the crucial point revolves around the question how to explain the alcohol-related sex difference on frontal interhemispheric connectivity and at present, the precise physiological mechanisms through which alcohol reduces frontal interhemispheric connectivity in females remain to be elucidated.

A possible role for steroid hormones in explaining the presently observed sex differences is evidenced by a study in which testosterone was found to counteracts some of the effects of alcohol (156). In this study testosterone was shown to diminish alcohol-induced deficits in spatial memory (156). Interestingly, acute alcohol administration reduces

testosterone production in both males and females (157, 158). Together with the notion that men have multiple times more testosterone than females, testosterone may play a role in the currently observed reductions of IHI in females exclusively. In agreement, we recently found evidence that a single administration of testosterone significantly increases frontal interhemispheric connectivity in healthy female subjects (Hoppenbrouwers et al., submitted). In sum, even though sex differences in steroid hormones may provide for an explanation of our findings, it remains elusive whether these sex differences already surface after an acute administration of alcohol. It is suggested that the decrease in frontal interhemispheric connectivity observed in females will most likely involve complex interactions between steroid hormones and the combined action of alcohol on GABAergic interneurons and NMDA-glutamate receptor functioning in the corpus callosum.

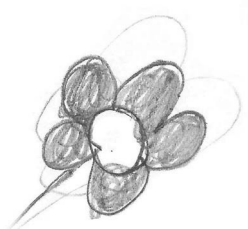
Despite the observed female vulnerability to the effects of alcohol on frontal interhemispheric connectivity, several issues should be mentioned. First, the relationship between alcohol-related effects on frontal interhemispheric connectivity and behavior is of importance. Executive functions including behavioural inhibition and cognitive regulation are normally ascribed to the prefrontal cortex (PFC) rather than M1. Even though both M1 and PFC are part of the frontal cortex our current findings on M1 interhemispheric connectivity cannot simply be extrapolated to the PFC. Defensibly, there is evidence from recent interleaved TMS-EEG studies showing that M1 and the PFC share similar physiological properties (85). Second, the fact that we observed reductions in frontal interhemispheric to alcohol consumption in females only does not in any way imply that men are immune to the effects of alcohol. In other words, males will likely demonstrate similar reductions in frontal interhemispheric connectivity at higher BAC levels. Third, in our sample all female participants were taking oral contraceptives to abolish fluctuations in steroid levels at the time of testing. However, oral contraceptives have been shown to reduce plasma levels of progesterone metabolites in female rats and women (159). Some of these metabolites (e.g., allopregnanolone) are highly potent endogenous positive modulators of the GABA-a receptor (160). It has been suggested that the combined effects of endogenous steroids and alcohol modulate GABA-a receptor functioning (161). In contrast, alcohol has also been shown to increase allopregnanolone levels in the cerebral cortex (162). An increase that has proven effective to potentiate GABA-a receptor-mediated inhibition in the brain (162) and explain some of the physiological and behavioural effects of alcohol (162, 163). Taken

together, these findings suggest that the contraceptive- and alcohol-related increases in allopregnanolone levels may have contributed to the presently observed reductions in IHI. As it stands, the present findings can only be generalized to males and females taking oral contraceptives. Finally, an additional line of evidence consisting of conventional TMS measures of GABA function such as short-interval intracortical inhibition (SICI) and long-interval intracortical cortical inhibition (LICI) could potentially have given more direct evidence for the exact mechanisms underlying the observed effect.

In conclusion, the present study provides the first evidence for reductions in frontal interhemispheric connectivity in females, but not in males following a moderate dose of alcohol. Future research may focus on alcohol dose-response patterns in males and the involvement of steroid hormones to further explain the observed sex differences in interhemispheric connectivity. In addition, to clarify the potential role of contraceptives future research may also look into the effects of alcohol on interhemispheric inhibition in females not using contraceptives.

Appendix Chapter 2.2

We conducted exploratory analyses in the female subject group to see whether there was one particular direction (right to left versus left to right IHI) that might be more strongly affected by alcohol. These additional analyses provided results suggesting that alcohol induced right-to-left IHI decreases when compared to placebo, $t(11)= 2.09$; $p= 0.030$ (one-tailed). As evidenced by a reduction in MEP size compared to placebo right frontal cortex excitability decreased significantly, $t(11)= 2.59$; $p= 0.0125$ (one-tailed). Finally, left-to-right IHI, $t(11)= 0.74$; $p= 0.47$, and left frontal cortical excitability as indexed through MEP sizes remained unaffected, $t(11)= 1.17$; $p= 0.27$. The implications of these data will be discussed in further detail in the General Discussion.

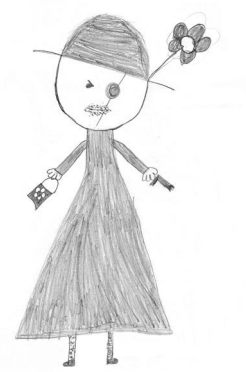


§2.3

On the relation between interhemispheric signal propagation and interhemispheric inhibition: A transcranial magnetic stimulation study

Sylco S. Hoppenbrouwers, Dennis J.L.G. Schutter, Danilo R. De Jesus, Faranak Farzan, Paul B. Fitzgerald, Aristotle N. Voineskos & Zafiris, J. Daskalakis

Submitted



Abstract

Interhemispheric inhibition (IHI) and interhemispheric signal propagation (ISP) are measures of transcallosal connectivity that can be studied with transcranial magnetic stimulation (TMS). Both IHI and IPS depend on the structural integrity of callosal white matter fibres, but a direct comparison between the two functional measures has not yet been made. Therefore, our goal was to directly evaluate the relationship between these two measures of functional interhemispheric connectivity. Using transcranial magnetic stimulation and electroencephalography, IHI and ISP were measured from the left and right primary motor cortex in sixteen healthy right-handed male volunteers. Results demonstrated that from the right to the left hemisphere higher ISP correlated with stronger IHI, while an inverse correlation was observed from the left to the right hemisphere. These findings show that IHI and ISP are correlated, but that the direction of the association depends on the direction of callosal signal transfer.

Introduction

Studies using transcranial magnetic stimulation (TMS) have provided important insights into functional interhemispheric connectivity (88, 114, 164, 165). These studies provide a model of interhemispheric connectivity in which excitatory fibers in the corpus callosum synapse on local inhibitory interneurons (114) resulting in suppression of contralateral activity (88). This phenomenon termed interhemispheric inhibition (IHI) can be studied with TMS. IHI can be measured from the abductor pollicis brevis (APB) and involves the pairing of a conditioning stimulus (CS) over the ipsilateral primary motor cortex (M1) with a test stimulus (TS) over the contralateral homotopical area. When the CS precedes the TS by 10 ms, the motor evoked potential (MEP) in the APB is attenuated by roughly 50% when compared with a MEP elicited by the TS alone (88). In line with the proposed model of interhemispheric connectivity, IHI depends on the microstructural integrity of the motor fibers in the corpus callosum, i.e., higher integrity of the white matter fibers in the motor tract of the corpus callosum correlates positively with greater IHI (165, 166). This result is consistent with evidence that stronger activation of the excitatory fibers in the corpus callosum results in greater activation of local inhibitory interneurons and, as a corollary, larger suppression of the MEP by the CS (114). Recently, the combination of TMS with electroencephalography (EEG) provided another measure for functional interhemispheric connectivity, namely interhemispheric signal propagation (ISP). ISP can be recorded by stimulating one hemisphere and recording the subsequent cortical activity in the contralateral hemisphere. ISP is then calculated as the ratio of the contralateral cortical evoked activity to the ipsilateral (stimulated) cortical activity (89). This electrophysiological index of interhemispheric connectivity was also found to depend on the microstructural integrity of the corpus callosum (89). Therefore, it appears that there are two distinct TMS-based neurophysiological methods that can index functional connectivity across the corpus callosum, IHI and ISP. However, while both relate to interhemispheric connectivity, the nature of the relationship between IHI and ISP has not been directly evaluated. The aim of the present study, therefore, was to evaluate the relationship between IHI and ISP from left and right hemispheres in sixteen healthy right-handed male subjects.

Part 2

Methods

Participants

Sixteen healthy right-handed males were enrolled in the study. Right-handedness was confirmed with the Edinburgh Handedness Inventory (109). Before inclusion subjects were screened for contraindications to TMS in a standard clinical interview (149). All subjects were non-smoking and were asked not to consume any alcohol in the 24 hours before the testing session. Subjects were instructed not to consume any caffeinated beverages in the 4 hours before testing and to use their last meal at least 2 hours prior to testing. Psychopathology was ruled out with the Personality Assessment Inventory (Personality Assessment Resources, Inc.). The PAI is a self-administered, objective inventory of adult personality and psychopathology (e.g., personality, depression, somatic disorders, anxiety, anxiety-related disorders, suicidal ideation and schizophrenia). It is composed by non-overlapping clinical, treatment, interpersonal and validity scales. Specifically, the PAI measures manifestation of clinical syndromes, providing information to assist diagnosis, treatment, and screening for all psychopathology corresponding DSM-IV categories (167, 168).

Transcranial magnetic stimulation

Single monophasic pulses were applied to the left and right motor cortex using a 7cm figure of eight coil connected to a Magstim 200 stimulator (Magstim Company, Carmarthenshire, Wales). The coil was placed over the site (usually between electrode FC3 and C3 (110)) that elicited the strongest motor evoked potentials (MEPs) from the abductor pollicus brevis (APB). This site was marked to ensure stable placement over the same spot throughout the testing session. Resting motor threshold and the intensity needed to evoke MEPs of 1mV peak-to-peak were assessed and the site that generated the largest and most consistent MEPs was marked. Before testing, the intensity to reach a MEP of 1mV peak to peak was measured. On the left and right motor cortex 100 suprathreshold pulses were administered with an ISI of 5 seconds. Conditions were counterbalanced between subjects. Sham stimulation was administered in order to control for the effects of auditory activation and TMS-induced cutaneous sensation on cortical evoked potentials in a subset of 8 subjects. For sham stimulation the magnetic pulses do not enter the brain as the coil is held at an approximate angle of 90^{o} from the scalp while resting on one wing of the coil

(169).

Motor threshold

Motor threshold was measured before testing with and without EEG cap on the left and right motor cortex. Resting motor threshold was defined as the minimum intensity that would evoke a MEP of at least 50μV in 5 out of 10 consecutive trials. Without the EEG cap the mean motor threshold (mean ± SD) was 38.1 % ± 5.7 on the left hemisphere and 40.7% ±8.0 on the right hemisphere. With the EEG cap the mean motor threshold was 54.7% ±8.7 on the left hemisphere and 53.1% ±7.2 on the right hemisphere.

EMG recording

Surface EMG was recorded from the right and left first abductor pollicis brevis (APB) muscles with disposable disc electrodes placed in a tendon-belly arrangement over the bulk of the APB muscle and the first metacarpo-phalangeal joint. The subject maintained relaxation throughout the experiment and the EMG was monitored on a computer screen and via speakers at high gain. The signal was amplified (Intronix Technologies Corporation Model 2024F, Bolton, Ontario, Canada), filtered (band-pass 2 Hz to 5 kHz), digitized at 5 kHz (Micro 1401, Cambridge Electronics Design, Cambridge, UK) and stored in a laboratory computer for offline analysis.

Interhemispheric inhibition

IHI was measured in both directions, right-to-left and left-to-right, and performed in accordance with previously described methods (114). The left motor cortex was stimulated with a 7cm diameter figure-of-eight coil while the right motor cortex was activated with a figure-of-eight coil with an 8cm loop. The interstimulus interval was set at 10 ms and 12 trials were conducted per condition (i.e., 12 TS and 12 CS-TS per hemisphere) amounting to a total of 48 trials. IHI was calculated as [1-(MEPtest/MEPconditioned)*100].

Interhemispheric signal propagation

ISP was measured according to previously described methods (89, 90). One hundred unconditioned monophasic pulses were applied to the left and right motor cortex (89, 90) using a 7cm figure of eight coil connected to the Bistim Module which was

connected to two Magstim 200 stimulators (Magstim Company, Carmarthenshire, Wales). EEG was recorded with a 64 channel Synamps2 DC-coupled EEG system (Compumedics). Four electrodes were used to record eye movement induced artifact, two on the outer side of the eyes and one above and one below the left eye. EEG was sampled at 20 kHZ and low-pass filtered at 100Hz. Off-line analyses were performed with Neuroscan (Compumedics). Data was first down-sampled to 1000Hz and cut into segments that included 1000ms pre-TS and 1000ms post-TS activity. Segments were baseline-corrected until 110ms pre-TS to ensure a TMS-free baseline. Post-TS intervals (25-1000msec) that were artifact-free were extracted and digitally filtered using a zero-phase shift 1-100 Hz bandpass filter (48dB/Oct). Trials containing movement artefacts, TMS artefacts and/or, eye blinks were excluded for further analysis through visual inspection (on average 5.6% of trials was removed). Good trials were averaged, eye blink corrected and the average cortical evoked potentials were bandpass filtered (1-50Hz) for each subject. Over the left hemisphere cortical evoked potentials were measured over electrode C3 while electrode C4 was used to measure cortical evoked potentials over the right hemisphere. Previous studies have shown that these electrodes are closest to the optimal site for APB activation using TMS (170). In the stimulated hemisphere the area under the rectified curve was measured 50-150ms post-stimulus. An onset of 50ms was chosen as it reflects the earliest time frame of artefact-free data (89). An offset of 150ms was used as TMS-induced activation of gamma-amino butyric acid (GABA)-B inhibitory neurotransmission lasts on average 150ms (113). An interhemispheric conduction time of approximately 10 ms (88, 89, 114) was assumed and contralateral activity was measured 60-160ms post-stimulus. By means of equation 1 we quantified TMS-induced signal propagation.

Equation 1: $$\%\,ISP = \left[\frac{\text{Area under rectified curve } (Right\ Cortex)}{\text{Area under rectified curve } (Left\ Cortex)}\right] \times 100$$

Results

Results showed significant correlations between IHI and ISP. We found a significant positive relation between right-to-left IHI and right-to-left ISP (r= .571; p= .02) (See Figure 2), and a significant negative correlation between left-to-right IHI and left-to-right ISP (r= -.517; p= .04) (See Figure 1). No significant differences between IHI left-to-right (mean ± SD; 48.5% ± 33.6%) and IHI right-to-left (mean ± SD; 49.5% ± 29.0%) were observed,

F(1,15)=0.011; p= .918. Also, no differences between ISP left-to-right (mean ± SD; 46.8% ± 22.5%) and ISP right-to-left (mean ± SD; 48.8% ± 28.3%) were found, F(1,15)= .039; p= .847.

Non-parametric correlations were also calculated. Data showed that IHI left-to-right correlated negatively with ISP left to right, ρ= -.517; p= .04 and not with ISP right to left, ρ = .09; p= .738. IHI right-to-left correlated positively with ISP right-to-left, ρ = .570; p= .021 and not with ISP left-to-right, ρ = .129; p= .635. In addition, partial correlations showed that the correlation between ISP left to right and IHI left to right remained significant when controlled for cortical excitability of the left hemisphere, r= -.519; p=.049; df=13. Also the correlation between ISP right to left and IHI right to left remained significant when controlled for excitability of the right hemisphere, r=.549; p=.034; df=13.

Motor thresholds for the left and right motor cortex did not differ without EEG cap (p= .246), nor with EEG cap (p= .354). In addition, for IHI the intensity needed to achieve 1mV MEPs did not differ between hemispheres (for CS, p=. 416; for TS, p=. 734). Stimulus intensities for achievement of 1mV MEPs for ISP also did not differ between hemispheres (p= .747) nor did cortical evoked potentials (p= .951). These additional analyses suggest that the opposite direction of the correlations are not due to differences in baseline or stimulus intensity but in fact may reflect genuinely different functional interhemispheric interactions.

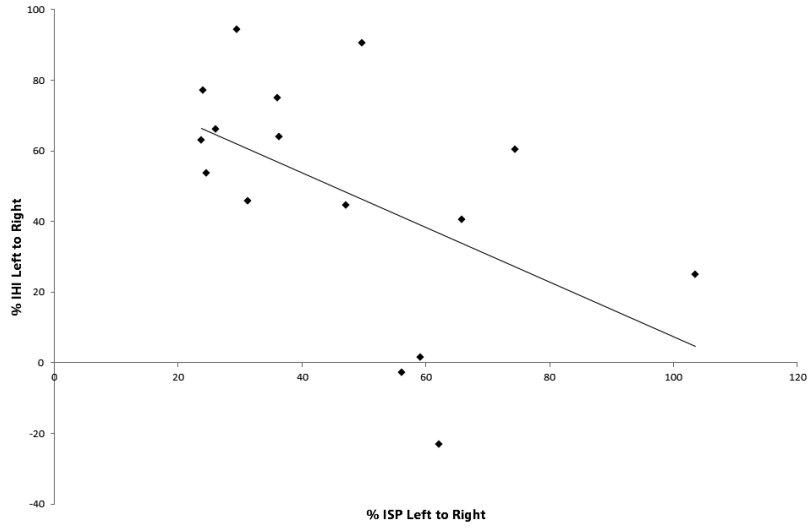


Figure 1. Left to right ISP correlates negatively with left to right IHI.

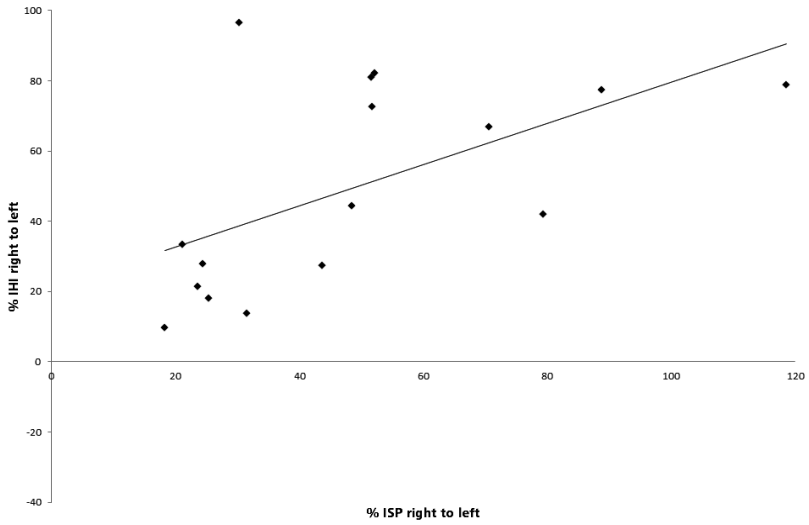


Figure 2. Unlike for left to right connectivity, the two functional measures of right to left connectivity are positively correlated.

Discussion

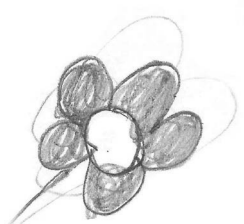
Unexpectedly, we found contrasting correlations showing that more propagated signal from right-to-left corresponds to stronger IHI while the opposite is true for left-to-right connectivity. The present findings may relate to the nature of the contralaterally evoked activity measured with EEG. That is, the contralaterally evoked potential could reflect either predominantly excitatory or inhibitory activity. A possible explanation for the contrasting correlations may then be that the positive relation between right–to-left IHI and ISP is accounted for by TMS-induced activation of inhibitory fibers in the corpus callosum. That is, although the majority of callosal projecting neurons are excitatory and use glutamate (171) it is estimated that up to 5% of callosal fibers are inhibitory (171, 172) and terminate on superficial and deep cortical layers (171) of the contralateral hemisphere. In contrast to a disynaptic pathway (excitatory callosal fibers and inhibitory interneurons), a monosynaptic pathway has also been argued to play a role in IHI (172). In this mechanism inhibitory fibers are thought to directly synapse on contralateral pyramidal cells that may provide for fast and precise transcallosal inhibition (171, 172). In line with the positive correlation between right-to-left IHI and ISP, higher ISP would then relate to stronger IHI. When considered with previous evidence, it is possible that - within the currently used

parameters - stimulation of the right motor cortex induces mainly inhibitory contralateral activity.

Functionally, the opposite correlations could reflect an interhemispheric asymmetry in the suppression of unwanted mirror movements. Through the employment of functional magnetic resonance imaging and TMS, Kobayashi et al. (173) showed that during movement of the (dominant) right index finger only the contralateral dominant hemisphere is activated. By contrast, movement of the (non-dominant) left index finger resulted in activation of both the contralateral and ipsilateral hemisphere (173) suggesting that the non-dominant motor cortex advances activation to the dominant motor cortex. This asymmetry in interhemispheric connectivity was interpreted as indicating that the non-dominant hemisphere actively inhibits the dominant hemisphere to prevent unwanted mirror movements (173). While mirror movements are normal in children, they decrease with increased myelination of the corpus callosum (174), underscoring the importance of interhemispheric connectivity through the corpus callosum as a mechanism for the prevention of mirror movements. In line, both IHI and ISP depend on the microstructural integrity of the fibers that constitute the corpus callosum (89, 165) and could be argued to be involved in the suppression of mirror movement.

Alternatively, one could argue that the contrasting correlations reflect hand preference. It has been suggested that IHI is a function of handedness (166) but, in our study, the laterality quotient derived from the Edinburgh Handedness Inventory (109) did not correlate with IHI or ISP in either direction (all p's > .192). However, one might not expect such a simple relationship as a study by Duque and colleagues (175) suggests that movement preparation, rather than hand preference, is an important modulator of IHI. That is, IHI is balanced in rest but shifts during movement preparation favouring the dominant hemisphere (175). Specifically, in right-handed subjects movement of the right dominant hand results in relative disinhibition of the dominant left hemisphere (175). In our study, IHI and ISP were measured during rest and we are therefore presently unable to determine to what extent handedness contributes to this finding. As this is the first study showing contrasting functional interhemispheric interactions this intriguing finding deserves further research. To elucidate the influence of handedness future studies are advised to measure IHI and ISP, during both rest and action preparation.

PART 3



§3.1

Abnormal interhemispheric connectivity in male psychopathic offenders

Sylco S. Hoppenbrouwers, Danilo R. De Jesus, Tania Stirpe, Dennis Hofman, Jeff McMaster
Ginny Hughes, Zafiris, J. Daskalakis & Dennis J.L.G. Schutter

In revision

Abstract

Psychopathic offenders inevitably violate interpersonal norms and frequently resort to aggressive and criminal behaviour. The affective and cognitive deficits underlying these behaviors have been linked to abnormalities in functional interhemispheric connectivity. Direct neurophysiological evidence of dysfunctional connectivity in psychopathic offenders is however lacking. In the present study we employed transcranial magnetic stimulation (TMS) combined with electroencephalography (EEG) to compare interhemispheric connectivity in the dorsolateral and motor cortex in psychopathic offenders to healthy controls. Intracortical inhibition and facilitation were also measured over the left and right motor cortex to examine the influence of local inhibitory and facilitatory hemispheric abnormalities on interhemispheric connectivity. Results showed global abnormalities in right to left functional connectivity in psychopathic offenders as compared to healthy individuals. Also, in contrast to healthy controls increased intracortical inhibition was observed in the right, but not left hemisphere of psychopathic offenders. This is the first direct physiological evidence for dysfunctional interhemispheric connectivity in psychopathic offenders and our findings may provide a neurophysiological basis for our understanding of the disruptive antisociality of these offenders.

Introduction

Psychopathic individuals show profound impairments in affective functioning and live a life characterized by impulsivity, irresponsibility, and recurrent criminal behaviour. Dysfunctional interhemispheric connectivity is often overlooked as an important contributor to the pathogenesis of antisocial personality disorder (ASPD) and psychopathy, but evidence suggests it is affected in these individuals (18, 38, 176). Interhemispheric connectivity reflects the process of exchange and integration of information between the cerebral hemispheres in which the corpus callosum plays a vital role (22). Consistent with the idea of impaired interhemispheric connectivity, patients with ASPD show bilateral reductions in white matter integrity in the genu, the anterior part of the corpus callosum (18). Additional evidence for interhemispheric connectivity deficits in psychopathic individuals has been provided by Raine and colleagues who showed that psychopathic individuals have increased callosal white matter, increased callosal length, but reduced callosal thickness (38). Indirect functional evidence from the same study (through functional magnetic resonance imaging (fMRI)) suggests functional interhemispheric connectivity is increased in psychopathic offenders (38). It has been suggested that the corpus callosum serves to maintain functional cerebral specialization (i.e., the lateralization of cognitive functions), in which psychopaths show profound impairments (29, 30, 177). That is, psychopathic offenders have unusual lateralization of functions such as language and divided attention (29, 34, 36). In general, cognitive functions involve a complex interplay of facilitation and inhibition of contralateral activity. Specifically, although some functions involve facilitation of interhemispheric connectivity, other functions (e.g., language and motor-related behaviors) are lateralized and involve the upregulation of activity in one hemisphere while simultaneously inhibiting activity in the contralateral hemisphere (37). Deficits in connectivity mechanisms that are so highly involved in cognition and affect may, in part, lead to impaired cognitive functioning, e.g., attention, which has been observed in psychopathic offenders (4, 36, 178).

Raine and colleagues (38) have found fMRI evidence in support of an overall increase in functional interhemispheric connectivity in psychopathic offenders. Hiatt and Newman (176) however suggest a directional component to these connectivity abnormalities. That is, they reported that psychopathic offenders have a prolonged interhemispheric transfer time, but also suggest right–to-left connectivity may be specifically affected in

psychopathic offenders (176). However, direct neurophysiological evidence providing substantiation of right to left interhemispheric connectivity abnormalities in psychopathic offenders is lacking.

Transcranial magnetic stimulation (TMS) is an important research tool for measuring physiological aspects of interhemispheric connectivity (88, 114). Interhemispheric signal propagation (ISP) represents a novel and reliable approach to measuring interhemispheric connectivity in motor and non-motor regions of the cortex through combined TMS with electroencephalography (EEG) (89, 90). In this paradigm, magnetic pulses are applied to the cerebral cortex to activate excitatory neurons that run through the corpus callosum to the contralateral hemisphere where they terminate on inhibitory interneurons to inhibit the contralateral hemisphere (82, 114, 165). Specifically, TMS-induced activation of a cerebral hemisphere induces a contralateral response in homotopical regions which was recently shown to depend on the microstructural integrity of the corpus callosum using diffusion tensor imaging (DTI) (89). Importantly, the contralateral response is approximately half of the ipsilateral activation which is proposed to reflect the contralateral inhibitory processes described above (89). Measuring ISP, therefore, provides an index of interhemispheric connectivity from the dorsolateral prefrontal cortex (89, 90), a cortical region that is more closely associated with social behaviour and cognition (90, 179).

In sum, the combination of TMS and EEG provides a means to directly tap into intercortical circuits and study potential deficits in functional interhemispheric connectivity. Therefore, the aim of the present study was to explore functional interhemispheric connectivity in psychopathic offenders by measuring ISP. In keeping with earlier findings we hypothesized that psychopathic offenders would demonstrate deficiencies in right-to-left interhemispheric connectivity.

Methods

Participants

Eighteen right-handed (109) male psychopathic offenders (mean age ± standard deviation (SD) = 33.4 ± 6.8 years) participated, all of whom scored 25 or higher on the Hare Psychopathy Checklist-revised second edition (PCL-R) (46) (mean ± SD= 28.8 ± 2.7). Psychopathic offenders were recruited through posters displayed in halfway houses in

the Greater Toronto Area and through the Law and Mental Health Program at the Centre for Addiction and Mental Health (CAMH). Offenders were informed about the study and screened with a standard clinical interview to check for contraindications to TMS (149), medication usage and neurological disorders. Next, offenders were asked to sign a release of information, after which a review of case notes and psychological assessments was carried out to retrieve the PCL-R score. Exclusion criteria included age under 18 or over 65, diagnosis of schizophrenia, schizophreniform/psychotic disorders, mood disorders, anxiety disorders, or any comorbid personality disorders (e.g., borderline personality disorder). These were ruled out by way of a standard screening interview (conducted by SH) and confirmed with a review of previous psychological assessments completed by an experienced clinician (TS). Exclusion criteria for all subjects included substance abuse or dependence in the last 6 months as per the Diagnostic Statistical Manual-IV-TR (DSM-IV-TR). All psychopathic offenders were subjected to regular drug screening as part of the terms of their parole and these drug tests indicated none had been using drugs at or around the time of testing. All psychopathic offenders had previously been administered the Shipley Institute of Living Scale and all scored in the average range corresponding to a score of 90-110 on the Wechsler Adult Intelligence Scale-R (WAIS-R) (180). The Shipley Institute of Living Scale screens for organic brain damage and has a high correlation (r=0.85) with the full scale WAIS-R (181).

Fifteen right-handed (109) healthy subjects (mean age ± SD= 32.1 ± 9.1) were screened with a standard clinical interview assessing contraindication to TMS (149) and right handedness was confirmed (109). Psychopathology was ruled out using the Personality Assessment Screener (PAS; Psychological Assessment Resources Inc.). The PAS is a self-administered, objective inventory of adult personality and psychopathology (e.g., personality, depression, somatic disorders, anxiety, anxiety-related disorders and schizophrenia). It is composed of non-overlapping clinical, treatment, interpersonal and validity scales. Specifically, the PAS measures manifestation of clinical syndromes, providing information to assist diagnosis, treatment, and screening for all psychopathology corresponding to DSM-IV categories (167). This study was approved by the Ethics committee at the Centre for Addiction and Mental Health, and written informed consent was obtained from each participant. All subjects were paid for participation.

The study consisted of a 6 hour TMS-EEG session and a 2 hour TMS session which

was done on a separate day. In the TMS only session, cortical inhibition and facilitation were measured from the left and right motor cortex. In the TMS-EEG session, 13 psychopathic offenders were enrolled; ten of whom also participated in the TMS only session. Of the 5 remaining psychopathic offenders, 3 participated only in the TMS-EEG session, and 2 participated only in the TMS part. All healthy controls participated in both the TMS-EEG session and the TMS only session.

Interhemispheric signal propagation

Single monophasic pulses were applied to the left and right motor cortex and DLPFC using a 7cm figure of eight coil connected to the Bistim Module. The Bistim Module was connected to two Magstim 200 stimulators (Magstim Company, Carmarthenshire, Wales). Due to the persistent reoffending of psychopathic offenders in the community, we decided not to do an MRI scan for localization of the DLPFC in order to increase the chance that offenders would finish the study. For activation of the DLPFC, electrodes F5 (left hemisphere) and F6 (right hemisphere) were used. Stimulation over these electrodes approximates ideal activation of the DLPFC when MRI-based co-registration is not available (111). For motor cortex, the coil was placed over the site that elicited the strongest motor evoked potentials (MEPs) from the abductor pollicis brevis (APB). This site was marked to ensure stable placement over the same spot throughout the testing session. Over the left and right motor cortex and DLPFC 100 suprathreshold pulses were administered with an interstimulus interval (ISI) of 5 seconds. Conditions were counterbalanced between subjects. EEG was recorded with a 64 channel Synamps2 DC-coupled EEG system (Compumedics). Four electrodes were used to record eye movement induced artifacts, two on the outer side of the eyes and one above and one below the left eye. The reference electrode was placed over the vertex just posterior to the CZ electrode. EEG signals were recorded DC at a sampling rate of 20 kHZ and low-pass filtered at 100Hz. Offline processing was done with Neuroscan (Compumedics). Data was first downsampled to 1 kHZ and cut into segments that included 1000ms pre-stimulus and 1000ms post-stimulus activity. Segments were baseline-corrected until 110ms pre-TS to ensure a TMS-free baseline. Post-TS intervals (25-1000msec) that were artifact-free were extracted and digitally filtered using a zero-phase shift 1-100 Hz bandpass filter (48dB/Oct). Hereafter, epochs were visually inspected to exclude movement, eye blink or TMS artifacts. The remaining epochs were averaged

and eye blink corrected according to previously described methods (83, 85). The average cortical evoked potentials were bandpass filtered (1-50Hz) for each subject. Over the left hemisphere cortical evoked potentials were measured under electrode C3, while electrode C4 was used to measure cortical evoked potentials over the right hemisphere. Previous studies have shown that these electrodes are closest to the optimal site for APB activation using TMS (170). In the stimulated hemisphere, the area under the rectified curve was measured 50-150ms post-stimulus. An onset of 50ms was chosen as it reflects the earliest time frame of artefact-free data (89, 90). An offset of 150ms was used as TMS-induced activation of gamma-amino butyric acid (GABA)-B inhibitory neurotransmission lasts on average 150ms (113). In keeping with previous findings (88, 89, 114), an interhemispheric conduction time of 10ms was employed and therefore, the propagated signal to the contralateral hemisphere was measured 60-160ms post-stimulus. ISP is calculated as the ratio of cortical evoked potential on the stimulated hemisphere to the contralateral cortical evoked activity (see equation 1) (89).

Equation 1: $$\%\, ISP = \left[\frac{\text{Area under rectified curve } (Right\ Cortex)}{\text{Area under rectified curve } (Left\ Cortex)} \right] \times 100$$

Interhemispheric inhibition

Using a paired pulse paradigm we also indexed a second measure for interhemispheric connectivity, interhemispheric inhibition (IHI). IHI was assessed by applying a conditioning stimulus (CS) to the ipsilateral motor cortex followed by a test stimulus to the contralateral motor cortex (88). When compared to a motor evoked potential (MEP) induced by a single pulse to the contralateral hemisphere, the CS attenuates the MEP by about 50% (88, 114). The interstimulus interval was set at 10ms. Interhemispheric inhibition was measured without the EEG cap and without the Bistim Module. For the left hemisphere a Magstim figure-of-eight coil with a 7cm loop diameter was used and for the right hemisphere a Magstim figure-of-eight coil with an 8cm loop diameter was used.

Cortical inhibition and facilitation

To check for possible abnormalities in local hemispheric processing, baseline cortical inhibition and facilitation were measured over the left and right motor cortex. For this we indexed the cortical silent period (CSP), short interval intracortical inhibition (SICI) and intracortical facilitation (ICF). CSP taps into GABAB-receptor mediated neurotransmission whereas SICI is more commonly associated with GABAA-receptor functioning (80). ICF relates to N-methyl D-aspartate (NMDA)-receptor mediated mechanisms (182). TMS was applied to the hand area of the left and right motor cortex with a 70 mm loop figure-of-eight magnetic coil and two Magstim 200 magnetic stimulators (Magstim, Whitland, Dyfed, Wales). The coil was held tangentially on the head with the handle pointing backward at 45 degrees laterally from the midline.

The cortical silent period (CSP) is measured after motor cortical stimulation in a moderately contracted (hand) muscle (183): stimulation induces a MEP after which electromyographic activity is momentarily absent, commonly referred to as the CSP (183). Measurement of the cortical silent period duration was obtained in moderately tonically active APB (i.e., 20% of maximum contraction) by stimulating the motor cortex with intensities of 140% of RMT. Ten trials were performed. The CSP duration was the time from the MEP onset to the return of any voluntary EMG activity. This is referred to as the absolute CSP and ends with a deflection in the EMG waveform (184). For SICI and ICF, a subthreshold CS (80% of RMT) preceded the suprathreshold TS, which was adjusted to produce an average MEP of 0.5–1.5-mV peak-to-peak amplitude in the contralateral APB muscle (185). Conditioning stimuli were applied to the motor cortex before the TS at one of five interstimulus intervals (ISIs): 2 msec and 4 msec for SICI and 10 msec, 15 msec, and 20 msec for intracortical facilitation (ICF). Seventy-two trials were performed, 12 for each condition. For SICI and ICF, changes in the TS MEP amplitude at each ISI were expressed as a percentage of the mean unconditioned MEP amplitude (186). SICI and ICF were averaged over the different ISIs. The order of administration of the two paradigms was counterbalanced over hemispheres and between subjects.

EMG recording

Surface EMG was recorded from the right and left first abductor pollicis brevis (APB) muscles with disposable disc electrodes placed in a tendon-belly arrangement.The subject maintained relaxation throughout the experiment and the EMG was monitored

on a computer screen and via speakers at high gain. The signal was amplified (Intronix Technologies Corporation Model 2024F, Bolton, Ontario, Canada), filtered (band-pass 2 Hz to 5 kHz), digitized at 5 kHz (Micro 1401, Cambridge Electronics Design, Cambridge, UK) and stored in a laboratory computer for offline analysis.

Resting motor threshold

Resting motor threshold was measured before testing with and without EEG cap on the left and right motor cortex (see Table 1). rMT was defined as the minimum intensity that would evoke a MEP of at least 50μV in 5 out of 10 consecutive trials (185). Prior to testing, the intensity needed for 1mV MEPs were measured with and without cap and from both hemispheres.

Statistical analyses

To test for differences in ISP a repeated measures general linear model (GLM) was conducted with region (motor cortex vs DLPFC) and direction (left to right vs right to left) as within-subjects variables and group (psychopathic offenders vs control) as a between-subjects variable. Separate independent samples t-tests were applied to check for differences in cortical evoked potentials on the left and right motor cortex and DLPFC.

For IHI a repeated-measures GLM was conducted with direction (left to right vs right to left) as within-subjects variable and group (psychopathic offenders vs controls) as a between-subjects variable. As intensity of the CS and TS have been shown to influence IHI (114), CS and TS were checked for differences between conditions and between groups.

For CSP, SICI, and ICF, three separate repeated measures GLMs were conducted with hemisphere (left hemisphere vs right hemisphere) as within-subjects variable and group (psychopathic offenders vs controls) as a between-subjects variable. Additional independent samples t-tests were conducted to check for differences in test pulses in the SICI and ICF paradigm.

The PCL-R consists of two main factors - Factor 1 represents the affective/ interpersonal deficits, whereas the antisocial lifestyle aspects map onto Factor 2 (46). Pearson product-moment correlation coefficient was used to check for linear dependence between both factors and TMS measures. Alpha level of significance was set at .05.

Results

TMS was well tolerated by all subjects and no adverse events occurred. TMS-EEG ISP data of one healthy subject was excluded due to inferior signal quality. TMS-EEG ISP data of one psychopathy subject was excluded due to the fact that this data was an outlier (>3 SDs above the mean). No differences were found in MT or in the intensity needed for 1mV MEPs (see Table 1).

Table 1.

	Without cap				**With cap**			
	MT left	*MT right*	*1mV left*	*1mV right*	*MT left*	*MT right*	*1mV left*	*1mV right*
Control	37.7 (5.7)	40.9 (8.7)	52.0 (9.8)	59.3 (15.1)	53.7 (8.7)	53.1 (7.2)	64.1 (10.0)	67.3 (10.3)
Psychopath	37.9 (5.6)	42.0 (8.7)	48.4 (10.8)	66.0 (18.3)	52.5 (7.4)	54.0 (10.4)	64.1 (11.5)	72.3 (±6.7)
P-value	.921	.722	.338	.274	.430	.883	.999	.344

Table 1. No significant differences between psychopathic offenders and controls were found in motor threshold (MT) or the intensity needed for 1mV MEPs peak to peak (1mV). The terms 'left' and 'right' refer to the left and right hemisphere, respectively. The table specifies the mean and the standard deviation (in brackets).

Interhemispheric signal propagation

The repeated measured GLM yielded a significant direction*group interaction [$F(1,25)= 5.375$; $p= .029$; $\eta p2= .177$], and showed that psychopathic offenders have a global increase in right to left ISP (See Figure 1). The region*direction*group interaction was not significant, [$F(1,25)= 0.924$; $p= .346$]. No difference was observed between psychopathic offenders and healthy controls in the cortical evoked potentials on either hemisphere [(left motor cortex; $F(1,25)= 0.001$; $p= .971$; left DLPFC; $F(1,25)= .379$; $p= .544$) and (right motor cortex; $F(1,25)= 0.191$; $p= .665$; right DLPFC; $F(1,25)= 0.252$; $p= .620$)]. The repeated measures GLM did not generate a significant direction*group interaction, [$F(1, 25)= 1.335$; $p= .258$] (See Figure 2.). There was no main effect for direction [$F(1,25)= 0.283$; $p= .599$]. Test pulses on either hemisphere did not differ between psychopathic offenders and healthy controls [(left hemisphere,[$F(1,25)= 0.29$; $p= .1$)]; [(right hemisphere, $F(1,25)= 0.31$; $p= .9$)]. Conditioning stimuli also did not differ [(left hemisphere,[$F(1,25)= 2.8$; $p= .103$)]; [(right hemisphere, $F(1,25)= 0.073$; $p= .79$)].

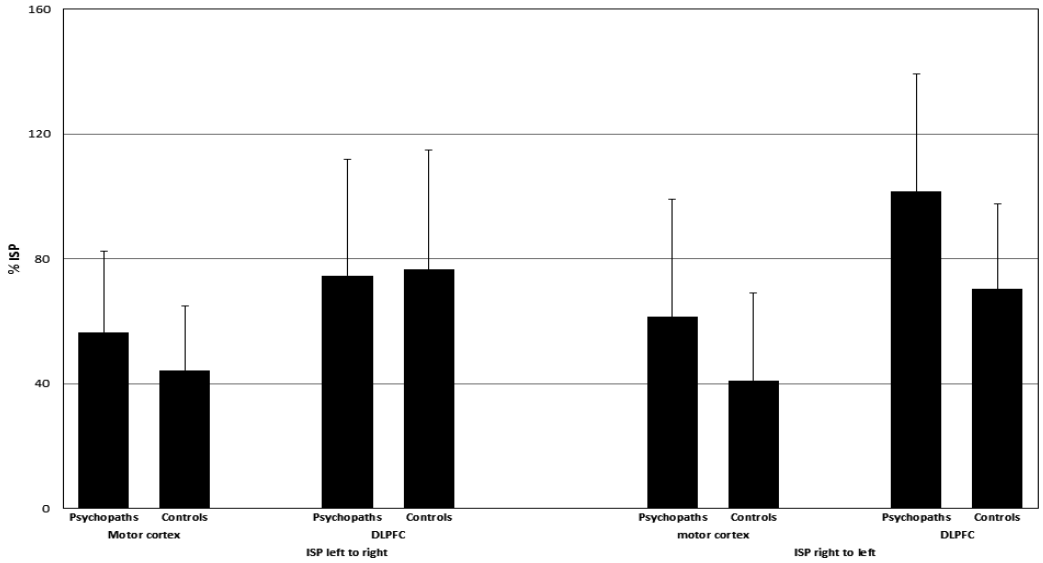


Figure 1. This figure represents interhemispheric signal propagation in psychopathic offenders and healthy controls. Average ISP from the left to the right DLFPC is 101% suggesting that activation of the right DLPFC produces a contralateral activation of similar magnitude.

Interhemispheric inhibition

The repeated measures GLM did not generate a significant direction*group interaction, [F(1, 25)= 1.335; p= .258] (See Figure 2.). There was no main effect for direction [F(1,25)= 0.283; p= .599]. Test pulses on either hemisphere did not differ between psychopathic offenders and healthy controls [(left hemisphere,[F(1,25)= 0.29; p= .1)]; [(right hemisphere, F(1,25)= 0.31; p= .9)]. Conditioning stimuli also did not differ [(left hemisphere,[F(1,25)= 2.8; p= .103)]; [(right hemisphere, F(1,25)= 0.073; p= .79)].

Cortical inhibition and facilitation

For CSP a significant hemisphere*group interaction effect was observed, [F(1,26)= 10.350; p=.003; ηp2 = .270]. Post-hoc one-way analyses of variance showed that compared to healthy controls, psychopaths exhibit significantly longer CSPs in the right hemisphere [F(1,26)= 4.267; p= .048; ηp2=], but not in the left hemisphere [F(1,26)= 0.381; p= .542] (See Figure 3). CSPs measured from the left and right motor cortex did not differ significantly in healthy controls [F(1,14)= 0.018; p= .895], but did in psychopathic offenders [F(1,14)= 19.66;p= .001).

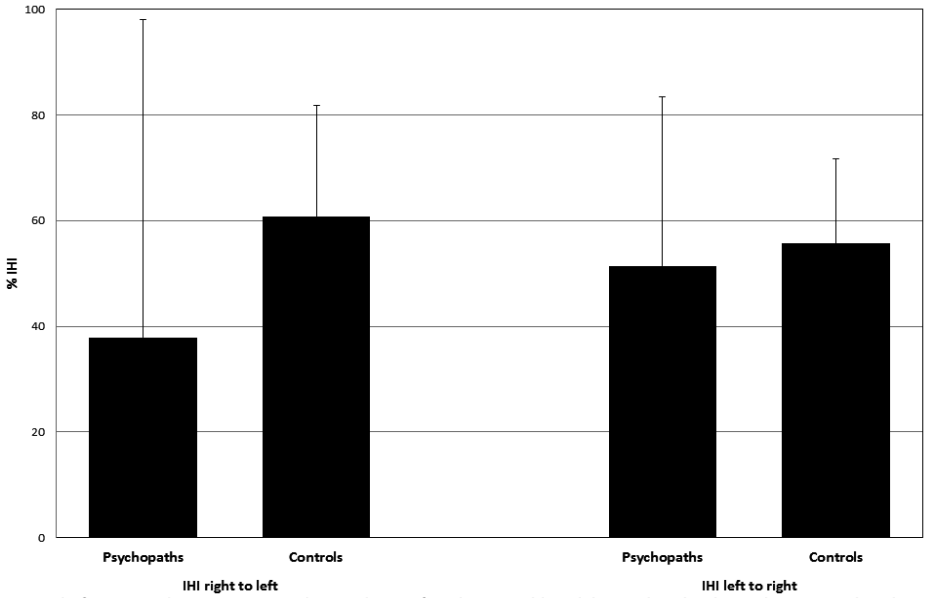


Figure 2. No differences between psychopathic offenders and healthy individuals in this paired pulse paradigm measuring IHI were found.

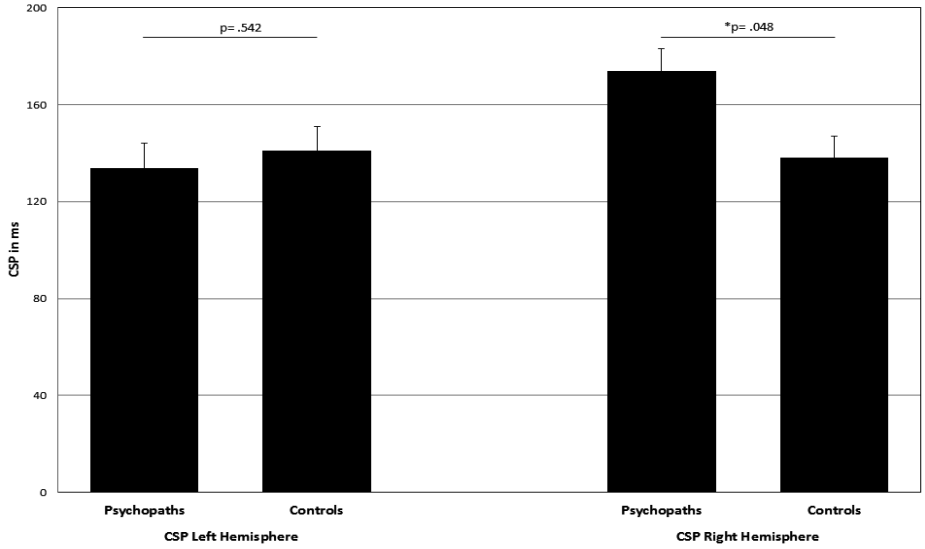


Figure 3. Whereas SICI and ICF were not significantly different between groups, psychopathic offenders demonstrated an unexpected increase in CSP in the right motor cortex. This specific increase in CSP may reflect increased activity of GABAb receptor mediated neurotransmission whereas GABAa neurotransmission may relatively intact.

For SICI, the crucial hemisphere*group interaction was not significant [F(1,26)= 0.319; p=

.577]. Also, the hemisphere*group interaction for ICF was not significant [F(1,26)= 0.708; p= .407]. No group differences in the magnitude of the test pulses were observed for SICI and ICF, [left hemisphere (F(1,26)= 2.002; p= .169); right hemisphere (F(1,26)=0.263; p=.612).

No correlations between Factor 1 and 2 of the PCL-R and TMS measures were found, all p's > .09 (uncorrected for multiple comparisons).

Discussion

In the present study we examined interhemispheric connectivity in psychopathic offenders compared to healthy controls and we found abnormalities in right-to left interhemispheric connectivity, as evidenced by higher right-to-left ISP in psychopathic offenders. In addition, psychopathic offenders showed increased cortical inhibition of the right motor cortex, but not of the left motor cortex.

Functional and structural interhemispheric connectivity deficits have been reported in psychopaths (38) and patients with antisocial personality disorder (18). Our study supports these findings and extends them by showing that right-to-left connectivity is affected in psychopathic offenders whereas left-to-right connectivity is intact. In psychopathic offenders, TMS-induced activation of the right hemisphere results in a similarly large cortical evoked potential in the left hemisphere, especially in prefrontal areas. Whereas in healthy controls TMS-induced activation is propagated to the contralateral hemisphere and subsequently tuned down, our data suggest that in psychopathic offenders, the left hemisphere does not adequately process input from the right hemisphere. While specific contributions to cognition and behavior of the left and right DLPFC have been identified (179, 187-189), much less is known about the connectivity between these regions that presumably underlie cognition and behavior. Some evidence suggests connectivity between homotopical prefrontal regions may be implicated in approach versus withdrawal behaviour (106, 190) in which psychopathic offenders may have subtle deficits (54). Approach behaviour -behaviour directed at the attainment of rewards- recruits the left prefrontal cortex whereas behavioural withdrawal –behaviour intended to avoid potential punishment- is associated with the right prefrontal cortex (25). Once psychopaths initiate goal-directed behaviour they have difficulty reallocating attention and regulating their behaviour based on new peripheral information (191). In line, evidence shows that psychopathic offenders have superior selective attention but are

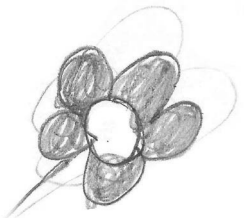
unresponsive to information that is peripheral to the attainment of their goal which may account for the poor response modulation that has been observed in this disorder (191-193). In other words, when engaged in approach behaviour, psychopathic offenders tend to persevere their initial responses (63) and are unable to modulate their behaviour (54). One could argue this is explained by the suboptimal processing of input from the right prefrontal cortex mediating behavioural withdrawal (18, 25, 26, 54).

We also observed that psychopathic offenders demonstrate increased CSP, but not SICI or ICF, in the right motor cortex. CSP reflects the activity of GABAergic inhibitory interneurons, specifically GABAB-mediated inhibitory neurotransmission, while SICI is more commonly associated with GABAA-receptor functioning (114, 194). The exact mechanisms of interhemispheric connectivity remain subject of debate (82), but evidence suggests that GABAB-receptors are strongly involved in interhemispheric connectivity (82, 114). Therefore, the increase in GABAB -mediated neurotransmission in the right motor cortex in psychopathic offenders may contribute to the changes in interhemispheric connectivity. By contrast, the rise in GABAB–receptor mediated inhibitory neurotransmission in the right motor cortex of psychopathic offenders may also be a local response to increased interhemispheric connectivity. Both are conceivable and have been reported in the literature (37), but the current data does not provide conclusive evidence. Given the possible neurodevelopmental aspect of interhemispheric connectivity deficits in psychopathy (38), research in children or adolescents with psychopathic traits may provide more conclusive evidence for this.

Some limitations of this study should be mentioned. Although not significantly different, ISP from right-to-left was higher in prefrontal areas (101%) in psychopathic offenders, suggesting that right-to-left connectivity deficits may be more pronounced between the prefrontal cortices (See Figure 1). However, due to the relatively small sample, we could not demonstrate significantly impaired connectivity in these prefrontal areas. Second, decreases in cortical inhibition are often detected in psychiatric patients (182, 195-197). In contrast, increases in cortical inhibition have also been reported, for instance in abstinent cocaine dependent patients (198). Similar to cocaine, drugs that target the dopamine system (e.g., pergolide, L-DOPA, clozapine) prolong CSP (199-202). As disruption of dopamine and the mesolimbic reward pathway has been observed in psychopathy (13-15), one could speculate that, to a certain extent, cortical dysfunction in psychopathic

offenders could be a corollary of aberrant subcortical dopaminergic activity impacting negatively on interhemispheric connectivity. Finally, we recently showed decreased cortical inhibition in the left DLPFC (Hoppenbrouwers et al, under review) in psychopathic offenders. Whether cortical inhibition in the right DLPFC is, similar to the right motor cortex, overly inhibited, remains unclear, but these findings could be considered to suggest that psychopathic offenders show a unique neurophysiological profile in which the left frontal cortex shows signs of decreased inhibition, while the right hemisphere appears overly inhibited. This exciting possibility warrants further investigation with research tools that provide other evidence than the traditional methods, such as fMRI, are able to generate.

In closing, this is the first TMS-EEG study to provide direct neurophysiological evidence for deficits in right to left interhemispheric connectivity in psychopathic offenders. These novel findings may provide a neurophysiological basis for our understanding of the immensely disruptive antisocial behavior of psychopathic offenders.



§3.2

White Matter Correlates of Psychopathy

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Under review

Abstract

As the neural correlates of psychopathy are beginning to be unraveled, it is becoming increasingly clear that altered neural circuitry, especially in white matter, may be disrupted in this disorder. Therefore, we completed a diffusion tensor imaging analysis of white matter throughout the brain in psychopathic offenders compared to healthy controls to determine (i) potential alterations of white matter circuitry, and (ii) the relationship between these altered white matter circuits to the underlying factor structure of this disorder. Diffusion tensor imaging followed by tract based spatial statistics analysis in 11 psychopathic offenders matched to 11 healthy controls was completed. Fractional anisotropy was calculated within each voxel and comparisons were made between groups using a 5% family wise error rate correction. Any clusters of white matter voxels different between groups were submitted to probabilistic tractography. Finally, any significantly different white matter clusters were examined in relation to Factor 1 and Factor 2 Psychopathy Checklist-revised (PCL-R) scores. Differences in fractional anisotropy were found between psychopathic offenders and healthy controls in three main white matter clusters. These three clusters represented two major networks: an amygdalo-prefrontal network, and a striato-thalamo-frontal network. The interpersonal/affective component of the PCL-R correlated with white matter deficits in the orbitofrontal cortex and frontal pole whereas the antisocial component of the PCL-R correlated with deficits in the striato-thalamo-frontal network. Overall, our findings provide an explanatory model linking specific disruptions in white matter circuitry with the devastating behavioural abnormalities of this disorder.

Introduction

In 1812, Benjamin Rush observed that individuals characterized by a psychopathy-like disorder were primarily afflicted by a 'derangement in the moral faculties' (6). Recent conceptualisations of psychopathy suggest that it is a disorder characterized by callousness, egocentricity, grandiosity and antisocial behaviour (203). Psychopathic offenders understand moral and societal rules, but show a striking indifference to those rules or any consequence of breaking them (204). When confronted with moral choices, psychopaths show no reluctance to inflict personal harm if it helps to achieve their goals (205). The extraordinarily destructive effects and massive societal cost of antisocial and psychopathic behavior underscores the paramount importance of making progress in our understanding of this disorder.

The current conceptualization of psychopathy, as understood from Hare's Psychopathy Checklist-revised second edition (46) and factor structure analysis reveal two dimensions of this disorder. Factor 1 items are interpersonal/affective traits, simplified with the term 'emotional detachment' and Factor 2 items are behavioural symptoms such as impulsivity or criminality simplified with the term 'antisocial behavior'. Although the neurobiology of psychopathy in general is not well understood, recent data has begun to offer clues to the underlying circuitry disrupted in this disorder. In particular, the affective dysfunction of psychopaths may be related to (para)limbic dysfunction (43). Limbic structures such as the amygdala are strongly involved in emotion, the processing of emotionally laden information and the learning of conventional and moral rules (20). Recent work (45) shows that psychopathic offenders have smaller amygdala volumes bilaterally, including deformations in the basolateral, lateral, cortical and central nuclei. The amygdala is connected with cortical regions that control and modulate subcortical functioning (49). Connectivity between the amygdala and the prefrontal cortex (PFC) (e.g., the orbitofrontal cortex (OFC) and ventromedial PFC (vmPFC)) has recently been shown as deficient in psychopathic offenders and individuals with antisocial personality disorder (18, 19) using diffusion tensor imaging (DTI). In a functional imaging study, deficits in connectivity between the amygdala and PFC were present in boys with psychopathic traits (50). Furthermore, lesion studies show that damage to the vmPFC decreases the likelihood that individuals will avoid emotionally aversive outcomes (51). In addition, during fear conditioning psychopaths show no significant activation of the amygdala-OFC network

that is recruited in healthy controls (53).

While evidence for disruption in amygdalo-prefrontal circuitry is mounting in psychopathy, others have shown alterations in temporal, parietal and limbic structures (206-208). In addition, recent functional neuroimaging work has implicated mesolimbic dopaminergic abnormalities in healthy individuals with psychopathic traits (14), whereby projections from the nucleus accumbens to prefrontal cortex may play an important role in a disrupted reward/impulsivity system which may explain the striking antisocial behavior of psychopathy. In healthy individuals, stronger psychopathic tendencies are accompanied by greater activation of the ventral striatum and anterior cingulate cortex during reward anticipation (209). Impairments in the mesolimbic reward system were recently found in psychopaths, suggestive of strong reward drives without consideration of potential punishment (13). Therefore, neural disruption in psychopathy may be more widespread than previously thought and different circuits may be associated with the different factor structures of this disorder.

The major objective of our study was to examine diffusion based measures of white matter throughout the brain in psychopathy to clarify the disrupted neural circuitry in this disorder. Therefore, we completed diffusion tensor imaging (DTI) in psychopaths, using a tract based spatial statistics (TBSS) approach that provides us with analysis of diffusion-based measures in white matter. Such an approach is not limited by a priori assumptions regarding which circuitry is vulnerable in this disorder. Based on recent findings, we hypothesized that (i) psychopathic offenders would be characterized by disruption of white matter connecting amygdala to prefrontal cortex, and (ii) we would find disruption of white matter from nucleus accumbens to prefrontal cortex, corresponding to vulnerability of this network from recent functional imaging studies.

Methods

Participants

Psychopathic offenders (mean age ± standard deviation (SD); 33.5 ± 7.4) were recruited from halfway houses in the Greater Toronto Area and through the Law and Mental Health Program at the Centre for Addiction and Mental Health (CAMH). Thirty-eight male offenders were interviewed of which 23 offenders met PCL-R inclusion criteria for this study.

Offences included aggravated sexual assault, homicide, human trafficking and kidnap. Of these individuals, 12 psychopathic offenders reoffended within the duration of the study (October 20th 2010-May 24th 2011) and had either been arrested or were unlawfully at large. Therefore, 11 male psychopathic offenders were able to complete the entire study. Psychopathic offenders were included if they scored 23 or higher on the Psychopathy Checklist-Revised edition (PCL-R) (46) (average ± SD; 28.1 ± 3.3; range 23-34). In this community sample a relatively liberal cut-off of 23 was chosen to increase the number of subjects that could be enrolled in the study. This cut-off ensures moderate to strong psychopathic traits in criminal populations (46) and allows for a correlational approach to psychopathy which is beneficial with relatively small sample sizes. All included psychopathic offenders signed a Release of Information after which a review of previous psychological assessments was conducted to retrieve the PCL-R score and to screen for psychiatric disorders. As part of the psychological screening of dangerous offenders, Correctional Services of Canada regularly conducts PCL-R interviews, which are led by experienced forensic psychologists. For this study PCL-R scores were not based on file reviews. Exclusion criteria included schizophrenia or any primary psychotic disorder, bipolar disorder, depressive or anxiety disorders and other personality disorders, e.g., borderline personality disorder which was confirmed based on a file review by an experienced clinician (TS). Psychopathic offenders were also excluded if they currently met Diagnostic Statistical Manual-IV-TR (DSM-IV-TR) criteria for substance abuse disorder, that is, no history of substance abuse or dependence for at least 6 months. All offenders were subjected to regular drug screens as part of the terms of their parole which indicated none had abused drugs at the time during which they were participants in the study. During a standard clinical interview psychopathic offenders were screened for neurological disorders (e.g., seizures, history of stroke) and these self-reports regarding health were subsequently checked with a file review. Right-handedness was confirmed with the Edinburgh Handedness Inventory (109). All psychopaths had previously been administered the Shipley Institute of Living Scale and all scored at least in the average range (corresponding to a WAIS-R score ranging from 90-110 ((180)) indicating likely absence of organic brain damage. The Shipley Institute of Living Scale screens for organic brain damage and has a high correlation (r=0.85) with the full scale WAIS-R (181).

Healthy age-matched male controls (mean age ± SD; 32.1 ± 6) were recruited

through advertisement in and around the Centre for Addiction and Mental Health (CAMH). Psychopathology including a lifetime history of substance dependence, or substance abuse in the past 6 months in the control group was also ruled out through a structured clinical interview for DSM-IV disorders (SCID) and the Personality Assessment Inventory (Psychological Assessment Resources, Inc.). The PAI is an objective self-administered inventory of adult personality and psychopathology (e.g., somatic disorders, anxiety, anxiety-related disorders, suicidal ideation and personality disorders) (167, 168). All healthy controls also received a urine toxicology screen to rule out current substance use. In accordance with the Declaration of Helsinki the Research Ethics Board of CAMH approved of the study and written informed was obtained for all participants.

Image Acquisition

DTI images were acquired using an eight-channel head coil on a 1.5 Tesla GE Echospeed system (General Electric Medical Systems, Milwaukee, WI), which permits maximum gradient amplitudes of 40 mT/m. A single shot spin echo planar sequence was used with diffusion gradients applied in 23 non-collinear directions and b = 1000 s/mm2. Two b = 0 images were obtained. Whole brain coverage was obtained (no gap), oblique to the axial plane. Slice thickness was 2.6 mm and voxels were isotropic. The field of view was 330 mm and the size of the acquisition matrix was 128 × 128 mm2, with echo time = 85.5 ms and repetition time = 15000 ms. To improve the signal to noise ratio, the entire sequence was repeated three times.

Tract-based Spatial Statistics

The DTI data were converted to 4D NIfTI volumes. The resulting images for all three repetitions were merged for each subject, corrected for motion and eddy current distortion and ultimately averaged using standard tools available from FSL (www.fmrib.ox.ac.uk/fsl) (210)). After brain-extraction using BET (211), FA images were created by fitting a tensor model at each voxel to the averaged diffusion data using DTIFit (FMRIB's Diffusion Toolbox), implemented in FSL. Voxelwise statistical analysis of the FA data was carried out using TBSS (Tract-Based Spatial Statistics (92)), part of FSL. All FA images were nonlinearly registered to the target image (FMRIB58_FA) provided by the FSL software. Next, the mean FA image was created and the tracts were narrowed to generate a mean FA skeleton which represents

the centres of all tracts common to the all subjects. An FA threshold of 0.2 was chosen to discard non-white matter voxels (92). The area surrounding the skeleton in each subject's aligned FA map was searched perpendicular to the skeleton voxel and the locally highest FA values were projected onto the skeleton. The resulting individual skeletonised images were fed into voxelwise cross-subject statistics. This ensures that each subject's skeleton remains in the group space while representing the centers of each individual's own unique fiber tracts. Finally, group comparisons between subjects with psychopathy and normal controls were carried out with permutation-based analysis (212). This was achieved with Randomise implemented in FSL, utilizing threshold-free cluster-enhancement method (TFCE) (213). Statistical maps were then thresholded at $p<0.05$ fully corrected for multiple comparison (TFCE-corrected). The most probable anatomical localizations for each cluster showing significant between-group differences in FA were determined with the FSL atlas tool using Talairach atlas, Harvard-Oxford cortical and subcortical structural atlases, and the JHU white matter tractography atlas (http://www.fmrib.ox.ac.uk/fsl/data/atlas-descriptions.html).

Region of Interest Analysis

Region of interest (ROI) analyses were conducted as post hoc tests on mean FA values extracted from significant clusters resulting from TBSS. Independent-samples t-tests were performed on each cluster to assess group differences. In psychopathic offenders, partial correlation coefficients were then computed between mean FA values extracted from significant clusters (with more than 100 voxels) and PCL-R factors, while controlling for effects of age (214). Statistical analyses were performed using SPSS v.17.0 for Windows (SPSS Inc., Chicago, IL).

Probabilistic Tractography

To further elucidate the disrupted neural circuitry of psychopathy, significant different voxels between groups were used to seed the tractography algorithm. To generate individualized seed masks, significant voxels resulting from TBSS were projected back onto each control subject's native space. The use of this approach (i.e. fiber tracking in healthy controls using abnormal voxel clusters identified in a disease group) has been recently described (215). Probabilistic fiber tracking was conducted separately in each control

subject using PROBTRACKX implemented in FMRIB's Diffusion Toolbox (FDT). Using this algorithm, estimates of fiber orientation and their uncertainty were calculated at each voxel (216). This model also accounts for the possibility of crossing fibers within each voxel (bedpostX) (217).

We used the default parameters with 5000 sample pathways per each seed voxel with a curvature threshold of 0.2 (corresponding to ±80°). Pathways were also terminated after 2000 steps, using a step length of 0.5 mm. Tractography results were then transformed to the Montreal Neurological Institute (MNI) space and averaged using the FA image that required the least warping among all other images during TBSS registration as the registration target (92). Transformation fields from the TBSS registration stage were used to warp tractography results into the target image space. The transformed images were then averaged and linearly transformed to MNI standard space using the linear transformation matrix between the target image and the MNI standard brain. Finally, the resulting averaged image was thresholded to confine it to probabilities only greater than 0.5% of the maximum possible number of probabilistic pathways in a voxel (i.e. 5000 × total number of seed voxels).

Results

The TBSS analysis showed five non-contiguous clusters of significantly decreased FA in white matter tracts of the psychopathic group as compared with controls ($p < 0.05$) (Table1, Figure1). These clusters involved uncinate fasciculus (UNF) and inferior occipitofrontal (IFOF) bilaterally, extending towards both subgenual anterior cingulate (sACC), left amygdala, left orbitofrontal cortex (OFC) and left frontal pole. In addition, decreased FA was also noted in regions involving bilateral anterior thalamic radiations (ATR) and their medial extensions pointing to sACC.

Table 1.

		MNI Coordinates (mm)					p values	
Clusters	**Clusters size (mm^3)**	**X**	**Y**	**Z**	**Associated WM Tracts**	**Associated Cortical and Subcortical structures**	**Uncorrected**	**Corrected**
1	1562	-15	12	-2	Left ATR, IFOF, UNF	Left thalamus, amygdala, striatum, pallidum, sACC	$1.6x10^{-5}$	$8.2x10^{-5}$
2	887	-35	22	-16	Left UNF, IFOF and ATR	Left OFC and frontal pole	$1.8x10^{-6}$	$9.0x10^{-6}$
3	793	15	16	-6	Right ATR, UNF and IFOF	Right thalamus, striatum, pallidum, and sACC	$1.5x10^{-6}$	$7.5x10^{-6}$
4	98	-33	45	5	Left ATR	Frontal pole	$5.4x10^{-4}$	0.0027
5	14	-29	5	-9	Left UNF		0.0067	0.035

Table 1. MNI atlas coordinates of clusters with significantly decreased FA values in the psychopathic group compared with the control group. ATR=anterior thalamic radiation; UNF=uncinate fasciculus; IFOF=Inferior occipitofrontal fasciculus.

Cluster one corresponded to the subcortical and limbic portions of these white matter tracts (in amygdala, thalamus, sACC) and cluster two corresponded to the frontal components of these white matter tracts (in orbitofrontal cortex and frontal pole). The right sided cluster (cluster 3) stemmed from ATR and UNF with extensions to thalamus, striatum, pallidum and sACC. In general, FA deficits were more pronounced in the left hemisphere. Results showed no significant regions with increased FA value in psychopathic individuals compared with the controls.

Table 2.

Mean FA values	PCL-R total score	Factor 1	Factor 2
Cluster 1	0.353(0.176)	-0.014(0.485)	0.181 (0.321)
Cluster 2	-0.428 (0.125)	-0.627 (0.035)	-0.041 (0.458)
Cluster 3	-0.488 (0.091)	0.335 (0.189)	-0.681 (0.022)

Table 2. Partial correlation coefficients between mean FA values extracted from clusters that showed significant differences between psychopaths and healthy controls and one sided (p values) uncorrected for multiple comparions

In the psychopathy group, we found significant correlations between PCL-R subfactors and mean FA values extracted from two of the clusters, while controlling for age (Table 2, Figure 2). Mean FA of the cluster 2, which mainly involved WM in ventral regions of left frontal lobe, was negatively correlated with Factor 1 (r = -0.627, pone-tailed = 0.035,

n = 10). In addition, there was a negative correlation between mean FAs derived from the right-sided cluster (cluster 3) and Factor 2 (r = -0.681, pone-tailed = 0.022, n = 10). However, there were no significant correlations between cluster 1 and PCL-R subscores.

The probabilistic tractography seeded from voxels with abnormal FA encompassed the following pathways (Figure 3): (i) left and right ATR extending from thalamic nuclei rostrally towards frontal pole and medially to sACC and nucleus accumbens (NAcc) (ii) bilateral caudal continuation of ATR towards diencephalon and midbrain approaching medial ventral tegmental area/substantia nigra (VTA/SN) area (iii) left UNF bridging temporal pole (adjacent to the amygdala) and multiple regions in prefrontal cortex (including OFC, Frontal pole, vmPFC and sACC).

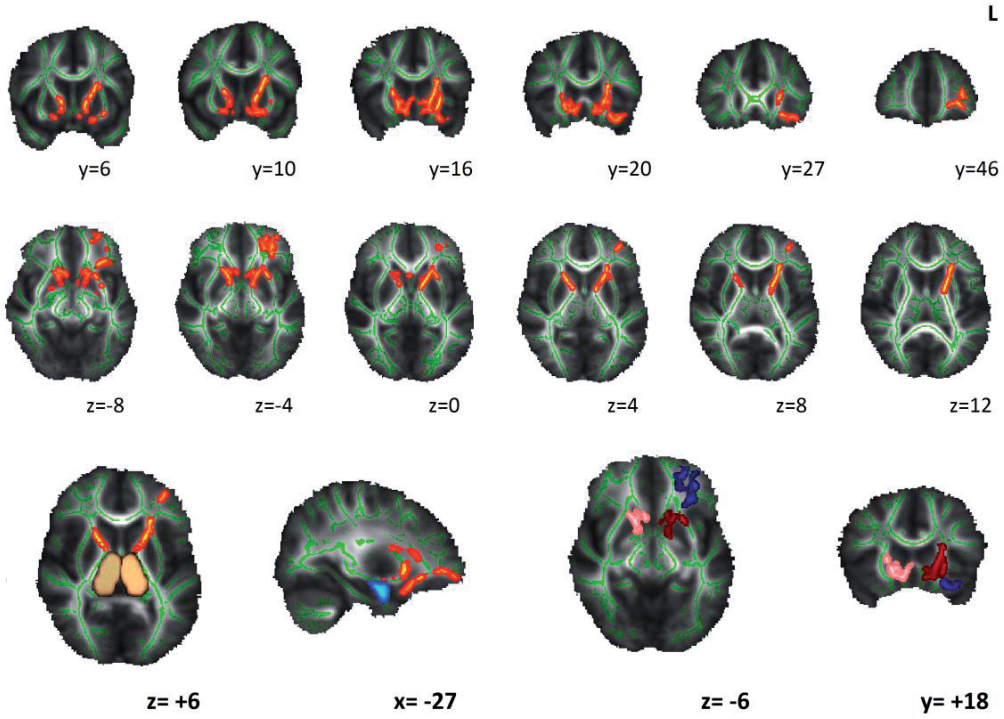


Figure 1. TBSS results showing decreased anisotropy in psychopathic group as compared with normal controls ($p<0.05$). On an MNI brain (grayscale) the white matter skeleton is projected (green), as well as the location of significantly lower FA values in psychopaths as compared with normal controls (red-yellow). Amygdala (lightblue) and thalamic nuclei (copper) derived from Harvard-Oxford subcortical atlas. At the bottom right Cluster1 (dark-red), Cluster2 (dark-blue) and Cluster3 (pink) are shown.

Discussion

In this study, we examined microstructural integrity of white matter throughout the brain in antisocial psychopathic offenders compared to healthy controls. We found that psychopathic offenders had profound white matter deficits compared to healthy controls in white matter tracts connecting amygdala to prefrontal cortex, nucleus accumbens to prefrontal cortex, and thalamus to prefrontal cortex. Correlations with the underlying factor structures of psychopathy were found with integrity of those white matter tracts forming the hypothesized circuitry of specific abnormal behavioural constructs:

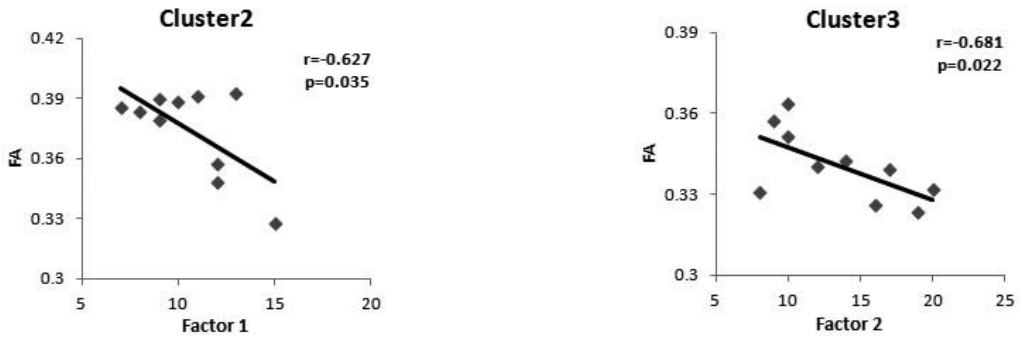


Figure 2. Scatterplots of PCL-R subscores–mean FA correlations for Table 3 voxel clusters

(i) between PCL-R factor 1 and integrity of projections from amygdala to medial prefrontal and orbitofrontal cortex, and (ii) between PCL-R factor 2 and projections from ventral tegmental area and nucleus accumbens through the anterior limb of internal capsule to thalamus and prefrontal cortex.

Our data support and advance our knowledge regarding structural and functional abnormalities of amygdalo-prefrontal circuitry in psychopathy. Disruption of this circuitry, particularly from amygdala to OFC and vmPFC has been hypothesized to underlie the substantial impairment of morality and moral behaviour in this disorder (39, 218). Here our findings align with recent data from antisocial personality disorder (18), children with callous-unemotional traits (219), boys with conduct disorder (220) and psychopaths (19), all pointing to disrupted white matter within these regions. Recently, disruption of the uncinate fasciculus, which connects amygdala to vmPFC and OFC was implicated in psychopaths, supporting our findings (19), providing evidence for the theory that the social and emotional deficits in psychopaths reflects a deficient interaction between

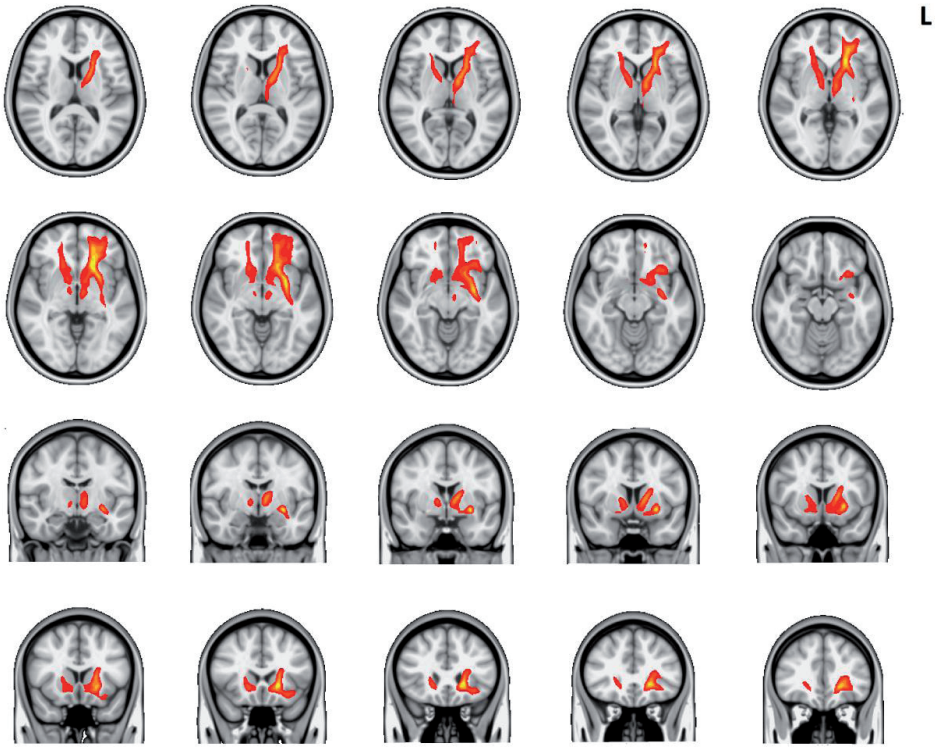


Figure 3. Probabilistic tractography results from healthy controls using seed voxels with abnormal FA in psychopathy. On a T1 MNI brain (grayscale) probabilistic tractography results (red-yellow) are demonstrated.

OFC/vmPFC and amygdala (20). A subsequent study that included the same 9 psychopathic individuals from the Craig et al study, plus another six (total n=15) with antisocial personality disorder found white matter disruption in frontally-based white matter tracts (18) connecting to the limbic system, providing further support for this notion. Furthermore, a recent study of boys with psychopathic tendencies found reduced white matter concentration in frontal cortex (221), raising the possibility that even mild neural alterations may lead to subclinical behaviors along a continuum.

While evidence continues to accumulate for disruption in prefrontal structures and connections from prefrontal cortex to amygdala, there is substantial evidence for structural and functional disruption of the amygdala itself in psychopathy and related disorders. In youths with both conduct disorder and strong psychopathic traits, the amygdala and the OFC are shown to be significantly less active during early reinforcement learning (50). Blair

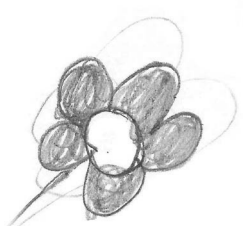
has suggested that in psychopaths a dysfunctioning amygdala is pivotally important as it results in poor fear conditioning and passive avoidance learning (39), both of which are implicated in the pathogenesis of psychopathy (20). In fact, poor fear conditioning in childhood is significantly predictive of adult criminal behaviour suggesting a neurodevelopmental aspect of amygdala damage in psychopathy (222). Within the limbic system, significant bilateral volume reductions in the amygdala, accompanied by surface deformations in specific amygdalar nuclei provide further evidence for disruption of this core circuitry which correlate strongly with the affective and interpersonal aspects of psychopathy (45). When our findings are taken together with the existing literature, it is becoming increasingly clear that disruption of white matter in the OFC, vmPFC and frontal pole, and white matter connections to these regions from the limbic system may explain the dysfunctional interpersonal and affective aspects of psychopathy.

Our implication of disrupted striato-thalamo-frontal (i.e. in white matter tracts connecting nucleus accumbens and ventral tegmental area through anterior limb of internal capsule to thalamus to frontal cortex) circuitry highlights a key second system that may be disrupted in psychopathic offenders. Indeed, we found that disruption in striato-thalamo-frontal circuitry was correlated with the antisocial factor 2 from the PCL-R. Recent accounts of striatal functioning in antisocial populations have suggested a particular pattern of impairment (223). In externalizing and antisocial populations, the striatum may respond relatively normal to the presence of potentially rewarding stimuli but abnormal to the omission of reward (223). While normal controls recruit activity in the anterior cingulate when stimuli lose their rewarding properties, antisocial individuals retain activity in the striatum (224). Once these individuals are motivated to obtain a reward, striatal impairments may result in the inability to flexibly use contextual information to terminate certain behaviors, for instance aggressive or antisocial behavior (223). A recent study examined mesolimbic dopamine reward system hypersensitivity in healthy individuals with psychopathic traits (14). Using a combination of PET and fMRI in the same individuals, neurochemical and neurophysiological hyperreactivity of the dopaminergic reward system was correlated with impulsive-antisocial temperament, providing potential explanations for increased substance use, impulsivity, and violence in this population (14). These data align very closely with our finding of an inverse correlation between FA in subcortical regions corresponding to nucleus accumbens and ventral tegmental area

with the antisocial lifestyle component of the PCL-R. Moreover, dopaminergic networks in the VTA and striatum correlate with trait impulsivity, where higher dopamine release in the striatum is predictive of stronger individual desire for drugs (55). When our data are taken together with these recent findings, there is compelling evidence that disruption of reward system circuitry may underlie a group of behaviors common to psychopathic offenders, including aggression/violence and impulsivity/substance abuse.

An important limitation of our study was the relatively small sample size for a neuroimaging study. Although 23 individuals had consented to our protocol, consistent with the nature of this population, nearly half re-offended during the relatively brief time course of the study. One could argue that this particular feature of our group 'validated' the severity of their condition. Another important limitation is that we did not control for a past history of substance abuse in comparing psychopathic offenders to controls, and there is good evidence to suggest that effects of substances themselves can influence white matter measures (13). In this study 36% of psychopathic offenders had a history of substance abuse and should be considered a serious confound. A recent study did however show that gray matter deficiencies in mesolimbic circuitry in psychopaths are associated with violent behaviour and psychopathy and may be relatively independent of substance abuse whereas integrity of prefrontal regions such as the OFC may be more susceptible to drug use (13). Psychopathic offenders who completed all protocols were not using substances during the time period of the study, as they were subject to regular drug screens as a condition of their parole. Ideally, a third group of substance abusing non-psychopathic offenders could have been included to control for a history of substance abuse. Although our data replicates earlier findings and correlations between specific disrupted pathways and PCL-R scores were found, it is possible that these correlations are contaminated by variables that covary with antisocial behavior, e.g., history of abuse, trauma, and substance use. Finally, the DTI-based measure of fractional anisotropy does not provide us with which cellular correlates within white matter are disrupted, as it indirectly indexes microstructural integrity of white matter. Changes in FA could be due to alteration of axonal membranes, changed axon number, disruption of the myelin sheath, or all of the above. Post-mortem investigations in this population combined with post-mortem DTI scanning could be especially valuable in elucidating these correlates, which may then be translatable to potential treatment.

In summary, we found profound disruption of white matter circuitry in psychopathic offenders compared to healthy controls. Our data suggest that the neural correlates of the interpersonal affective dysfunction lies in disruption of amygdalo-prefrontal circuitry and the neural correlates of antisocial/violent behavior lie in disruption of striato-thalamo-frontal reward circuitry that is tightly linked to impulsivity and substance abuse. The extent of white matter damage attributed to neurodevelopment versus that acquired over time in psychopathy is a potentially exciting area of future investigation that deserves further exploration.



§3.3

Inhibitory Deficits in the Dorsolateral Prefrontal Cortex in Psychopathic Offenders

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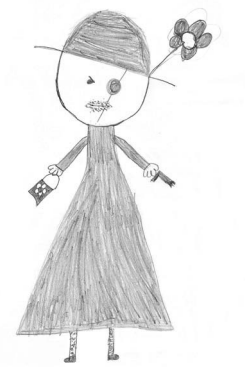
Aristotle N. Voineskos, Dennis J.L.G. Schutter & Zafiris, J. Daskalakis

Cortex



Abstract

Often typified as cunning social predators, psychopathic offenders show a persistent pattern of impulsive and reckless behaviour, the pathophysiology of which has been related to dysfunction in the dorsolateral prefrontal cortex. That is, the dorsolateral prefrontal cortex is important for the regulatory control of impulses and emotion as well as working memory and psychopathic offenders show impairments in all three dimensions. In the present study, we used combined transcranial magnetic stimulation and electroencephalography to compare the physiology of the dorsolateral prefrontal cortex in 13 psychopathic offenders and 15 healthy subjects vis à vis excitability and inhibition. In addition, working memory performance was measured through the letter-number sequencing test. Results showed that compared to healthy subjects, psychopathic offenders had inhibition not excitability deficits in the dorsolateral prefrontal cortex that were accompanied by deficits in working memory performance. In healthy controls and psychopathic offenders working memory performance correlated with the extent of inhibition over the dorsolateral prefrontal cortex. Taken together, these findings suggest that psychopathic offenders suffer from dysfunctional inhibitory neurotransmission in the dorsolateral prefrontal cortex and impaired working memory which may account for the behavioural impairments associated with this disorder.

Introduction

Psychopaths are notorious for their callous unemotional personality style and Machiavellianistic use of others. Likely to engage in criminal and aggressive behaviour they burden society with enormous costs in addition to inflicting severe emotional harm on their victims (8). Although psychopathic offenders are capable of executing well-planned crimes (225), they typically act impulsively and do not deliberate the consequences of their actions, neither for themselves nor for others. As reflected in Hare's Psychopathy Checklist-revised second edition (PCL-R:2) (46) psychopaths display poor behavioural controls, are impulsive and irresponsible and lack the ability to formulate realistic long-term goals (46). In line, Patrick et al. (7) proposed a tripartite conceptualisation of psychopathy in which meanness, boldness and disinhibition are emphasized. According to this conceptualisation, disinhibition refers to "impulse control problems, lack of planfulness and foresight, impaired regulation of affect and urges, insistence on immediate gratification and deficient behavioral restraint" (7). Whereas psychopaths may describe this behaviour as 'living in the moment' (226), in reality these clinical observations point toward cognitive dysfunction, i.e., the incapacity to inhibit impulses and regulate emotion and behaviour. Indeed, psychopathic offenders present with higher levels of impulsive-reactive anger (227), response perseverance (63), attention deficits (178, 228) and are generally unresponsive to inhibitory information (e.g., potential punishment or negative outcomes) (229). Therefore, psychopathic offenders are thought to exhibit deficits in higher order cognitive processes (61, 230) making them vulnerable to a disinhibited antisocial lifestyle.

The dorsolateral prefrontal cortex (DLPFC) is important in the regulation of emotion and behaviour and is dysfunctional in psychopathy (231, 232), particularly the left DLPFC (61). Damage to the left DLPFC generates impairments in attention, cognitive flexibility and impulse control that are involved in regulatory control (61). The authors subsequently suggest that decreased functioning of the left DLPFC in psychopathic offenders can result in antisocial behaviour including impulsivity and behavioural disinhibition (61). The DLPFC is also involved in higher order cognitive functions such as working memory (59, 86, 233). Working memory involves the online storage and manipulation of information (234, 235) while resisting interference (236, 237). Working memory is important for impulse control (238), goal-directed behaviour (239) and response inhibition (240). Lower working memory capacity results in less control of emotional responding (241) and reduced emotional self-

regulation after negative feedback (242). Working memory deficits are also correlated with characteristics of secondary psychopathy, i.e., the impulsive antisocial lifestyle (193). Deficits in working memory may therefore result in the impulsive disinhibited behaviour and poor emotion regulation observed in psychopathic offenders.

At a neurophysiological level, working memory involves the recruitment of inhibitory interneurons in the DLPFC (59). The phenomenon of cortical inhibition (CI) is defined as the neurophysiological suppression of cortical output neurons by inhibitory interneurons that use γ-aminobutyric acid (GABA) as their primary neurotransmitter (113, 243). This form of inhibitory neurotransmission can be quantified with paired pulse transcranial magnetic stimulation (TMS). That is, TMS generates magnetic fields that travel through the cranium to both inhibitory and excitatory interneurons that can, in turn, be measured. Traditionally confined to measurement from motor areas, the combination of TMS with electroencephalography (EEG) has enabled researchers to study inhibitory and excitatory processes from non-motor cortical areas such as the DLPFC (84, 86). The advantage of TMS combined with EEG is that it measures real time physiological processes and networks in the brain. GABAergic inhibitory neurotransmission in the DLPFC has been reported to correlate positively with working memory performance (86) and suggests a strong interplay between inhibition in the DLPFC and working memory performance, both of which are important in the control of behaviour.

The aim of this study was to assess inhibition and excitability directly from the left DLPFC in psychopathic offenders compared to healthy subjects whilst measuring working memory performance. We hypothesized that psychopathic offenders would demonstrate poorer working memory performance and decreased CI over the DLPFC but not over the motor cortex. In addition, we anticipated that the previously observed relationship between working memory and CI over the DLPFC (86) would be replicated.

Methods and Materials

Participants

Thirteen right-handed male psychopathic offenders (age in years: mean ± standard deviation (SD), 34.2 ± 9.2; age range 22-55) and fifteen right-handed (109) age-matched healthy male subjects (age in years: mean ± SD, 34.0 ± 9.9; age range 22-51) were enrolled in the study. Psychopathic offenders were recruited through posters displayed in halfway

houses in the Greater Toronto Area and through the Law and Mental Health Program at the Centre for Addiction and Mental Health (CAMH). Halfway houses are residential facilities for men on conditional release to the community. Their function is to assist in gradual community reintegration while providing supervision. Thirty-eight violent offenders were interviewed of which twenty-one offenders met criteria for inclusion, although 6 reoffended before they could be included in the study. The thirteen psychopathic offenders that were included scored 25 or higher (mean ± SD, 28.8 ± 3.0) on the Psychopathy Checklist-Revised second edition (PCL-R) (46). Offenders were asked to sign a Release of Information after which a review of case notes and psychological assessments was carried out to retrieve the PCL-R score and to exclude co-morbid psychiatric or neurological disorders. Exclusion criteria included age under 18 or over 65, schizophrenia, schizophreniform/psychotic disorders, bipolar disorder, affective or anxiety disorders or any comorbid personality disorders. Exclusion criteria for all subjects included substance abuse or dependence in the last 6 months determined through the Diagnostic Statistical Manual-IV-TR (DSM-IV-TR). However, 87% of the included psychopaths reported a history of drug use and had previously met criteria for substance use disorder. Drug screening at the halfway houses indicated none of the psychopathic offenders were abusing drugs around the time of testing. Psychopaths had previously been administered the Shipley Institute of Living Scale and all scored in the average range. The Shipley Institute of Living Scale screens for organic brain damage and has a high correlation (r=0.85) with the full scale Wechsler Adult Intelligence Scale-R (181).

Healthy controls were recruited through advertisement. Six healthy volunteers were unemployed at the time of testing. Psychopathology in the control group was ruled out through a standard clinical interview and the Personality Assessment Screener (PAS) (Psychological Assessment Resources, Inc.) The PAS is a self-administered, objective inventory of adult personality and psychopathology (e.g., personality disorder, depression, somatic disorders, anxiety, anxiety-related disorders, suicidal ideation and schizophrenia). Specifically, the PAS measures manifestations of clinical syndromes, providing information to assist diagnosis, treatment, and screening for all psychopathology corresponding to DSM-IV categories (167, 168). All participants were free of contraindications to TMS confirmed by a standard interview (149). This study was approved by the Research Ethics Board. Written informed consent was obtained for all participants. All subjects were paid

for participation.

Procedure

TMS pulses were administered with a 7-cm figure-of-eight coil connected to a Bistim module powered by two Magstim 200 stimulators (Magstim Company Ltd, UK). Motor evoked potentials (MEP) were recorded and analyzed with Signal (Cambridge Electronics Design, UK). TMS pulses were administered to the left motor cortex and left DLPFC. Motor threshold (MT) was defined as the minimum stimulus intensity that elicits a motor evoked potential (MEP) of 50 μV in 5 out of 10 trials (112) and was measured with and without the EEG cap. Given the unpredictable nature of this population and the high likelihood of re-offending, we decided not to conduct a magnetic resonance imaging (MRI)-based localization of the DLPFC prior to the TMS session, in order to improve the chances that subjects would complete the study. Stimulation of the left DLPFC was therefore done through a previously reported method that suggests that stimulation over F5 is the optimal location for targeting the DLPFC when MRI-based co-registration is not available (111). The handle of the coil pointed backward, perpendicularly to the presumed direction of the central sulcus, approximately 45º to the mid-sagittal line.

Measurement of CI

CI was indexed through measurement of long interval intracortical inhibition (LICI) which involves a suprathreshold conditioning stimulus (CS) and a suprathreshold test stimulus (TS) separated by a long interstimulus interval (ISI), e.g., 100msec (244). At an ISI of 100msec LICI has been shown to be optimal (245), that is, inhibition is strongest at this ISI. Stimulus intensity was adjusted to generate MEPs of 1mV peak-to-peak which was on average 53% of maximum machine output for the control group and 47% of maximum machine output for the psychopathy group. Although it has been shown that CI measured through EEG strongly relates to CI measured through MEPs, these measures of CI are not identical and therefore, as an extra check, we also recorded MEPs. Per condition (TS alone or CS-TS) one hundred trials were applied, i.e., each block consisted of only test stimuli or both conditioning and test stimuli and these separate blocks were compared against each other to calculate CI. Pulses were administered at a frequency of 0.2 Hz which prevents habituation to repeated stimulation (185, 245, 246).

Electroencephalography

EEG was recorded with a 64 channel Synamps2 DC-coupled EEG system (Compumedics). Four electrodes were used to record eye movement induced artifact, two on the outer side of the eyes and one above and one below the left eye. The reference electrode was placed on the vertex just posterior to the CZ electrode. EEG signals were recorded DC at a sampling rate of 20 kHZ and low-pass filtered at 100Hz. Offline processing was done with Neuroscan (Compumedics). Data was first downsampled to 1 kHZ and cut into segments that included 1000ms pre-TS and 1000ms post-TS activity. Segments were baseline-corrected until 110ms pre-TS to ensure a TMS-free baseline. Post-TS intervals (25-1000msec) that were artifact-free were extracted and digitally filtered using a zero-phase shift 1-100 Hz bandpass filter (48dB/Oct). Hereafter, epochs were visually inspected to exclude movement, eye blink or TMS artifacts. The remaining epochs were averaged and eye blink corrected according to previously described methods (83, 85, 247). Finally, the average eye blink-corrected EEG waveforms were imported into MATLAB (The Mathworks Inc., Natick, MA) where further analyses were carried out with the EEGLAB toolbox (115).

Measures of LICI

MEPs were measured from the abductor pollicis brevis (APB) muscle by two disposable disc electrodes in a tendon-belly arrangement. LICI was expressed through [1-(MEPconditioned/MEPunconditioned) $\times$ 100] in which 0% expresses no inhibition and 100% expresses complete inhibition (86, 114, 248). For LICI measured from EEG the following formula was used:

[1- (area under rectified curve (conditioned)/area under rectified curve (unconditioned)) $\times$ 100].

The eyeblink-corrected average wave forms were bandpass filtered (1-50Hz) and the area under the curve for the conditioned and unconditioned waveforms was generated. The area under the curve was measured between 50 and 150msec post stimulus for both the CS and TS. The first time (i.e., 50 msec post stimulus) was chosen as it represents the earliest artifact-free data that can be recorded post stimulus, and the second time (i.e., 150 ms post stimulus) was chosen as it represents the duration of GABAB receptor-mediated

inhibitory postsynaptic potentials (IPSPs) (249) (i.e., 250 ms) elicited by the CS (245). For measurement of cortical evoked potentials (CEPs) over the motor cortex the C3 electrode was used (85, 170) whereas for measurement of CEPs from the DLPFC electrode AF3 was used (83-85, 89, 90, 110).

Working Memory

The Letter-number Sequencing (LNS) test from the Wechsler Adult Intelligence Scale (WAIS)-III reliably measures working memory performance (250, 251). In this test a list of random numbers and letters are read out loud to the participant who is then asked to repeat back the numbers and letters. The letters and numbers are presented in alternating order with difficulty increasing across blocks of trials. Subjects are instructed to first say the numbers in order from smallest to biggest and then the letters in alphabetical order. For every correct sequence one point is given amounting to a maximum score of 24.

Medication

Two psychopathic offenders used methadone as a treatment for previous opioid addiction (i.e., heroin). One of these offenders also used pantoprazole for gastroesophageal reflux disease. Two offenders received quarterly intramuscular depots of leuprolide (for reduction of testosterone levels) due to repeated sexual offences. Last, two offenders occasionally used quetiapine as needed for sleeping purposes but self-reports indicated that they had not used this medication in the two weeks prior to TMS assessment.

Data analyses

A multivariate General Linear Model (GLM) was conducted with LICI over the DLPFC and primary motor cortex (M1) as dependent variables and Group (psychopaths versus controls) as a fixed factor. To check for differences in cortical excitability, a second multivariate GLM was conducted with CEP over M1 and DLPFC in response to single pulse TMS as dependent variables and Group (psychopaths versus controls) as a between-subjects factor. Independent samples t-tests were performed to check for differences in LNS scores, LICI measured over the APB, MT (with and without EEG cap), and intensity to achieve a MEP of 1mV peak-to-peak. In order to exclude a confounding influence of methadone on CI (252, 253) post-hoc analyses were conducted without the methadone treated subjects. Last,

separate univariate GLMs were done to check for differences between sham-corrected and sham-uncorrected CI.

The PCL-R is composed of two factors; Factor 1, the interpersonal/affective factor and Factor 2, the deviant lifestyle. Pearson's product moment correlation coefficient was used to check for correlations between LNS scores and LICI over the DLPFC and M1 and to check for a correlation between overall PCL-R scores, Factor 1 and 2 and CI over the DLPFC. Alpha level of significance was set at .05.

Results

TMS was well-tolerated by all subjects without any adverse events. In the control group 10% of all trials were deleted and in the psychopathy group 15% of all trials were deleted due to TMS, movement or eye blink artefacts.

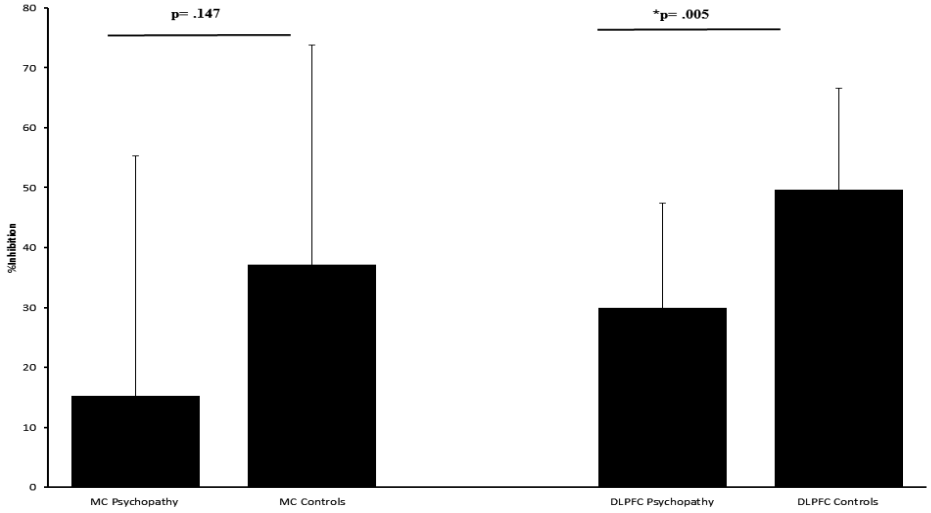


Figure 1. This Figure shows that psychopathic offenders present with significantly less CI on the DLPFC. The error bars represent the standard deviations.

Cortical inhibition

The multivariate GLM showed a significant group effect for the difference in CI measured on EEG, $F(2,25)= 4.807$; $p= .017$; $\eta p2= .278$. Test of between-subjects effects showed that psychopathic offenders demonstrated significantly lower CI over the DLPFC, $F(1,26)=9.229$; $p=.005$; $\eta p2 = .262$ but not over the M1, $F(1,26)= 2.238$; $p= .147$; $\eta p2= .079$ (See Figure 1).

The second multivariate GLM showed no differences in CEPs in response to single pulse TMS between controls and psychopaths, F(2,25)= .482; p= .623. Psychopathic offenders showed no difference in LICI measured from the APB muscle compared to controls, t(27)=0.808; p= .426.

The post-hoc multivariate GLM that was conducted without the methadone treated subjects to exclude methadone treatment as a potential confound also yielded a significant group effect, F(2,23)= 4.076; p= .029; ηp2= .246 and test of between-subjects effects showed that psychopathic offenders demonstrate significantly lower LICI over the DLPFC, F(1,25)=8.468; p= .007; ηp2 = .246, but not over M1, F(1,25)= 2.060; p= .163; ηp2 = .073. LICI measured from the APB muscle did also not reach significance after excluding the methadone treated subjects, t(24)=0.327, p= .746.

Letter-number sequencing

Compared to controls, psychopaths performed significantly worse on the LNS test, t(26)= -3.063, p=.005. In healthy controls performance on the LNS test correlated with LICI over the DLFPC (r=.679; p= .005) (See Figure 2A) but not with LICI over M1(r=.114; p= .685). In psychopaths, performance on the LNS test showed a trend toward a significant correlation with LICI over the DLPFC (r=.519, p= .069) (See Figure 2B) but not with LICI over M1 (r=-.114, p= .685). Neither LNS nor CI over the DLPFC correlated with the PCL-R or with factor 1 or 2 of the PCL-R, all p values > .110.

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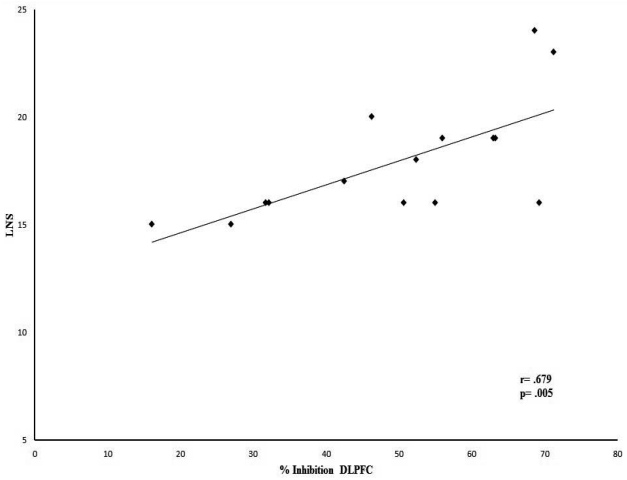
Motor threshold

Controls and psychopaths did not differ in MT without cap, [t(26)= -0.550; p= 0.587] or in MT with cap [t(26)= -1.340, p= .192]. No differences in intensities necessary to reach 1mV peak-to-peak without cap, [t(26)= -1.723, p= 0.097] or with cap [t(26)= -0.401, p= .691] were observed.



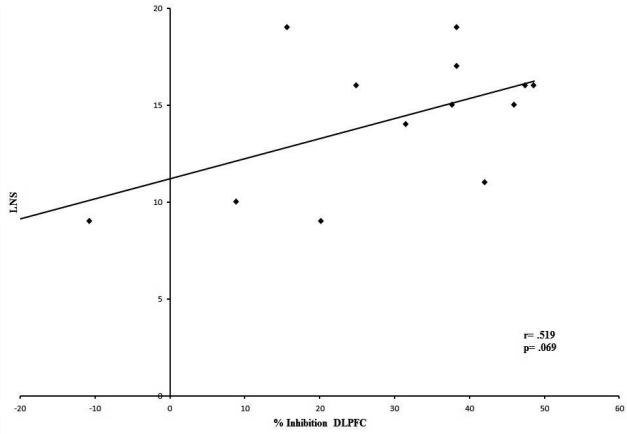


Figure 2A. Stronger CI in the DLPFC is associated with better WM performance in healthy controls. This correlation shows the importance of GABAergic interneurons in the DLPFC in cognitive processing, specifically in WM. Figure 2B. This Figure depicts the correlation between CI in the DPFC and WM performance in psychopathic offenders. The data shows a strong trend towards significance although the correlation is not statistically significant.

Sham

In a subset of both the control and psychopathy group (6 subjects per group) sham

stimulation was applied to control for TMS click-induced auditory activation on the cortical evoked potentials. For sham stimulation the coil was angled at 90º from the cranium resting on one wing of the coil. Sham stimulation did not significantly change CI in the M1 (in psychopaths; Clactive= 16.1% ± 43.9% versus CIsham= -18.8% ± 48.4%, p= 0.112; in controls; Clactive=31.2% ± 37.5% versus CIsham50.6% ± 21.3%; p= 0.199) or DLPFC (in psychopaths; Clactive= 17.3% ± 15.9% versus CIsham= 28.7% ± 60.9%; p= 0.612; in controls Clactive= 41.1% ± 19.5% versus CIsham=48.9% ± 19.7%; p= 0.544).

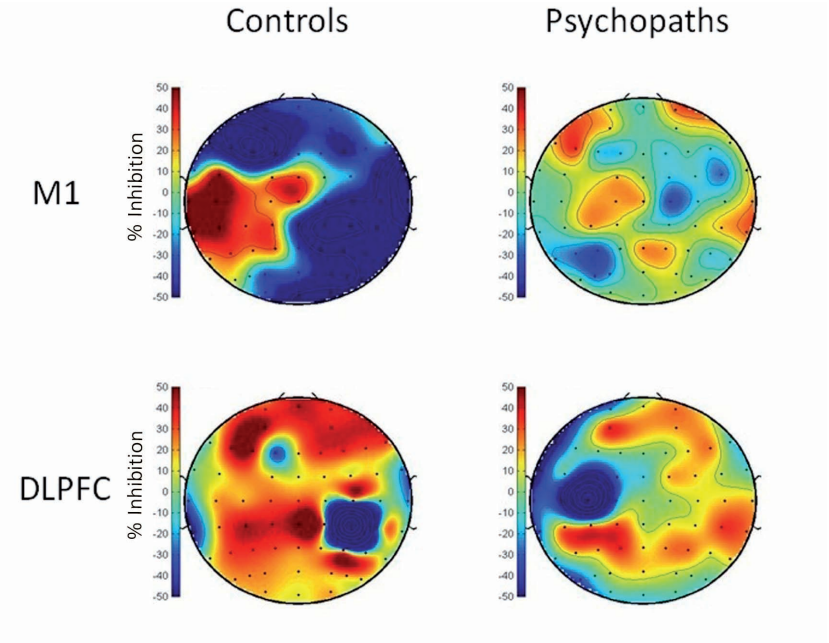


Figure 3. This figure represents LICI averaged over all subjects in each group. The 'hot' colours represent strong inhibition whereas 'cooler' colours show a lack of inhibition or facilitation. Psychopaths show less cortical inhibition as compared to healthy controls. Topographic headplots were created with EEGLAB Toolbox (115).

Discussion

Through combined TMS and EEG we demonstrate that psychopathy is associated with deficient inhibition in the DLPFC (see Figure 3). The relationship between inhibition in the DLPFC and working memory that was previously reported (86) was also replicated in healthy subjects but was disrupted in psychopathic offenders which may, in part, explain the behavioural and emotional disinhibition observed in these individuals.

The DLPFC has been proposed to control subcortical areas (e.g., amygdala and brainstem) that are involved in the experience of aggressive impulses (48). Damage to the DLPFC

may then result in impulsive reactive aggression. This is reflected in the observation that psychopathic offenders are not only capable of instrumental aggression, but also display increased levels of reactive aggression (227). Individuals that show more reactive aggression are disinhibited and aggress without consideration of the outcomes of their actions (48). Furthermore, the importance of intact functioning of the DLPFC is highlighted by a recent study by Boy et al. (254) in which they show that GABA concentrations in the DLPFC correlate negatively with 'trait urgency', one of four facets of impulsivity. Trait urgency, or 'rash impulsivity,' is defined as 'the tendency to act rashly in response to distress or other strong emotions and urges' and is related to drug abuse, aggression and risky sexual behaviour (254). The paired pulse TMS paradigm that was used in this study taps into GABAergic neurotransmission, particularly GABAB receptor mediated inhibitory neurotransmission (255), and suggests that GABAB receptor mediated neurotransmission in the DLPFC may be dysfunctional in psychopathic offenders. Consistently, in offenders with a history of conduct disorder baclofen, a GABAB receptor agonist, induces a reduction in aggressive responses which suggests an important role of GABAB in the regulation of aggressive behaviour (256). The current finding corroborates the study by Cherek et al. (256) by showing that GABAB receptor functioning in offenders is indeed abnormal. Together these findings suggest that GABAB receptor mediated inhibitory neurotransmission in the DLPFC in psychopathic offenders is likely to contribute significantly to their behavioural disinhibition and aggressive behaviour.

Working memory performance is impaired in psychopathic offenders which is demonstrated by poorer performance on the letter number sequencing test. However, the somewhat disrupted correlation between CI in the DLPFC and working memory performance can also be considered evidence for reduced cognitive functioning in psychopathic offenders. Recently, higher-order cognitive functions (e.g., attention and working memory) in psychopathy have gathered more interest (178, 228, 229) and have been shown to influence personality features of the psychopath (178). For instance, reduced cognitive control has been shown to relate to psychopathic traits (193), specifically secondary psychopathy. Secondary psychopathy is characterized by high levels of impulsivity, irresponsibility and lack of planning whereas the primary psychopath displays a callous, narcissistic and manipulative personality style (257). Patients with antisocial personality disorder have a broad range of cognitive deficits related to DLPFC functioning

(232). Research using the Psychopathic Personality Inventory (PPI) (258), a questionnaire that approaches psychopathy as a cluster of extreme scores on normal personality traits, shows that deficits in cognitive control are related to the social deviance subfactor of the PPI (259, 260). These findings suggest that poor cognitive functioning is associated with poor regulation of emotion and behaviour which, in concert with subcortical deficits (48), may result in impulsivity and reactive aggression. In line with our suggestion that reduced DLPFC dysfunction results in increased behavioural and emotional disinhibition, reduced WM capacity may reflect an important cognitive function through which DLPFC dysfunction predisposes to impulsive and aggressive behaviour. Related to this issue, is the close connection between working memory and goal-directed attention. Psychopathic offenders have difficulty reallocating attention once they have initiated goal-oriented behavior (54). That is, psychopathic offenders show an interesting impairment in paying attention to information that is peripheral to their ongoing principal behaviour. This may result in a rigidity toward continuing with their predominant response set (228, 261, 262). As a corollary, psychopathic offenders have difficulty regulating their behavior based on emotionally relevant information while they are engaged in goal-directed behavior. It could be argued, therefore, that DLPFC dysfunction leads to such regulation deficits as it closely involved in both working memory (59, 86) and goal-directed attention (263).

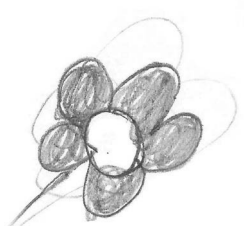
Our findings may also help provide a rationale for novel treatment approaches for specific deficits in psychopathy. High frequency (e.g., 20Hz) repetitive TMS (rTMS), is capable of increasing CI, particularly in subjects that have lower baseline CI (264). Research using rTMS over the left DLPFC has suggested that rTMS may work as a cognitive enhancer in psychiatric populations (265). rTMS may be employed as a treatment to normalize CI in the DLPFC and WM performance which may enable psychopaths to better control their behaviour. However, high frequency rTMS diminishes attention for angry facial expression in healthy volunteers (188) which has been suggested to predispose to antisocial behaviour (266). Therefore, in order to avoid aggravating the psychopath's antisociality brain stimulation studies in psychopathic offenders should be conducted very cautiously and should be closely monitored.

Some limitations of the present study should be mentioned. First, high incidence of drug abuse is common to many psychiatric disorders and it is certainly prevalent in psychopathy. Unfortunately, the high incidence of previous drug abuse (87%) in this

sample could contribute to the decreased inhibition in the DLPFC (13) and potentially to decreased WM performance. However, if behavioural disinhibition related to DLPFC dysfunction is indeed an intrinsic component of psychopathy, the high incidence of drug abuse among psychopaths would be predicted by DLPFC dysfunction and could also be a corollary of behavioural disinhibition. Second, researchers have made a distinction between successful and unsuccessful psychopaths (267, 268). In contrast to the successful (nonconvicted) psychopaths who are thought to show normal or even superior cognitive functioning, unsuccessful psychopaths have deficiencies in cognitive processing making them more prone to behavioural disinhibition and overt violence (230). The current findings may therefore only represent cognitive abilities in unsuccessful psychopathic offenders. Importantly, unsuccessful psychopathic offenders report higher rates of childhood abuse (269) which, as was already noted by McCord and McCord (270), may contribute to the pathogenesis of an emotionally cold and aggressive personality style. In fact, research has shown childhood abuse to result in prefrontal cortical thinning (271, 272) which could potentially contribute to dysfunction of inhibitory activity. In our sample 40% of the psychopathic offenders reported a history of childhood abuse, i.e., sexual, physical or verbal abuse. Therefore, the question remains whether DLPFC dysfunction is innate to behavioural disinhibition in psychopathy or whether it is also partly a function of environment. Third, CI measured in the M1 in psychopathic offenders also suggests inhibitory deficits but, given the relatively large variance, does not reach significance. CI indexed from the APB does however not show signs of impairments in inhibition and therefore, it remains unclear whether the motor cortex is also affected in psychopathy. Lastly, evidence shows amygdala (13, 273, 274), orbitofrontal cortex (21, 273, 275) ventromedial prefrontal cortex (276) and uncinate fasciculus (19) dysfunction in psychopathy. It is therefore important to emphasize that DLPFC deficits are not likely to be the sole cause of psychopathic disinhibition. Rather, behavioural disinhibition is more likely to result from a complex interplay between deficits in CI, aberrant subcortical activity and hormonal imbalances.

In sum, our TMS-EEG study shows impaired CI in the DLPFC and poor working memory performance in psychopathic offenders. Although it is unlikely that deficits in CI and working memory are solely responsible for psychopathic disinhibition, these impairments may very well render the psychopath unable to regulate impulses subjecting them to a disinhibited, antisocial life.

PART 4

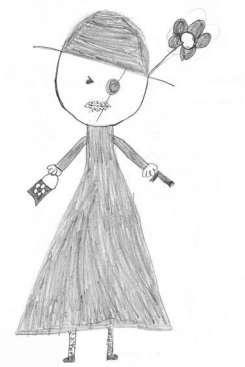


§4.1

The Role of the Cerebellum in the Pathophysiology and Treatment of Neuropsychiatric Disorders: A Review

Sylco S. Hoppenbrouwers, Dennis J.L.G Schutter, Paul B. Fitzgerald, Robert Chen & Zafiris J. Daskalakis

Brain Research Reviews



Abstract

The cerebellum has traditionally been looked upon as a brain area primarily involved in motor behaviour. The last decade has however heralded the cerebellum as a brain region of renewed interest for neuropsychiatric disorders. This renewed interest is fuelled by new insights obtained from neuroanatomical research, modern functional neuroimaging and transcranial magnetic stimulation studies. In this review, evidence in support of cerebellar involvement in neuropsychiatric disorders will be presented. In addition, transcranial magnetic stimulation will be introduced as a novel way to study cerebellar contributions to the pathophysiology of psychiatric disorders. In conclusion, a new functional concept of the cerebellum as more than simply a brain area regulating motor control appears mandatory and the involvement of the cerebellum should be considered when studying the neurological basis of neuropsychiatric disorders.

Introduction

The cerebellum is Latin for 'little brain' and traditionally argued to play a pivotal role in posture, balance and the coordination of movement. However, there is increasing evidence that the cerebellum is also involved in emotion and cognition (for a review see, (277)). Furthermore, novel insights gathered from neuroanatomical research, modern functional neuroimaging and transcranial magnetic stimulation studies have pointed towards the involvement of the cerebellum in the pathophysiology of psychiatric disorders. In this review, evidence that may support cerebellar involvement in autism, schizophrenia, mood and anxiety disorders and attention deficit/ hyperactivity disorder will be discussed.

The anatomy of the cerebellum

The cerebellum is a structure situated at the base of the brain where it takes up approximately 10% of the brain volume but contains more than four times the number of neurons in the cerebral cortex (278). The cerebellum has a uniform synaptic structure. That is, it has a vast numbers of neurons yet only a few types of neurons which are extensively interconnected (for a review on cerebellar anatomy see (279)). It has been proposed that this neural organisation makes the cerebellum particularly suitable for the regulation of brain processes (280, 281).

The cerebellum is functionally divided into several parts and includes the flocculonodular lobe, the vermis and the cerebellar hemispheres (282). The flocculonodular lobe is considered the oldest part of the cerebellum and has connections to the brain stem and spinal cord. The flocculonodular lobe is argued to support basic motor functions including maintaining balance and posture.

The vermis is traditionally associated with muscle tone and movement, but lesions to the cerebellar vermis can also give rise to affective changes. The latter findings are consistent with the reciprocal anatomical connections between the vermis and structures of the limbic system including the septum, amygdala, hippocampus and hypothalamus (65). The fastigial nucleus is part of the deep cerebellar nuclei (DCN) and is the intermediary between the vermis and the inferior peduncle. This nucleus is connected with the reticular formation which is intricately involved in arousal as evidenced by its involvement in blood pressure and heart rate (283). Moreover, stimulation of the fastigial nucleus results in changes in the septum and hippocampus of the limbic system (66). Projections from

the paravermal region of the cerebellum run through the interposed nucleus and the middle cerebellar peduncle. This nucleus exerts a modulatory influence on learned motor responses (284).

Finally, the lateral hemispheres of the cerebellum are connected to the dentate nucleus and project to the cerebral cortex via the superior cerebellar peduncle. The dentate nucleus is topographically linked with different motor and non-motor regions of the cerebral cortex areas, including the primary motor cortex and the prefrontal and parietal cortex (74, 285, 286). These connections are assumed to be of critical importance to the alleged involvement of the cerebellum in cognitive functions.

In sum, the neuroanatomical connections between the cerebellum and non-motor areas imply that the role of the cerebellum extends beyond its involvement in motor behaviour.

The cerebellar cognitive affective syndrome

The cerebellar cognitive affective syndrome (CCAS) was introduced by Schmahmann and Sherman (73) based on clinical observations in patients with lesions confined to the cerebellum. In addition to motor impairments damage to the cerebellum can also give rise to a wide range of clinically relevant non-motor symptoms including anxiety, ruminativeness, perseveration, anhedonia and aggression (71). These symptoms are roughly categorized by their cognitive and affective nature. The cognitive impairments associated with CCAS fall in three broad classes: 1) executive dysfunction (e.g., working memory, planning); 2) visuo-spatial abnormalities (e.g., impairments in visual memory and visuospatial organization); 3) and linguistic dysfunction (e.g. dysprosodia, agrammatism and mild anomia) (73). Posterior cerebellar lobe lesions are mainly associated with cognitive dysfunctions whereas anterior lobe dysfunctions have less marked intellectual deficits (73). Furthermore, right cerebellar hemisphere lesions are more commonly linked to visuo-spatial impairments (287).

The affective component of CCAS is commonly characterized by lethargy, depression, lack of empathy and dysregulation (71). Such symptoms are often seen in acquired cerebellar dysfunction (71) but are also observed in congenital malformations of the cerebellum (72) as well as in children following cerebellar tumour resection (288). The connections between the vermis and the reticular system, hippocampus and amygdala

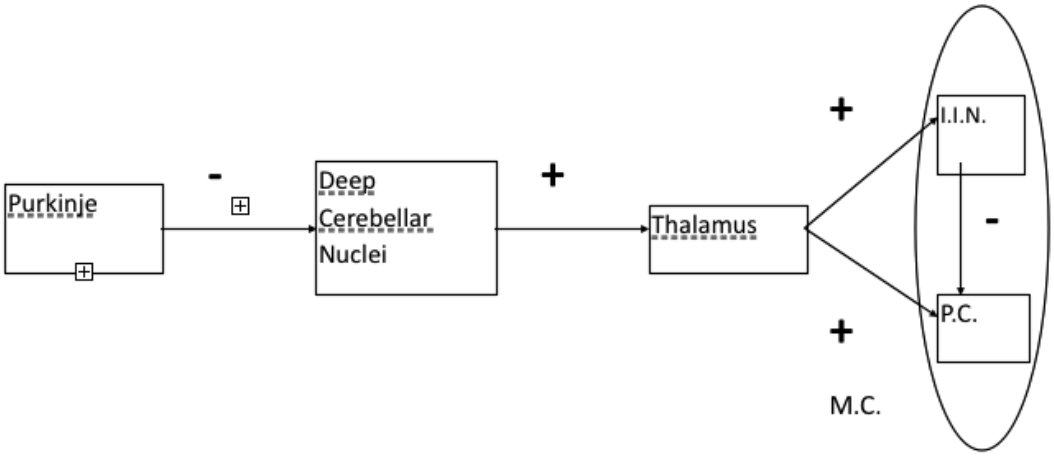


Figure 1a. Cerebellar inhibition is thought to be mediated by this pathway. The Purkinje cells inhibit the deep cerebellar nuclei (DCN) which excite the thalamus. An excitatory pathway runs from the thalamus to the motor cortex (M.C.). (I.I.N.= inhibitory interneurons; P.C.= pyramidal cells)

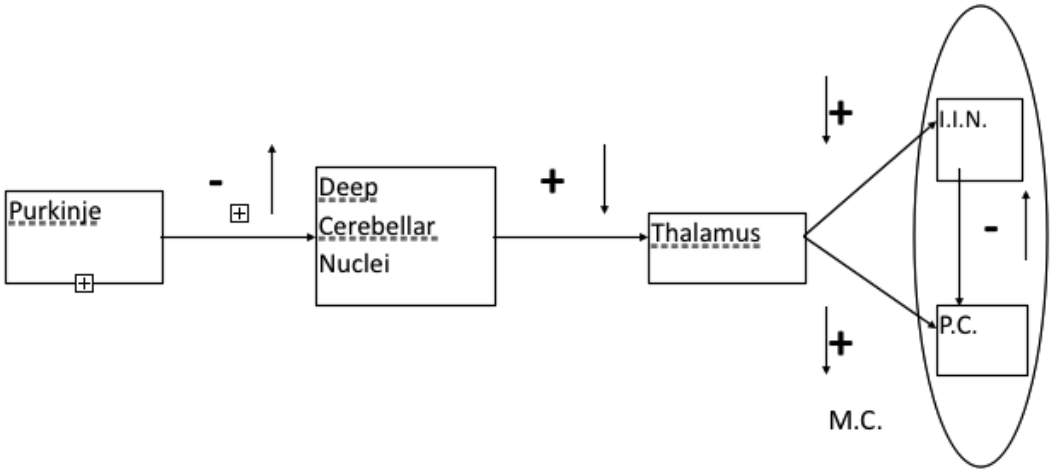


Figure 1b. When a TMS pulse is administered over the cerebellum the inhibitory pathway to the DCN is activated. Increased inhibition of the DCN results in decreased excitation of the thalamus and subsequently of the motor cortex. Decreased excitation, or relative inhibition, of the pyramidal cells would manifest as an attenuated MEP. .). (I.I.N.= inhibitory interneurons; P.C.= pyramidal cells)

imply that the vermis plays an important role in the regulation of affect. Indeed, in vermal agenesis severe mental retardation and autism spectrum disorders have been observed in addition to abnormal motor development (72). Vermal lesions are also associated with affective and relational disorders. For example, patients with vermal lesions have been reported to demonstrate behaviour that is overly trusting and child-like but may also display oppositionality and irritability (71).

In addition, spinocerebellar ataxias (SCAs) are neurodegenerative diseases associated with heterogeneous symptoms, including motor, attentional, memory and executive impairments (289). SCAs are caused partly by cerebellar degeneration and cognitive impairment occurs in several subtype of SCAs (289). For example, patients with SCA3 or SCA6 may present with frontal executive dysfunction (289), that may be explained by frontal hypoperfusion secondary to deactivation of the cerebello-thalamo-cortical pathway (290). Moreover, the finding that patients with SCA3 and SCA6 demonstrated impairments on a theory of mind task (i.e., a task that probes social cognition) suggests that the cerebellum plays a role in social cognition (289).

A further example of the CCAS model or 'dysmetria of thought' hypothesis (73) has been explored in schizophrenia research (291) and has been named 'cognitive dysmetria'. Schizophrenia is a disorder characterized by a broad spectrum of disorganization symptoms (292) and it has been proposed that the wide variety of symptoms present in schizophrenia can be accounted for, in part, by a dysfunctional cognitive process or 'misregulation of information' (292). Cognitive dysmetria, therefore, is proposed to be the resultant of a dysfunctional basic cognitive process caused by abnormalities in cortico-cerebellar circuitry (293). Moreover, the concept of cognitive dysmetria may, in theory, explain the heterogeneous phenotype of schizophrenia (291). That is, if the cerebellum is indeed involved in a very basic cognitive process that underlies or supports other cognitive processes, then impaired function of this central brain structure should result in a myriad of behavioural impairments seen in this disorder.

It has been suggested that the cerebellum fulfils an important modulatory role in behaviour. For example, it has been suggested that the cerebellum acts as a comparator which matches intentions with actual performance (294) to maintain homeostatic functioning (71). Cerebellar lesions may therefore result in a wide variety of cognitive, affective and behavioural abnormalities many of which will be discussed in more detail

below. In sum, the CCAS model provides compelling evidence for cerebellar contributions to cognition and emotion.

Cerebellar dysfunction in neuropsychiatric disorders

Autism

Autism Spectrum Disorders (ASD) are severely disabling and affect approximately 30-60 individuals per 10,000 (295). ASD includes prototypical autism, Asperger syndrome and pervasive developmental disorder-not otherwise specified (PDD-NOS). The core deficits of these disorders include impaired communicative skills, abnormal social interactions and stereotypical behaviour. The most consistent neurobiological abnormalities found in ASD are cerebellar degeneration, specifically reduced numbers of Purkinje cells (296-298), cerebral dysgenesis (298-300), gray and white matter abnormalities (301) and high levels of serotonin that may negatively affect cerebellar function (302-306). Moreover, recently involvement of the amygdala in ASD has also been highlighted (307, 308). However, it should be noted that the variation in core deficits plus co-morbid disorders make the phenotype in ASD quite heterogeneous (309). As a result one must be cautious in postulating brain abnormalities specific to ASD (310).

Several studies have consistently demonstrated anatomic and histological abnormalities of the cerebellum in ASD (see Table 1.).

Table 1.

Study	Method	Finding
(297)	Structural MRI	Hypoplasia vermal lobules VI and VII
(296)	Reanalysis of structural MRI data	Bimodal distribution of hyper- and hypoplasia of vermis
(299)	Brain tissue and CSF analysis	Neuroinflammatory process in multiple brain areas including cerebellum
(311)	Review autopsy and MRI data	Reduced number of Purkinje cells, hypoplasia posterior cerebellum
(312)	Autopsy comparing healthy controls and autistic patients	Purkinje cell size is decreased in autistic patients

(313)	Structural MRI	Less cerebellar gray matter; more cerebral and cerebellar white matter in young patients
(314)	Structural MRI	Cerebellum and brainstem smaller in autism though they develop at the same rate
(315)	MRI meta-analysis	Cerebellum is increased in volume in autism
(316)	MRI and behavioural measures	Measures of stereotyped behaviour correlated negatively with volume of vermal lobules VI and VII. Decreased exploration correlated with hypoplasia of vermal lobules VI and VII.
(317)	Autopsy of autistic and control cerebellar cortices	Lower Bcl-2 protein in cerebellum suggesting higher programmed cell death
(318)	Autopsy of autistic and control cerebellar cortices	Reduction in Reelin and Bcl-2 in autistic cerebellum
(319)	PET during language task	Autism was associated with impairment of the dentato-thalamo-cortical pathway
(320)	Volumetric MRI	Decreased size of cerebellar hemispheres and vermal lobules VI-VII in autistic patients
(321)	Attention shifting task in autistic and cerebellar lesion patients and healthy controls	Autistic and cerebellar patients were equally impaired on attention shifting task
(322)	Catching adaption test in high functioning autistic patients and normal controls	High functioning autistic patients show normal motor adaptation
(323)	Autistic patients and healthy controls were tested on time judgement and procedural learning (tasks thought to recruit cerebellar activity)	Autistic patients performed worse on procedural learning tasks, possibly due to abnormalities in cerebellar-fronto circuitry
(324)	Autistic patients and healthy controls were tested in classical eye-blink conditioning	Autistic patients showed abnormal eye-blink conditioning
(325)	Autistic patients were tested with a tasks thought to recruit cerebellar activity ie oculomotor paradigms	No evidence was found for cerebellar dysfunction
(326)	Autistic subjects were tested with two oculomotor paradigms	Cerebellar-brainstem networks appear to be functionally intact

Cerebellar studies in autism Abbreviations: fMRI = functional magnetic resonance imaging, PET = positron emission tomography, CT = computerized tomography

For example, evidence of a neuroinflammatory response in gray and white matter in the frontal cortex and in the cerebellum was reported with degeneration and loss of Purkinje and granule cells (299). Other studies have also reported loss of Purkinje cells (311) as well as reduction in Purkinje cell size (312). Interestingly, cerebellar malformations in autism fall in a bimodal distribution (296). In 78 autistic patients the authors found hypoplasia of posterior vermal lobules VI and VII and cerebellar hemispheres in ~88% of autistic cases. Hyperplasia of posterior vermal lobules VI and VII was found in ~12% of subjects. Moreover, the brains of young autistic individuals have less cerebellar gray matter but more cerebral and cerebellar white matter (313). In addition, significantly smaller vermis sizes at all ages in autistic subjects as compared to controls have been found (314). In contrast, the pons, the cerebellar vermis I-V and the cerebellar vermis VI-VII develop at a significantly faster rate compared to healthy controls (314). In a recent meta-analysis evidence was found for a global increase in cerebellum size in autistic individuals (315). A mediating effect of age and IQ on cerebellar vermal lobules VI-VII, which is partly consistent with the study by Hashimoto et al (314) was also reported (315). Interestingly, the vermal lobes VI-VII have been linked with one of the characteristic features of autism, namely stereotyped behaviour and reduced exploration (316). Hypoplasia of cerebellar lobules VI-VII was associated with reduced explorative behaviour. Moreover, stereotyped behaviour was inversely correlated with the area of vermal lobes VI-VII (316). Interestingly, measures of stereotyped behaviour correlated positively with frontal lobe volume. Thus, the behavioural impairments in autism (e.g., stereotypies and reduced exploration) may relate to cerebellar-frontal lobe dysfunction.

Several lines of evidence link dysfunctionality of the cerebellothalamocortical circuit to the cognitive and affective symptoms associated with ASD (74, 75, 291, 327). First, as Purkinje cells are the main output cells of the cerebellum, degeneration and loss of Purkinje cells seriously impairs cerebello-thalamo-cortical communication. That is, a reduction in the number of Purkinje cells is anticipated to result in a disinhibition of the DCN which in turn leads to increased excitatory output to the thalamus with a concomitant increase in thalamocortical output (328, 329). Recently, functional magnetic resonance imaging (fMRI) supported the hypothesis of increased thalamocortical output in autism (330).

The wide variety of clinical symptoms in ASD can thus in part be explained by

impaired frontal cortical functioning together with disruption of cerebellar connectivity. Both the frontal cortex and the cerebellum are thought of as brain areas integrating and fine-tuning information processing streams. It has, for instance, been suggested that the orbitofrontal cortex integrates limbic signalling into appropriate emotional behaviour whereas the dorsolateral prefrontal cortex is involved in the organization of information and facilitation of a response (331). Courchesne and Pierce (332) suggested that in autism the frontal cortex may not respond to processing from other cognitive networks (for details see Rubenstein and Merzenich (333)). That is to say, in autism the frontal cortex appears to be functionally disconnected (334). Similarly, the cerebellum may also be functionally disconnected since the decreased number of Purkinje cells impairs cerebellar functioning and output. In ASD, therefore, cerebellar malfunction may lead to a loss of modulatory control of the frontal cortex (335) and, as a corollary, fragmented neuronal processing.

Schizophrenia

In schizophrenia the larger part of structural and functional imaging data (336-339) supports cerebellar malfunction as does clinical evidence (340-342) (see Table 2.).

Table 2.

Study	Methods	Findings
(336)	CT scan	Vermal atrophy in 43.5% of patients; atrophy correlated with general psychopathology
(337)	Volumetric MRI	Patients demonstrated smaller cerebellar vermis
(339)	Volumetric MRI	Volume vermis significantly reduced; reduction correlated with Brief Psychiatric Rating Scale for Depression and Paranoia
(338)	Volumetric MRI	Patients showed smaller posterior superior vermis
(341)	Assessment of clinical symptoms of cerebellar dysfunction	High prevalence of dysdiadochokinesia and impaired stance and gait among schizophrenic patients

(342)	Assessment of clinical, cognitive and anatomic signs of cerebellar dysfunction	Higher incidence of impaired stance and gait among schizophrenic patients; presence of cerebellar dysfunction correlated with severity of negative symptoms, poorer cognitive perfor-
(340)	Assessment of Cerebellar Soft Signs (CSS) and Other Neurological Soft Signs (ONSS) in schizophrenia patients.	CSS total score and two subscores correlated with negative syndrome score
(343)	Volumetric MRI and assessment of Neurological Soft Signs.	Patients had smaller cerebellar hemispheres. Neurological Soft Signs correlated with reduction in cerebellar tissue. No correlations between cerebellar volume and psychopathological measures.
(344)	Structural MRI	No differences in cerebellar vermis were found between patients and controls.
(345)	Structural MRI	No significant size differences in posterior fossa structures.
(346)	PET scan during memory task	Patients show dysfunctional cerebellothalamocortical network during memory task
(347)	Measurement of NAA through proton magnetic resonance spectroscopic imaging (1H-MRSI)	Reduced NAA levels in anterior cerebellar vermis
(348)	1H-MRSI study	Patients showed lower NAA levels in cerebellar cortex and vermis
(349)	1H-MRSI study	Patients demonstrated with lower NAA levels in cerebellar cortex and vermis
(350)	Diffusion tensor imaging study	Patients showed neuronal disorganization in the superior peduncle.
(351)	fMRI during memory task	When compared with depressed patients, schizophrenic patients showed lower activation in the right cerebellum.

(352)	PET scan during assessment of pleasantness of images	Patients showed decreased cerebral blood flow (CBF) in subcortical structures including the ce-
(353)	Examination of emotional response through fMRI	Patients showed decreased activation of emotional network including the cerebellum
(354)	fMRI during presentation of sad and neutral film excerpts.	Schizophrenia patients with blunted affect showed significant activation of the cerebellum
(355)	Visual vigilance task during fMRI	Patients showed decreased response in a multitude of brain areas including the left cerebellum
(356)	Assessment of effects of rivastigmine during a sustained attention task using fMRI	Rivastigmine increased cerebellar activity and influenced task performance
(357)	fMRI during auditory oddball task	Patients show diffuse hypoactive network including the cerebellum

Cerebellar studies in schizophrenia. Abbreviations: fMRI = functional magnetic resonance imaging, PET = positron emission tomography, CT = computerized tomography

For example, first episode schizophrenia patients have been found to have smaller bilateral cerebellar volumes as compared to with controls (343). Some of the early magnetic resonance imaging (MRI) studies, however, have not reported these findings (344, 345, 358). One of the first studies to stress the importance of a dysfunctional cerebellar circuitry in schizophrenia was a positron emission tomography (PET) study (346). The authors examined memory performance in schizophrenic patients. The authors argued that reduced perfusion could cause poor performance on the memory task. However, poor performance could also lead to reduced blood flow. Therefore, two tasks were used, namely an easy and a relatively difficult one. While patients with schizophrenia showed normal performance on the practiced memory task they already demonstrated decreased blood flow in the cerebellothalamocortical pathway. By contrast, in the relatively more difficult memory task, schizophrenic patients performed worse than healthy controls and displayed significantly lowered frontal and cerebellar blood flow (346).

Consistent with the assumed disruption of the cerebellothalamocortical pathway in schizophrenia is evidence from two proton magnetic resonance spectroscopic imaging (H-MRSI) studies. Lower levels of N-acetylaspartate (NAA), a marker for neuron density

and viability, were found in the thalamus and cerebellar vermis (347) in patients with schizophrenia. In keeping with these findings, lower NAA levels in the vermis and cerebellar cortex have also been found (348) as well as in mediodorsal region of the thalamus (359). In addition, poor executive functioning in patients with schizophrenia was associated with volumetric reductions in the cerebellothalamocortical network (349). Moreover, a diffusion tensor imaging (DTI) study has shown that patients with schizophrenia demonstrate neuronal disorganization in the superior peduncle with neuronal disorganization being associated with poor cognitive performance (350). Finally, impaired working memory in schizophrenia is related to lower activation in the left inferior frontal cortex and right cerebellum, even when compared to working memory performance in depressed patients. (351). In addition to this effect, impaired working memory in schizophrenia is associated with over and underactivation along the cerebellothalamocortical pathway with underactivation of the left DLPFC and right cerebellum and overactivation of the left cerebellum (360).

However, an important potential confound when considering the role of the cerebellum in schizophrenia relates to dopaminergic neurotransmission. First, the cerebellum receives dopaminergic innervation (361) originating for instance from the ventral tegmental area suggesting limbic influences on cerebro-cerebellar loops (361). Consequently, as dopaminergic neurotransmission may be abnormally active in schizophrenia, it would be also be predicted that cerebellar activity, and as a corollary, cerebellar inhibitory output would also be rendered dysfunctional. Second, the cerebellum has been shown to have dysfunctional inhibitory Purkinje cells output in schizophrenia (362) which may result in increased frontal dopaminergic neurotransmission in schizophrenia (363). Taken together, these factors suggest that physiological of pharmacological alteration of dopaminergic neurotransmission may potentially confound studies examining cerebellar functioning in this disorder.

Cerebellar involvement in schizophrenia remains a subject of ongoing debate. In a recent comprehensive review on cerebellar involvement in motor, cognitive and affective functioning in schizophrenia, it was shown that motor impairments in schizophrenia are related to cerebellar malfunction. Moreover, it was postulated that there is thus far no compelling evidence for cognitive and affective impairments as a result of cerebellar dysfunction (364). However, several studies report that the cerebellum is indeed involved

in cognitive (355-357) and affective (353, 354, 365) impairments. These disparities are likely to arise out of the fact that there are only a limited number of studies investigating cerebellar involvement in cognitive and affective functioning in schizophrenia. The vital question is what conclusions should be drawn from these studies. That is, there are clearly too few studies to provide persuasive support for cerebellar involvement in cognitive and emotive dysfunction in schizophrenia, though stating that there is no evidence for cerebellar involvement in cognitive and affective impairment (364) may not be completely accurate.

Mood and anxiety disorders

Major depressive disorder

Major depressive disorder (MDD) is a mood disorder with an estimated life-time prevalence of approximately 25% (366). MDD presents with both affective (e.g., anhedonia, anergy and self-loathing) and cognitive (e.g., deficient working memory, impaired executive function) symptoms. Several neurobehavioural studies have linked MDD with abnormal cerebellar function (367, 368) (see Table 3.). These studies provide indirect evidence, relying on behavioural tasks that are closely linked to cerebellar activity. For example, oculomotor performance that is associated, in part, with cerebellar functioning (369) has been shown to be impaired in MDD (367, 368). These patients typically present with less accurate spatial memory, impairments in visually guided saccades and increased rates of saccadic intrusions during visual fixation (367).

Other lines of evidence also imply a role for the cerebellum in mood and affect. For example, electrical stimulation of the cerebellar vermis in rats increases noradrenergic and dopaminergic activity in the nucleus accumbens (370). Thus, the cerebellar vermis might exert its influence on emotional behaviour through modulation of dopaminergic and noradrenergic neurotransmission in the mesolimbic reward pathway (371). In addition, neuroanatomical studies comparing posterior fossa structures of MDD patients to healthy controls have found smaller brainstem and cerebellar vermal volumes in patients (372). As previously discussed, these structures are closely linked to a circuit including the right DLPFC, anterior cingulate gyrus, left superior temporal lobe and the cerebellum (373). Possibly, abnormal function of the anterior cingulate cortex in MDD (374-376) may in part be influenced by abnormal cerebellar functioning given its connections with the

cerebellum (74).

A recent meta-analysis (377) in which imaging studies in depressed patients were analyzed reported a complicated pattern of brain networks involved in this disorder. The first network is comprised of several cortical regions including the dorsal/pregenual anterior cingulate, bilateral middle frontal gyrus (dorsolateral prefrontal cortex (DLPFC)), insula and the superior temporal gyrus (377) and is mostly likely related to the cognitive deficits in MDD. Another dysfunctional network consisted of hyperactive cortical-limbic areas including medial and inferior frontal cortex, the basal ganglia, as well as amygdala and thalamic involvement (377). Further, abnormal cerebellar function was also reported. That is, in MDD resting anterior cerebellar activity was increased whereas posterior cerebellar activity was reduced (377).

Bipolar disorder

One of the few MRI studies on cerebellar involvement in bipolar disorder (378) reported smaller vermal V3 area in multi-episode bipolar patients when compared with first episode and healthy controls. This difference remained significant even when corrected for substance abuse (substance abuse disorders are frequently comorbid with bipolar disorder, though overdiagnosis might occur (379)). The relationship between the cerebellum and bipolar disorders should however be taken with caution. Bipolar disorder is often found to be comorbid with the abuse of alcohol and marijuana and may be a confounding factor when investigating the relationship between the cerebellum and bipolar disorder. Several lines of evidence suggest that both alcohol and the active compound in marijuana, tetrahydrocannabinol (THC), directly target the cerebellum. First, alcohol influences cerebellar function through actions on GABA and NMDA receptors (380) and long-term abuse can lead to cerebellar degeneration (381). Second, the cerebellum has the highest density of THC binding sites (382, 383). For example, cannabis negatively influences learning abilities thought to depend on cerebellar activity, e.g., conditioned eye-blink response (382). Therefore, comorbid substance abuse disorders might confound research on the cerebellum in bipolar disorder which could lead to the false assumption that abnormal cerebellar functioning is implicated in the pathophysiology of bipolar disorder.
A recent study (384) replicated the findings on vermal V3 area and found also smaller V2 areas in multi-episode patients when compared with first episode patients (see Table 3.).

These data suggest that the vermis might be subject to atrophy during the course of bipolar disorder. Another study by this group showed increased cerebellar volumes bilaterally (385). However, increased volumes in the left thalamus and elevations in anterior cingulate cortex gray matter density were also demonstrated (385). Evidence has been provided that reported that bipolar I patients showed larger left temporal lobes than bipolar II patients and controls suggesting that including both bipolar I and II diagnosed patients into one sample might seriously confound previous findings (386). Finally, mood disorders have been linked to impairments in a proposed network consisting of anterior limbic brain structures (e.g., prefrontal cortex, the thalamus, the limbic system and the cerebellum) (387), wherein cerebellum, together with the prefrontal cortex, exerts a modulatory influence on mood (387).

In sum, evidence suggests the cerebellum appears to play a larger role in bipolar disorder than in MDD. This is only partly due to concomitant substance abuse disorders though evidence is preliminary.

Table 3.

Study	Methods	Finding
(367)	Depressed patients were tested with a test battery thought to recruit cerebellar activity	Poor performance on these neurobehavioural tasks was associated with depression
(368)	Assessment of eye blink classical conditioning in depressed patients (EBCC)	Depression impairs EBCC which suggests cerebellar involvement
(377)	Meta-analysis in depression	Increased anterior cerebellar lobe activity and decreased posterior lobe activity in depressed patients
(378)	Volumetric MRI in bipolar patients	Cerebellar vermal lobule 3 was significantly smaller in multi-episode bipolar patients
(384)	Volumetric MRI in bipolar patients	Cerebellar vermal area 2 and 3 were smaller in multi-episode patients than in healthy controls. Vermal area 2 was also smaller in multi-episode patients than in first-episode patients
(385)	Volumetric MRI	Multiple brain abnormalities including increased volume in the cerebellum bilaterally.

(387)	Volumetric MRI	The cerebellum may play a role in affective disorders together with other brain regions

Cerebellar studies in mood disorders. Abbreviations: fMRI = functional magnetic resonance imaging, PET = positron emission tomography, CT = computerized tomography

Anxiety disorders

Perhaps the most compelling evidence for the role of the cerebellum in anxiety disorders is the finding of cerebellar-vestibular dysfunction. In a large study, patients with varying anxiety disorders were screened neurologically for cerebellar-vestibular dysfunction (e.g., imbalance, dyscoordination, impaired proprioception, sensory overload) (388). Of the total sample, 94% had cerebellar-vestibular dysfunction (388). Levinson suggests, therefore, that cerebellar-vestibular dysfunction might be an underlying factor in anxiety disorders.

Posttraumatic stress disorder

Investigation of the structural volumes of the cerebellar hemispheres in pediatric maltreatment-related posttraumatic stress disorder (PTSD) has shown that maltreated children and adolescents with PTSD had significantly smaller posterior fossa volumes than healthy controls (389). However, age-matched non-maltreated subjects with generalised anxiety disorder (GAD) did not show smaller posterior fossa volumes than healthy controls. Moreover, in a more recent study no relationship between PTSD and the cerebellum was reported (390). Since the vermis is linked to brain processes related to mood emotion vermal size was examined in adult monozygotic twins of which one of the two was exposed to military combat. Though vermis size was highly correlated between twins, combat exposure did not influence vermal size (390). Another study however demonstrated that adult trauma survivors with PTSD presented with significantly higher blood flow in the cerebellum (391) (see Table 4.). Therefore, for adult PTSD patients evidence is preliminary and currently inconclusive. Furthermore, it remains possible that early childhood trauma affects cerebellar development. In fact, the cerebellum develops up until two years after birth and is highly vulnerable to external stressors including malnutrition (392, 393) and toxicity (394).

Obsessive compulsive disorder

Research has linked obsessive compulsive disorder (OCD) with gray matter reduction in the medial frontal gyrus, orbitofrontal cortex and the left insulo-opercular region (395). Gray matter elevations however have also been related to OCD albeit in different brain regions: bilateral putamen and the anterior cerebellum (395). Moreover, since the striatum and the anterior cerebellum are structurally connected (285, 396) the cerebellum might be implicated in OCD pathology (395). Another imaging study also reported cerebellar abnormalities in OCD (397). However, in contrast to the these findings gray matter reductions in the left cerebellum and left cuneus (397) have also been found. Thus, at present there is evidence for cerebellar involvement in OCD but it should currently be regarded as preliminary.

Panic disorder

Panic disorder has also been associated with cerebellar abnormalities. Unlike other anxiety disorders panic disorders are most likely mediated by phylogenetically older and more primitive brain structures such as the brainstem and limbic system (398). Indeed, fear-like behaviour is frequently related to a variety of subcortical structures (49). Sacchetti et al. (399, 400) have shown that in rats the amygdala and cerebellum are key structures in fear conditioning. Adaptive emotional behaviour such as fear learning relies heavily on amygdala and cerebellar activity. Without these structures rats show amnesia for previously administered aversive stimuli (399). Interestingly, however, fear learning is conserved when the amygdala is inactivated, a phenomenon which, according to Sacchetti and colleagues, may be entirely attributable to the cerebellum (399). Thus animal research suggests cerebellar involvement in memory, specifically a phylogenetically old and fairly primitive memory system and second, involvement in adaptive emotional behaviour (399). Analogous to animal research, research in humans has also reported a fear network that is hyperactive in unmedicated panic disorder patients (401). This network partly includes the same structures: bilateral amygdala, hippocampus, and thalamus, and in the midbrain, caudal pons, medulla and cerebellum (401). Moreover, cognitive-behavioural therapy in panic disorder patients significantly reduces activation in parts of this network (402) suggesting that this subcategory of anxiety disorders relies partially on cerebellar dysfunction.

Table 4.

Study	Methods	Finding
(388)	Neurological and electronystagmographic (EMG) examinations of patients with anxiety disorders	Of the total sample 94% presented with cerebellar-vestibulo dysfunction
(389)	Anatomical MRI in pediatric PTSD patients, GAD patients and healthy controls	Left, right and total cerebellar volume was significantly smaller in PTSD patients than in GAD patients and healthy controls
(390)	MRI in combat-exposed PTSD patients	No significant differences between patients and controls
(391)	SPECT and MRI in PTSD trauma survivors	Regional cerebral blood flow was significantly higher in patients than in controls, specifically in the cerebellum
(395)	Volumetric MRI in OCD patients and healthy controls	Multitude of volumetric brain changes including gray matter elevations in the anterior cerebellum bilaterally
(397)	Structural MRI in OCD patients and controls	Multiple brain abnormalities with gray matter reductions in the left cerebellum
(399)	Fear conditioning experiment in rats	Adaptive emotional behaviour is dependent on both amygdala and cerebellum activity
(401)	PET in panic disorder patients and controls	Patients showed hyperactivated network including cerebellum
(402)	PET in panic disorder patients before and after cognitive-behavioural therapy	Cognitive-behavioural therapy decreased activity in a previously hyperactivated network including the cerebellum

Cerebellar studies in anxiety disorders. Abbreviations: fMRI = functional magnetic resonance imaging, PET = positron emission tomography, CT = computerized tomography

Attention Deficit/Hyperactivity Disorder

A psychiatric disorder that has recently been linked to cerebellar dysfunction is attention deficit/hyperactivity disorder (ADHD). Individuals with this disorder experience hyperactivity and the inability to focus with subsequent problems at school or work (403). The neurobiological underpinnings of this disorder are not fully understood but evidence suggests noradrenalin (NA) and dopamine (DA) dysfunction (404). In addition, structural brain abnormalities including reduced volumes, in the fronto-striato-cerebellar network

have been found (405). For example, a recent meta-analysis identified global reductions in volume in the right cerebral cortex, cerebellum, and splenium of the corpus callosum (406). Among these structures the cerebellar and cerebral abnormalities have been found to persist with aging patients (407). Possibly, cerebellar and frontal cerebral function may be altered by catecholamine actions since both noradrenalin and dopamine innervate the cerebellum and association cortices (408).

A recent treatment study in ADHD also showed underactivation of the dorsal ACC prior to methylphenidate treatment. After six weeks of drug treatment, activity of the ACC significantly increased (409). In addition, the caudate nucleus, premotor cortex, thalamus and cerebellum also showed increased activation in response to ongoing methylphenidate treatment (409). Other studies also highlighted a dysfunctional fronto-striato-cerebellar network which normalizes after methylphenidate treatment (410). Again, elevated cerebellar activity was found suggesting changes in fronto-striato-cerebellar circuitry (410) which may underlie the behavioural improvements in response to methylphenidate.

Towards a synthesis

Collectively these findings suggest cerebellar contributions to cognitive and affective functioning and cerebellar involvement in the pathogenesis of several neuropsychiatric disorders. Obviously, specific clinical descriptions require specific underlying neurophysiological underpinnings. Since the cerebellum has such wide connections with the limbic system and cortex it is highly likely that the cerebellum plays some role in the pathophysiology of neuropsychiatric disorders. On the other hand this feature makes it hard to disentangle specific cerebellar contributions to individual neuropsychiatric disorders. For example, in schizophrenia it has been proposed that a dysfunctional cerebellum and a subsequent malfunctioning cerebellothalamocortical pathway plays a role in the deregulation of information which characterizes schizophrenia (411). Disruption of this pathway is also evident in ASD which could explain the cognitive deficits in ASD; severity of disruption of this pathway might even correlate with severity of cognitive deficits. However, in mood and anxiety disorders this pathway has not yet been proven to be severely disrupted. MDD is associated with a multitude of interconnected cortical brain areas that are abnormally active (377). Therefore, the cerebellum is unmistakably involved (377) though how, and to what extent, remains unclear. In healthy controls positive affect,

which is completely absent in MDD, has been argued to reside in subcortical systems (412). It has also been suggested that the vermis is highly involved within this subcortical limbic system (71). A recent meta-analysis on imaging studies in MDD has provided evidence that the cerebellum together with limbic structures is hyperactive and hyperresponsive to negative and positive emotions in depression (377). Here it is proposed that cerebellar

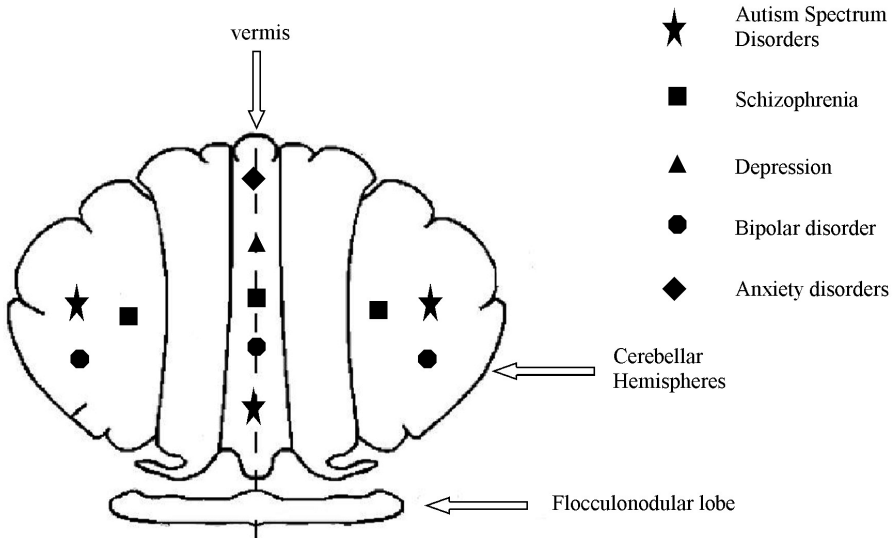


Figure 2. A schematic representation of the cerebellum and its mental disorders. Note the high prevalence of the vermis in neuropsychiatric disorders. However, this could be partly due to relative difficulties in structural imaging studies in parcellating the lateral cerebellum into saggital slices.

involvement in MDD is most likely confined to the affective deficits. The cognitive impairments associated with MDD are suggested to have a cortical origin and are secondary to subcortical hyperactivity that may result from reduced cerebellar modulatory function. One important point concerning several of the aforementioned imaging studies is the use of the cerebellum as a reference region in PET studies. Schutter and van Honk (413) have suggested that as the role of the cerebellum was conventionally linked to motor behaviour, it was frequently used as a reference region in blood flow imaging studies and, as a result, it is possible that cerebellar involvement in psychiatric disorders has been largely overlooked. It has been argued, therefore, that future PET studies must consider cerebellar activity in functional imaging studies rather than using it as a reference region.

While the majority of the aforementioned studies highlight the role of the cerebellum in neuropsychiatric disorders they are limited to anatomical studies which convey little information regarding the functional connectivity between the cerebellum and other cerebral structures. Moreover, functional imaging studies, while providing important information regarding coactivation of a variety of CNS structures during specific tasks, are limited by the fact that activation of these structures are merely associative and provide only indirect evidence suggesting functional connectivity between regions. Recently transcranial magnetic stimulation (TMS) has been introduced as a neurophysiological tool which applies magnetic pulses to directly study both cerebellar function and cerebellothalamocortical connectivity (248). TMS can provide direct evidence for cerebellar activity in neuropsychiatric disorders as well as having a prominent role in treatment. The following sections will highlight such studies.

Cerebellar TMS and neuropsychiatric disorders

Due to the fact that TMS is a relatively new technique only few studies have examined cerebellar involvement in neuropsychiatric disorders through this technique. Thus far TMS has been used to reveal impairments in cortical activity in schizophrenia (196, 414) and bipolar disorder (197). Moreover, rTMS treatment in MDD ((415, 416) and in auditory hallucinations in schizophrenia (417) has been reported to be effective. Given the fact that the cerebellum is becoming more widely acknowledged as being involved in higher order functioning, TMS might serve as a means to further elucidate the contributions of the cerebellum to neuropsychiatric disorders.

However, before venturing further into TMS studies in cerebellar function some TMS limitations should be noted. Although TMS is non-invasive, TMS can only provide direct functional and mechanistic insights into the cerebral and cerebellar cortex. Furthermore, the study of cerebello-cortical interactions with TMS has been limited to the modulatory effects of the cerebellum on the motor cortex. However, recent interleaved TMS-EEG studies have provided evidence that the physiological effects of motor cortex TMS are quite similar to the effects of prefrontal cortex TMS (85). These findings indicate generalisability of motor cortical TMS.

Cerebello-thalamo-cortical connectivity

One specific TMS paradigm has been developed to study the functional connectivity between the cerebellum and the cerebral cortex. This involves stimulating the cerebellum using a conditioning stimulus approximately 5 msec prior to motor cortical stimulation with a test stimulus and can be used to assess the inhibitory influence of the cerebellum on the cortex (i.e., cerebellar inhibition (CBI) (418). On average the conditioning stimulus over the cerebellum attenuates the motor evoked potential (MEP) produced by motor cortical stimulation by about 50% (419). Cerebellar stimulation is thought to activate Purkinje cells which, in turn, inhibit the excitatory output from the dentate nucleus to the thalamus (see Figure 2a,b). This in turn leads to inhibition of the thalamocortical pathway. Thalamocortical fibers terminate on both inhibitory interneurons and pyramidal cells (420). Stimulation of the cerebellum, therefore, results in inhibition of the pyramidal cells in the motor cortex which manifests as an attenuated MEP. However, applying a conditioning pulse over the cerebellum also affects cortical inhibitory interneurons. By combining paired pulse paradigms to study cerebello-cortical interactions evidence has been found that cerebellar stimulation reduced local cortical inhibitory activity (248). The most likely explanation for this phenomenon is that cerebellar stimulation reduces thalamocortical facilitation of cortical inhibitory interneurons (248).

As opposed to activating the cerebellum with TMS, cerebellar degeneration is characterised by decreased cerebellar function and should have an opposite effect. Decreased function of the cerebellum is anticipated to result in reduced inhibitory output by Purkinje cells which, in turn, would be associated with increased thalamocortical activity. Therefore, cerebellar degeneration paradoxically also leads to increased cortical inhibition. Nonetheless, opposite patterns have also been observed (421, 422). Possibly, cerebellar degeneration might affect both Purkinje cells and the deep cerebellar nuclei which would have differential effects on motor cortex excitability. Most importantly, both activation and degeneration of the cerebellum cause changes in the frontal cortex though the precise mechanism by which this occurs remain to be elucidated.

One limitation that applies to the suggestions for cerebellar rTMS in neuropsychiatric disorders needs to be considered here. The conditioning pulse over the cerebellum in CBI is usually applied with a double cone coil whereas cerebellar rTMS studies use a figure of eight coil (248, 362, 418, 423). The double cone coil activates the cerebellothalamocortical pathway and it remains to be established whether the flat figure of eight coil activates

such pathways in a similar way.

Below we will review studies that have evaluated TMS in psychiatric conditions consistent with those previously discussed. Where possible we will discuss TMS cerebellar findings directly. However, while such work is still in its infancy discussion will also centre on the potential use of both paired and repetitive TMS as a possible neuroinvestigational and treatment tool.

Autism

It has been suggested that TMS be used to clarify cognitive dysfunction in autism (424). In addition it has been proposed that repetitive transcranial magnetic stimulation (rTMS) be used as a treatment tool in ASD (425). To our knowledge, no TMS studies have been published yet in autistic subjects. However, given the plethora of evidence for cerebellar dysfunction in ASD, we propose TMS may be used to evaluate cerebellar function and cerebellothalamocortical connectivity in subjects with ASD.

It has been suggested that rTMS might be effective in autism for several reasons (425). There is some evidence (426, 427) that rTMS is a successful treatment in catatonia and since autism is closely associated clinically with catatonia this has led to the idea that rTMS could be a possible treatment tool in autism (425). Moreover, animal research has shown that chronic rTMS (applied over the vertex) modulates serotonergic activity (425). Hypothetically, rTMS could normalize abnormal serotonergic neurotransmission in autistic subjects. However, two factors argue against this possibility. First, the intuitive link between catatonia and autism is questionable since the phenotype of autism spectrum disorders is quite heterogeneous. Second, finding a suitable stimulation site in order to modulate serotonergic neurotransmission might not prove to be so straightforward. Therefore, advocating cerebellar rTMS appears to be preliminary and is not yet supported by substantial evidence.

Schizophrenia

Cerebellar function in schizophrenia has been directly measured with TMS. Patients with schizophrenia demonstrated a 29.8% reduction in CBI compared to healthy subjects (Daskalakis et al. 2005). The authors provide two possible explanations for this finding. First, the reduction in CBI could be the result of abnormal cerebellar inhibitory output

which is one possible explanation since a reduction in number of Purkinje cells has been established in schizophrenia (428). Second, impaired CBI could also reflect a disruptive cerebellothalamocortical pathway. Unfortunately, the TMS CBI paradigm does not allow for disentanglement of these options though it shows that CBI is disrupted in schizophrenia.
In schizophrenia cerebral interhemispheric connectivity has been found to be dysfunctional (24, 196). Moreover, the cerebellum has been shown to affect cerebral intracortical processing, including local GABAergic inhibitory neurotransmission (248). Furthermore, Fitzgerald et al. (24) have suggested that dysfunctional cerebral interhemispheric connectivity is most likely due to local inhibitory abnormalities and not to corpus callosum ones. It is possible, therefore, that interhemispheric connectivity is rendered dysfunctional by abnormal cerebellar modulation of intra-cerebral transfer of information.

Mood and anxiety disorders

Electrophysiological data link theta frequency oscillations with the septo-hippocampal complex which is thought to be involved in emotion and memory (429). Research has shown that theta activity is associated with reduced anxiety and increased approach behaviour (430). Recently, Schutter and van Honk (430) showed that single-pulse TMS over the vermis increases frontal theta-activity. This finding underscored the importance of the cerebellar vermis in human emotional functions. However, this study only used single pulse TMS. In order to investigate the role of the cerebellar vermis in subconscious responses to emotional stimuli more thoroughly, high frequency rTMS was applied in a sham and occipital stimulation controlled within subjects design (Schutter, Enter et al., in revision). Again, the vermis was targeted. Results showed that exclusively after medial cerebellar stimulation participants showed significant increased emotional responses to happy facial expressions. Interestingly, these findings concur with pharmacological studies. It has been repeatedly shown that administration of antidepressants to healthy volunteers yields subconscious changes in attentional bias towards positive stimuli (431). In MDD it has been found that these subconscious changes precede consciously experienced improvements in mood. In short, this study suggests cerebellar involvement in mood and emotion and second, advocates the cerebellum as an alternative target location for rTMS treatment in MDD (413).

Future Directions

TMS has not yet been widely used in neuropsychiatric disorders, and its use to evaluate cerebellar function in these disorders is still developing. Here we will attempt to generate some hypotheses and suggest future TMS experiments.

Autism

Research in the autism field may benefit from the unique possibilities TMS offers. First, intactness of the cerebellothalamocortical tract should be indexed through CBI. Second, autism may be associated with a cortical imbalance between excitatory and inhibitory processes which is of pivotal importance in the effectiveness of rTMS (333). According to this model ASD is characterized by a hyperexcitable state of the cerebral cortex which may be associated with more 'neuronal noise' and over-representation of stimuli. Consequently, this could theoretically explain the aversive reactions autistic patients show to sensory stimulation (333). This theory can be readily evaluated in-vivo through TMS. That is, hyperexcitability of the cortex should be accompanied by a decrease in cortical inhibition. Moreover, reduced cortical inhibition would also be congruent with frequently reported lower levels of GABA in autism (432). Also, though highly speculative there is some evidence for potential therapeutic use of rTMS in autism. Recently, high frequency rTMS has been used in epileptic patients and has been shown to temporary decrease seizure frequency (433). Interestingly, the authors stimulated the cerebellar hemispheres. While the exact mechanisms are unknown, the authors suggest that cerebellar rTMS might have decreased cerebral cortical excitability. Given the aforementioned theory of a hyperexcitable cortex in autism and the high incidence of epilepsy in ASD, cerebellar rTMS treatment may prove to be beneficial for autistic individuals.

Schizophrenia

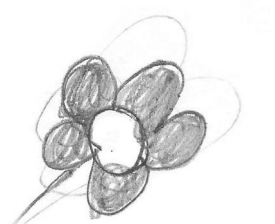
In schizophrenia there is also some preliminary evidence suggesting possibly beneficial effects of cerebellar rTMS in schizophrenia. First, there is quite a large body of date showing dopaminergic dysfunction in schizophrenia (434, 435). Dopamine dysregulation in schizophrenia may be associated with deficits in working memory, reward and motivation (435). As cerebellar stimulation results in changes in dopaminergic neurotransmission (363, 436) slow cerebellar vermal rTMS might readjust dopaminergic transmission in schizophrenic patients.

Major depressive disorder

As noted earlier cerebellar TMS induced changes in attentional bias coincide with early effects of antidepressants. At present, cerebellar stimulation in depressed patients appears promising. Moreover since rTMS applied over the prefrontal cortex has yielded significant but clinically modest effects the cerebellar vermis should be considered as an alternative location for rTMS in the treatment of depression.

Conclusions

Research evaluating the role of the cerebellum in neuropsychiatric disorders is clearly in its infancy. When compared to the vast number of studies that address the role of the cortex in neuropsychiatric disorders, the number of studies evaluating cerebellar involvement is quite small. It is therefore tempting to conclude that support for cerebellar contributions to cognitive and affective behaviour is lacking. However, what these studies do suggest is that the cerebellum is indeed involved in the pathophysiology of the several aforementioned disorders (299, 342, 377, 388, 437, 438). More research, however, is necessary to explicate the specific role of the cerebellum in these disorders. Since the cerebellum possesses locality of function (74) differential contributions of different parts of the cerebellum to cognition, emotion and its disorders warrant further research.



§4.2

Fast frequency repetitive transcranial magnetic stimulation to the cerebellum increases subliminal emotional responses to happy facial expressions

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Abstract

Previous research has demonstrated that the cerebellum is involved in emotive and cognitive processes. Furthermore, recent findings suggest high-frequency repetitive transcranial magnetic stimulation (rTMS) to the cerebellum has mood-improving properties. We sought to further explore the effects of cerebellar high-frequency rTMS on implicit processing of emotional stimuli and mood. In a double-blind, crossover study, 15 healthy volunteers received 15 minutes of 20 Hz (5 s on, 5 s off) rTMS over the medial cerebellum, occipital cortex or sham in a randomized counterbalanced order on 3 consecutive days. A masked emotional faces response task measured implicit emotional processing of happy, fearful and neutral facial expressions. We used positive and negative affect scales to evaluate rTMS-related changes in mood. High-frequency rTMS over the cerebellum was associated with significant increases in masked emotional responses to happy facial expressions only. We observed no changes in consciously experienced mood. Although the sham rTMS served as our baseline measurement, additional pre-rTMS data showing that reaction time increases immediately after cerebellar rTMS would have made our results more compelling. The results replicate and extend previous findings by establishing a direct relation between the cerebellum and emotive information-processing. The parallel between the present effects of high-frequency cerebellar rTMS and short-term antidepressant therapy regarding the change in implicit processing of positive stimuli in the absence of mood changes is notable and warrants further research.

Introduction

The concept that the cerebellum is implicated in the experience and regulation of emotions and mood was posited more than half a century ago (439, 440) The first empirical report of cerebellar involvement in the experience of emotions included a study of a patient who underwent electrical stimulation of the dentate nucleus and superior peduncle and experienced negative feelings (441). The link between the cerebellum and emotions was further strengthened by the seminal work of Heath and colleagues (66, 442-444) demonstrating that chronic electrical stimulation of the superficial parts of vermis normalized behaviour in severely emotionally disturbed patients. A neuroanatomical basis for cerebellar involvement in emotive processes is grounded in the multiple direct and indirect connections of the cerebellum to limbic and cortical areas of the brain. Functional neuroimaging studies have also demonstrated consistent cerebellar activation during emotive processing and mood (445). One of the prevailing models proposes that the cerebellum functions as a "general-purpose modulator" in governing mental activities (for a review see Andreasen and colleagues (446)). Further evidence of a direct link between the human cerebellum and emotive processes has been provided by repetitive transcranial magnetic stimulation (rTMS) studies. In a previous study, it was shown that a single session of high frequency rTMS over the cerebellum had positive effects on mood in healthy volunteers (429). Interestingly, mood elevations often go accompanied by increased attention for implicit positive stimuli that can even occur before actual changes in mood (431). These changes in implicit attention for positive stimuli can, for instance, be evaluated by measuring reaction times to the colour naming of a mask that is preceded by a short (nonconscious) presentation of a happy facial expression (447). Increased emotional responsiveness for implicit positive stimuli would then result in longer reaction times to the colour naming of the mask preceded by a happy facial expression and allow researchers to gather insights into information processes associated with mood. Building on the previous high-frequency rTMS study, we recently showed that low-frequency rTMS to the medial part of the cerebellum in healthy volunteers impairs emotion regulation and augments negative mood (448) These findings are not only in accordance with the alleged opposite actions of high- and low-frequency stimulation parameters, but also demonstrate the modulatory effects of a single session of cerebellar rTMS on behaviour.

We conducted a sham and occipital cortex controlled, double-blind, crossover

study to further explore the effects of high-frequency rTMS over the cerebellum on emotive information processing and mood. In keeping with our previous findings, we hypothesized that a single session of high frequency cerebellar rTMS would increase self-reported positive mood and facilitate information-processing of positive emotional stimuli.

Methods

Participants

We enrolled healthy, nonsmoking young women in the study. We obtained written informed consent and paid the volunteers for their participation. The study was approved by the medical ethical committee of the Utrecht University in accordance with the declaration of Helsinki. All volunteers were unaware of the hypotheses being tested in the study.

Transcranial magnetic stimulation

We performed high-frequency rTMS using a biphasic magnetic brain stimulator (maximum output 2300 A peak /1750 VAC peak) with an iron core coil (Neotonus). Maximum magnetic field strength was 2 Tesla. We performed sham rTMS using an identical coil with a built-in aluminum plate directly underneath the iron core (Neotonus). The coil mimics the sound click and sensation of real TMS, but the brain is shielded from actual stimulation.

The masked emotional faces response task

The masked emotional faces response task requires participants to name the colour of the ink in which the mask is printed. Performance in terms of slowing down or speeding up colour naming varies as a function of the participant's motivational state and the rapid emotional face presentation (14 ms) prior to the mask (447). In this task, the motivational state of the individual is presumed to direct pre-attentive (automatic) reactions to the emotional facial expressions and influence the colour naming of the subsequent presentation of the mask (449, 450). Thus, slower colour naming of the masking stimulus following happy facial expressions is indicative of increased appetitive motivation and reward sensitivity, whereas the opposite holds for relatively faster colour naming (451). Figure 1 depicts the outline of the masked emotional faces response task.

The general idea of the task is that presenting emotional facial expressions outside conscious awareness prevents cognitive elaborative strategies and subsequently gains access into the core aspects of the individual's motivational stance. We used stimuli from Ekman and Friesen's Pictures of facial affect (452) and Lundqvist and colleagues' Karolinska directed emotional faces set (453). In the masked emotional faces response task, we displayed a fixation point for 750 ms, followed by a 14-ms presentation of a happy, fearful or neutral facial expression that we then replaced by a masking stimulus. Masking stimuli included randomly cut, reassembled and rephotographed pictures of faces.

We presented 30 happy, 30 fearful and 30 neutral faces in random order, and the inter-trial interval randomly varied between 1500 and 2500 ms. All stimuli (14 × 9 cm) were coloured either red, green or blue and projected in the centre of a 17-inch computer screen (70 Hz refresh rate) on a black background at a distance of 150 cm. We instructed participants to name the colour of the masking stimulus as fast as possible. For optimizing stress-related workload, we used a rapid externally paced version of the task with a termination of mask display after 300 ms (454). We used the reaction time as the dependent variable. To check for the absence of conscious awareness, we used a 3-alternative, forced-choice happy–fear–neutral recognition check (3AFC). We showed a random set of 60 masked facial expressions to each participant. Prior to the check, we explicitly told participants that the set contained 20 happy, 20, fearful and 20 neutral faces, and we instructed them to indicate whether the presented stimulus was a happy, fearful or neutral emotional expression by pushing 1, 2 or 3, respectively, on the keypad. We set the critical level of perceptual threshold at 26 correct trials, as indicated by a nonparametric binomial test ($n = 60$, test proportion = 0.33).

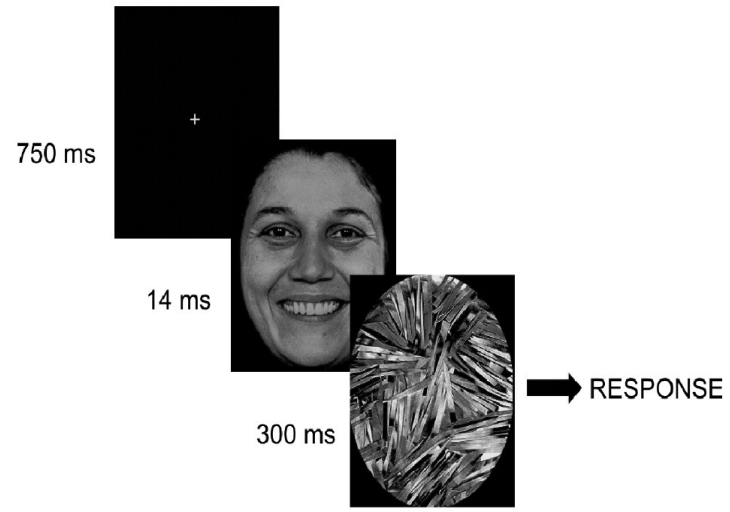

Figure 1. The masked emotional faces response task.

Self-reported mood questionnaire

We assessed consciously experienced mood using the positive and negative affect schedule (455). The questionnaire consisted of 20 items and visual analogue scales (0 = not at all, 100 = extremely).

Procedure

Participants received 15 minutes of 20 Hz rTMS (5 s on, 5 s off, 9000 pulses per session) over the midline cerebellum. Sham rTMS over the midline cerebellum and real rTMS over the occipital cortex served as the inactive and active control conditions, respectively. The current in the coil was directed downward to maximize cerebellar stimulation (418). We defined the midline cerebellum target site as the point located 1 cm below the inion (456, 457). The occipital cortex target site was located 3 cm above the inion. Stimulation intensity was 80% of the individual motor threshold. We randomized the order of sessions and counterbalanced it among participants. Sessions were 24 hours apart and controlled for daytime. Volunteers underwent 1 condition per session. Stimulation parameters were in accordance with the safety guidelines formulated by the International Federation of Clinical Neurophysiology (www.ifcn.info). On a separate day prior to the testing sessions, we used a safety-screening list to check for contraindications, and we assessed the health of all participants using a standard interview (149). In addition, we explained safety issues

and the experimental procedures to each participant and obtained informed consent. We assessed handedness using the Edinburgh handedness inventory (109), and we determined the average motor threshold of the left and right hemisphere using the 5-step motor threshold estimation procedure described by Schutter and van Honk (151). On testing days, we instructed participants to refrain from taking psychotropic substances, including alcohol, coffee, tea and chocolate, for 2 hours before the experiment. We administered the positive and negative affect schedule questionnaire immediately after high-frequency rTMS. Next, participants performed the masked emotional faces response task. Finally, at the end of the final session participants performed the 3AFC, and we debriefed them and paid them for participation.

Statistical analysis

We used a general linear model for repeated-measurements with 3 levels using cerebellar, occipital and sham rTMS as within-subject factors and order of rTMS conditions as the between-subject factor. We applied Greenhouse–Geisser correction (degrees of freedom > 1) to the p values and reported the ε. We performed post-hoc significance testing with simple paired-sample t tests. We set the α level of significance at ≤ 0.05, 2-tailed.

Results

Participants

All 15 participants were aged 18–22 (mean 20.4, standard deviation [SD] 1.9) years, right-handed (mean 45.9, SD 2.7, as per Edinburgh handedness inventory) and used oral contraceptives. The mean motor threshold of the left and right hemisphere was 57.7 (SD 10.0). None had a history of psychiatric or neurologic conditions, and all had normal or corrected-to-normal vision.

Procedure

TMS was well tolerated and, although some participants noticed differences in sensation between the sessions, blinding was effective because participants were not able to separate the experimental from the control conditions when interviewed. None of the volunteers passed the masked emotional faces awareness check criterion, and we enetered data on all 15 participants in the statistical analyses. We observed a significant main effect

of rTMS on reaction times to masked happy facial expressions ($F_{2,18} = 4.23$, $p = 0.032$, $\varepsilon = 0.99$); however, we observed no significant effect of the order of conditions ($F_{10,10} = 1.16$, $p = 0.37$, $\varepsilon = 0.99$). Post-hoc paired-samples t tests revealed that reaction times were significantly increased after cerebellar compared with sham ($t_{14} = 2.5$, $p = 0.021$) and occipital cortex rTMS ($t_{14} = 2.3$, $p = 0.037$). Reaction times between the sham and occipital rTMS condition did not statistically differ ($t_{14} = 0.18$, $p = 0.86$). We observed no main effects of rTMS on reaction times for the masked neutral ($F_{2,18} = 1.36$, $p = 0.28$, $\varepsilon = 0.85$) and fearful facial expressions ($F_{2,18} = 1.67$: $p = 0.22$, $\varepsilon = 0.69$). We found no order effects of TMS in the masked neutral and fearful facial expressions ($p > 0.36$). Figure 2 shows the mean and standard error of the mean colour naming reaction times to masked facial expressions for the rTMS conditions. Our repeated-measures multivariate analysis of variance did not yield significant differences between the rTMS conditions on positive ($F_{2,18} = 0.31$, $p = 0.68$, $\varepsilon = 0.75$) and negative mood scores ($F_{2,18} = 0.10$, $p = 0.90$, $\varepsilon = 0.98$). We observed no significant order effects of TMS in the mood scores (both p values > 0.38).

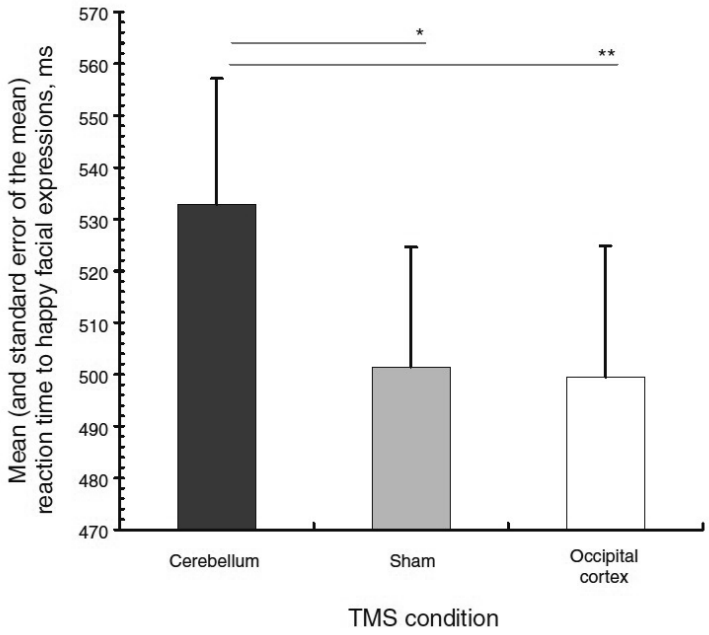

Figure 2. Mean and standard-error of the mean reaction times (in ms) showing increased emotional responses to non-conscious happy facial expressions after 15 minutes of fast frequency rTMS over the cerebellum. (Cbl: cerebellum, Shm: sham, Occ: occiput; * $p = 0.021$, ** $p = 0.037$.)

Discussion

Our goal was to examine the effects of high-frequency rTMS over the cerebellum on responses to masked emotional facial expressions and consciously experienced mood. Results showed that cerebellar rTMS, compared with occipital cortex and sham rTMS, resulted in the enhanced implicit processing of happy facial expressions without changes in self-reported mood. Our findings concur with those of pharmacological studies that found selective increases in implicit processing of positive emotional material, but no changes in consciously experienced mood related to antidepressant therapy in healthy non-depressed volunteers (431, 458, 459). Furthermore, our results are in agreement with findings of increased attentional biases (i.e., slower reaction times) to happy facial expressions in nondepressed versus depressed individuals (460). In contrast, the absence of a significant increase in self-reported positive mood is not consistent with our previous work in which we did find a positive effect on mood. Notably, the fact that the current rTMS findings were confined to the implicit level of information-processing coincides with the general idea that the early effects of antidepressants are manifested at the level of implicit and automatic aspects of information-processing rather than the conscious experience of mood (459). Our results further support the involvement of the cerebellum in affective information-processing. Admittedly, our study design does not permit us to draw strong inferences on the underlying biological mechanisms. There are at least 3 lines of indirect evidence suggesting that the effects of high frequency rTMS to the medial cerebellum involve the brain's reward circuitry. First, the vermis part of the human cerebellum has projections to the ventral tegmental area of the midbrain, showing that the vermis can modulate mesolimbic areas via dopaminergic fibre bundles (443). Second, a comparative study has demonstrated enhanced dopamine turnover in the nucleus accumbens to electric stimulation of the cerebellar vermis in rats (370, 461). The finding is further supported by observations of increased dopamine metabolite homovanillic acid in the cerebrospinal fluid of 2 patients with movement disorders who received chronic electrical cerebellar stimulation (462). Third, high-frequency electrical stimulation of Purkinje cells in the cerebellar cortex selectively modulates dopaminergic activity in the prefrontal cortex (363). Together, these findings suggest that the cerebellum plays a significant role in the modulation of brain regions associated with cognition and emotion (277, 463). Finally, it is proposed that the cerebellum may be a suitable entry point for targeting dopaminergic

pathways in the mesolimbic and mesocortical systems as an alternative way to treat depression, for instance, with high-frequency rTMS (413, 464).

Limitations

Our study has some limitations. First, we used a Likert-type scale to assess consciously experienced mood. Previous research has demonstrated that slight but systematic changes in mood may remain unnoticed when using Likert-type scales (465). Second, the fewer number of pulses that we applied in the present study (i.e., 9000 v. 20 000 pulses in our earlier study) to prevent coil heating and minimize participants' discomfort may explain the absence of a significant increase in self-reported positive mood among participants in the present study. Analogous to the therapeutic onset delays often observed in drug as well as in rTMS treatment studies, a greater number of magnetic pulses at higher intensities might be necessary to obtain changes in consciously experienced mood. Third, although the sham rTMS served as our baseline measurement, additional pre-rTMS data showing that reaction time increases immediately after cerebellar rTMS would have made the results more compelling. Finally, it should be noted that the conclusion of increased emotional responses is indirectly drawn from increased reaction times. Except for the fact that our results suggest a role for the cerebellum in the implicit processing of positive emotional stimuli, the brain mechanisms responsible for the change in emotional responsiveness remain speculative and additional research on this matter is needed (466, 467). In sum, the results of our high-frequency rTMS study replicate and extend previous findings by establishing a direct relation between the cerebellum and emotive information processing. The parallel between the present effects of high frequency cerebellar rTMS and short-term antidepressant therapy regarding the change in implicit processing of positive stimuli in the absence of mood changes is notable and warrants further research.

PART 5

§5.1 General Discussion

This thesis contains studies on brain connectivity in relation to antisocial behavior in healthy and psychopathic individuals for which we employed various imaging techniques. The first part of this thesis focused on functional interhemispheric connectivity between the (pre)frontal cortices and its association with pro- or antisocial behavior. The first empirical chapter (**§2.1**) showed that the superordinate personality trait 'Agreeableness' (derived from the NEO-PI-R) is associated with interhemispheric signal propagation (ISP) from the left to the right dorsolateral prefrontal cortex (DLPFC). Importantly, no correlations between ISP and the motor cortices weres found indicating that this association is specific to interhemispheric connectivity between the left and right DLPFC. Agreeableness is the tendency to strive for social coherence and harmony. People that score high on this personality trait are companionable, considerate and value prosocial behavior (116, 117). Our finding clearly suggests that the effectiveness of prefrontal interhemispheric connectivity relates to personality features, in this case Agreeableness. It almost goes without saying that aggressive patients with antisocial personality disorders (or psychopathy) score low on personality traits such as Agreeableness and Conscientiousness (468). In fact, PCL-R scores correlate negatively with Agreeableness (116) showing that the more psychopathic one is, the less one is inclined to take the social order into account. Interestingly, as both factor 1 and 2 of the PCL-R correlate negatively with Agreeableness this suggests that the relationship between Agreeableness and psychopathy is quite strong. From this premise it could therefore be concluded that psychopaths should show left-to-right prefrontal connectivity deficits. By contrast however, we found right-to-left interhemispheric connectivity abnormalities in psychopathic offenders (**§ 3.1**). The observed deficits could therefore relate to some aspect of their complex personality disorder. Based on the general functionality of interhemispheric connectivity in healthy individuals, some hypotheses can however be put forward. If these data were to be interpreted within the framework that is provided by the frontal lateralization theory of emotion and motivation, one could argue that psychopaths have difficulty integrating input from a brain area (right frontal lobe) that is thought to be involved in avoidance-related behavior. It has often been thought that psychopaths take extreme risks because they are highly sensitive to reward. These data suggest a somewhat more nuanced picture: the consequence of this directional interhemispheric connectivity dysfunction may

be that psychopaths are motivationally inflexible, the risk being that they get locked in approach behavior. Once they are motivated to obtain some reward they are at risk of rigidly persevering this behavior. Neurophysiologically, the interpretation of the deficits in right-to-left prefrontal interhemispheric connectivity in psychopathic offenders (**§3.1**) might relate to deficient cortical inhibition (CI) in the left DLPFC (**§3.3**). The GABAB-receptor mediated neurotransmission that was tested through assessment of long-interval intracortical inhibition (LICI), is also highly involved in the processing of neuronal signals from the contralateral hemisphere. That is to say, the neuronal populations that mediate LICI are also thought to mediate interhemispheric inhibition (IHI) (114), which relates to ISP (**§2.3**). By inference, suboptimal functionality of these neuronal populations in the left DLPFC may hamper the processing of input originating from the right DLPFC resulting in a pattern of aberrant prefrontal right-to-left interhemispheric connectivity. As described above, this may result in an inflexible motivational system.

Of all drugs, alcohol is the most harmful drug (469) yet it is readily available to virtually all members of society. It is associated with physical, psychological and social harm to the users but also with harm to others (469). Harm to others often includes aggressive or violent behavior. As noted in the Introduction, 50% of all violent crimes (93) and up to 86% of all murders (94) have been associated with alcohol (ab)use. Therefore, we used alcohol (0.5‰) as a pharmacological agent to challenge interhemispheric connectivity. Interhemispheric inhibition (IHI) was measured between the left and right motor cortex in both men and women and it was found that at comparable blood alcohol concentrations (BACs) women already show significant alterations in interhemispheric connectivity (**§2.2**). In particular, after alcohol administration IHI was lower in women suggesting vulnerability to the immediate, and potentially also chronic, effects of alcohol use. Also, in both men and women cortical excitability decreased as a result of alcohol replicating earlier work (143-145). In line with what has been hypothesized earlier, the decrease in cortical excitability may be the result of alcohol-induced potentiation of GABAA receptor functioning. However, alcohol also affects NMDA glutamate receptor functioning (which also influences cortical excitability), so a contribution of NMDA cannot be excluded. Thus, the observed effects may be mediated by alcohol's influence on both GABA and NMDA receptor functioning. It is interesting to speculate on the behavioral correlates of alcohol-induced reduction of interhemispheric connectivity in females. As we know that the initial

effects of alcohol intake include heightened impulsivity and reward sensitivity one may speculate that the reduction in IHI underlies specifically these behavioral changes. Argued from the frontal asymmetry model of emotion and motivation stronger left-to-right IHI (or lower right-to-left IHI) may result in a left-sided dominance which may be associated with reduced behavioural inhibition and higher approach-related behavior. Exploratory analyses in the female subject group did indeed provide some results supporting this view as right-to-left IHI decreased when compared to placebo (See appendix **§2.2**), Taken together, these findings suggest that a moderate dose of alcohol mainly affects right-to-left IHI and cortical excitability in the right frontal lobe of female participants. Clearly, men are not immune to the effects of alcohol and it is anticipated that they will show the same pattern of brain changes at higher BACs. This should however first be evaluated by conducting experiments involving various BACs.

Traditionally, TMS research was limited to brain areas that would yield a clear output measure, such as the MEP. The combination of TMS with electroencephalography (EEG) has provided a way to measure cortical processes from areas not directly involved in motor behavior. In addition, brain connectivity can now also be indexed with more advanced measures, e.g., ISP. TMS research is now entering a crucial period in which the older TMS techniques (such as IHI) are substantiated by data derived from other imaging techniques, e.g., dti. Therefore, IHI and ISP were measured in a group of healthy controls to see whether the newer techniques such as ISP are indices of the same neuronal processes that are tapped into in for instance IHI. This methodological intermezzo (**§2.3**) is the first study to show that (i) ISP and IHI are correlated from the left to right motor cortex and vice versa and (ii) that the functional interactions between the cerebral hemispheres are not identical. In other words, ISP and IHI are associated but the direction of the association appears to depend on the direction of transcallosal signal transfer. This was quite an unexpected result and difficult to explain. We sought to interpret this finding in close connection with the already existing literature and hypothesized that the contralateral activation as measured per EEG and in response to TMS could either be predominantly excitatory or inhibitory. At a more functional level, we speculated that motor dominance or hand preference may have contributed to the opposing correlations.

In summary, in the first part of this thesis (**§2.1**, **§2.2**, **§2.3**) interhemispheric connectivity was explored and it was shown that prosocial behavior (i.e., Agreeableness)

is associated with the efficacy of interhemispheric signal transfer. We also showed that interhemispheric connectivity is affected in females after a dose of alcohol, the consumption of which is highly predictive of vandalism and violence. Taken together, communication between the prefrontal cortices appears to to contribute to pro- and antisocial behavior. Therefore, in part 3, a group of twenty-three extremely violent psychopathic offenders was tested on brain connectivity measures, for which TMS, EEG and DTI were employed. First, interhemispheric connectivity as indexed through ISP was measured in a group of psychopathic offenders and a control group consisting of healthy individuals (§3.1). As mentioned earlier, we found that psychopathic offenders have abnormal ISP from the right to the left hemisphere and this deviation appeared stronger in prefrontal areas than in the motor cortices. However, intracortical inhibition and facilitation in the left and right motor cortex were also measured and it was demonstrated that the cortical silent period (CSP) in the right hemisphere was lengthened, whereas short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) were not affected in psychopathic offenders. This suggests that, whereas the left prefrontal cortex appears disinhibited in psychopathic offenders, the right frontal lobe may show an interesting pattern of increased inhibition, although we are far from understanding the origins of an increased cortical silent period (CSP) or the significance that should be attributed to it. Neurophysiologically, there are at least two ways of interpreting this finding. On the one hand, it could be a local hemispheric response to neurodevelopmental changes in callosal transfer (see **§3.1**) (38). That is, the right frontal hemisphere may need to compensate for the reduced processing of neuronal input originating from the left frontal lobe. On the other hand, it is possible that an increased CSP is a cerebral reaction to subcortical mesolimbic dopaminergic abnormalities. Psychopaths have damage in a striato-thalamo-frontal network that is largely confined to the right side of the brain (**§3.2**). In line, Buckholtz found that in healthy controls psychopathic traits selectively predict dopamine release in the nucleus accumbens in response to potential rewards (14). Importantly, this was found in the right nucleus accumbens exclusively (14). Albeit somewhat of a stretch, one could argue that right-sided abnormalities in a white matter-network that is highly involved in dopaminergic neurotransmission may result in an increase in inhibition at the cortical level. Evidence for this assertion comes from studies showing that dopaminergic drugs such as cocaine, L-Dopa, and pergolide typically increase CSP (198-201). As virtually all other psychiatric disorders are characterized by

decreases in CI (470) rather than increases, this could be considered an option worthy of further inquiry. Psychologically, the increase in CI in the right frontal lobe could have bearing for reduced anxiety and fear in psychopaths. CI measures have been associated with anxiety (102) with stronger CI predicting lower anxiety. In addition, rTMS of the right frontal lobe (specifically, right DLPFC) alleviates anxiety levels in controls (471, 472) and in post-traumatic stress disorder and panic disorder (473). This suggests a particular role of CI in the right frontal lobe in anxiety. By inference, increased right-sided CI may then be related to the lower levels of anxiety and fear that have been reported in psychopaths (474), although it remains to be elucidated whether this would only be explained by right frontal cortical deficits in psychopaths.

Alternatively, reduced anxiety and fear, and in general reduced emotional responding in psychopathy have also been related to more (para)limbic areas (43). As was discussed in the Introduction of this thesis, the amygdala and its connections with ventromedial areas of the prefrontal cortex (vmPFC) are thought to underlie the emotional deficits of the psychopath. Using DTI, the microstructural integrity of white matter in psychopaths and controls was explored (**§3.2**). We hypothesized dysfunction to be present in amygdalo-prefrontal connections and in the mesolimbic reward pathway. Results showed that psychopathic offenders have profound disruption in three white matter clusters that represent two main networks: 1) projections from the amygdala to the medial prefrontal and orbitofrontal cortex and 2) projections from the ventral tegmental area and nucleus accumbens through the anterior limb of the internal capsule to thalamus and prefrontal cortex, i.e., a striato-thalamo-frontal network. The first network significantly predicted the affective/interpersonal deficits of psychopathy (Factor 1 of the PCL-R). This finding is perfectly in line with what was described in the Introduction, namely that amygdalo-prefrontal connections would be related to the callous/unemotional personality style of the psychopath. Two learning principles related to amygdala and medial prefrontal cortex functioning were highlighted, i.e., passive avoidance learning and aversive conditioning. In line with the suggestions made in the Introduction, this could explain the fearlessness that has often been observed in psychopathic offenders.

As noted earlier, the idea is not that antisocial or psychopathic individuals are hypersensitive to reward (52). Rather, in antisocial populations the brain network that processes reward may not respond properly to the environment, resulting in the rigid

pursuance of potentially rewarding stimuli (54). This network, termed the mesolimbic reward pathway, consists of several nodes including the ventral tegmental area/substantia nigra, nucleus accumbens, neostriatum (caudate nucleus and putamen), medial thalamus and medial prefrontal areas. Of these, excessive activation of the neostriatum has been associated with compulsive behaviour and the 'wanting' aspect of substance abuse (475, 476). Volumetrically, the neostriatum is increased in antisocial populations (58) and its functioning is also increased under certain conditions (223). Simply put, the striatum should respond to reward, and not to non-rewards. However, Gatzke-Koppe and colleagues showed that in youths with externalizing disorders, the striatum reacted to non-rewards in a similar fashion (224). Whereas control subjects shift activation to the anterior cingulate when stimuli ceased to be rewarding, adolescents with conduct disorder retained activation of the striatum. (224). In these individuals the striatum may fail to detect when stimuli are no longer rewarding which, in turn, could lead to impairments in terminating antisocial or aggressive behaviors (223). Indeed, our finding of disruptions in a striato-thalamo-frontal network was significantly correlated with factor 2 of the PCL-R, i.e., antisocial lifestyle. In sum, the callous/unemotional personality style of the psychopath is predicted by disruption of amygdalo-prefrontal connectivity while the second striato-thalamo-frontal network was related to the antisocial lifestyle (Factor 2 of the PCL-R). This dissociation suggests that psychopathy as defined by the PCL-R is largely explained by disruption of 2 major networks that underlie precisely those behaviors that are affected in psychopathy.

In the last chapter of part 3 we employed TMS and EEG (**§3.3**) to measure CI in psychopathic offenders and healthy individuals. We found CI deficits in the left DLPFC in psychopathic offenders but not in the motor cortex. In addition, working memory was significantly worse in these offenders and the extent of deterioration of working memory performance was predicted by the amount of CI in the DLPFC. In line with recent theoretical accounts of disinhibition in psychopathy, we propose that inhibitory abnormalities in the DLPFC of psychopathic offenders may account for their persistently impulsive and irresponsible behavior. Working memory may reflect the neuropsychological function through which DLPFC dysfunction contributes to psychopathic behavioral disinhibition.

Although the clinical construct of psychopathy is not typically associated with cognitive deficits (230) the psychopaths that keep getting arrested time and time again

are likely to have some cognitive problems, such as working memory impairments (see **§3.3**). These psychopaths are commonly referred to as 'unsuccessful psychopaths' (230, 267, 269). For this particular group it may be worthwhile to improve cognitive functioning using brain stimulation techniques such as TMS and transcranial magnetic current stimulation (tDCS). What the following years will need to show is whether improving working memory in psychopathic offenders will help them in controlling their behavior. For instance, healthy individuals that score high on psychopathy traits show decreased prefrontal activity during social cooperation tasks (231). Specifically, when these individuals defect and do not engage in prosocial behavior they demonstrate weaker activation of the orbitofrontal and dorsolateral prefrontal cortex (231). Rilling and colleagues (231) conclude that while subjects that score low on psychopathy are biased to cooperate, higher scoring individuals are biased to do the opposite which, in the case of reduced cognitive control, may result in uninhibited violation of interpersonal norms. The pitfall is that working memory may merely be an incidental cognitive side issue that is not crucially involved in the psychopathic personality and, as such, improving working memory may not change the callous/unemotional and manipulative personality or the antisocial lifestyle. Working memory improvement may even make them more dangerous as psychopathic offenders will be able to recruit more cognitive resources in order to plan and execute antisocial behavior. Recently however, Newman and colleagues (178) showed that higher-order cognitive processes moderate the emotional deficits, i.e., the fearlessness, in psychopathy. In this experiment psychopaths were shown to have normal fear-potentiated startle but only when they focused attention on threat-relevant information, when attention was not paid to relevant cues the fear-potentiated startle significantly diminished (178). This view suggests an interesting interplay between presumably subcortical emotional deficits and cortical cognitive processing in which the cognitive processes may –under certain conditions- normalize the emotional deficits of the psychopath. As attention and WM are closely connected (236, 237) and may share a joint neural substrate (477-479), cognitive enhancement in psychopathic offenders could potentially have a beneficial influence on improving emotional processing. Similarly, a persistent pattern of aggression and antisocial behavior as found in for instance antisocial personality disorder, is associated with reduced higher order cognitive functioning (232). These patients suffer from dysfunction in a broad range of executive functions, such as working memory. In general, the idea is that reduced

cognitive functioning negatively influences behavioral control (193) and, when provoked, these individuals are quick to respond with anger.

With regards to possible interventions, there are at least two entries into the network that is involved in working memory capacity, which I will describe here. The first way to do this is through stimulating the cerebellum. Through the pons the cerebellum receives input from frontal, temporal, parietal and occipital cortical areas, and it provides feedback to these areas as well. Thus, the cerebellum gets information from non-motor areas and is also in a position to influence the functions subserved by these areas (480). For example, the cerebellar hemispheres are connected to prefrontal areas in a contralateral fashion through the deep cerebellar nuclei and ventral thalamus and it may be this pathway via which the cerebellum contributes to cognition (65, 327). It is not thought that it is the cerebellum itself that performs cognitive operations (279). Rather, the cerebellum supports cortical areas that execute these operations and loss of cerebellar support will induce cognitive deficits that are secondary to cerebellum malfunction.. As the cerebellum contains up to four times the amount of neurons as the cerebral cortex (278), one may speculate that boosting cerebellar function through brain stimulation methods may significantly improve various cognitive and affective functions. Subsequently, increased cerebellar function may increase the effectiveness of neurotransmission in areas such as the DLPFC. Interestingly, cathodal transcranial direct current stimulation (tDCS) over the right cerebellum improves working memory and attention (481). The mechanism behind this is not clear but cathodal tDCS over the cerebellum is thought to inhibit Purkinje cells in the cerebellar cortex (481). Subsequently, there is less inhibitory drive from the Purkinje cells to the cerebellar nuclei and stronger excitatory activation traveling to the thalamus followed by increased excitation of cortical areas. As the right cerebellar hemisphere is connected to the left cerebral hemisphere, stimulation of the right cerebellum will activate for instance the left DLPFC. Activity in the left DLPFC may increase after stimulation of the right cerebellum which may facilitate better cognitive performance. Further, in schizophrenia, DLPFC activity together with its connectivity with the cerebellum, predicts responsiveness to cognitive behavioral therapy (CBT) in psychosis (482). Particularly increased communication between the left DLPFC and the cerebellum strongly underlies the efficacy of CBT, potentially due to DLPFC-cerebellum contributions to executive functioning (482). In addition to the application of tDCS, rTMS may also be effective in increasing cognitive performance in aggressive

individuals. Continuous theta burst stimulation (cTBS) of the cerebellum results in an increase of LICI in the DLPFC (483). As we showed that LICI in the DLPFC correlates with working memory performance, potentiating LICI through cerebellar cTBS could lead to better cognitive control in psychopathic offenders.

The second way to improve cognitive performance is with rTMS over the (left) DLPFC. A systematic review recently stated that 'high frequency rTMS (10-20Hz) is most likely to cause significant cognitive improvement when applied over the left (dorsolateral) prefrontal cortex, within a range of 10-15 successive sessions' with stimulation intensities being between 80-110% of individual motor thresholds (484). This may potentiate GABAergic inhibitory neurotransmission in the DLPFC which will facilitate cognitive functions such as working memory. Interestingly, neuronal oscillations in the gamma frequency band (30-50Hz) are associated with such cognitive tasks (for instance working memory tasks) (234, 265). It was recently shown that in LICI gamma oscillations are specifically suppressed whereas other frequency bands are not (84). In addition, in the motor cortex gamma oscillations were not inhibited by LICI which suggests this particular frequency band represents an important neurophysiological process that may be highly involved in intact functioning of the prefrontal cortex (84). Importantly, rTMS over the left DLPFC normalizes gamma band activity in schizophrenia patients (485). That is, during WM tasks schizophrenia patients generate excessive gamma band activity but active rTMS enables them to inhibit gamma oscillations (234). Furthermore, high frequency rTMS applied to the DLPFC potentiates cognitive performance in healthy controls (485). In line, it has been suggested that GABAA receptor mediated inhibition generates gamma oscillations whereas GABAB receptor mediated inhibitory post-synaptic potentials are involved in the modulation of gamma oscillations (83, 265, 485). The deficits in LICI in the left DLPFC in psychopathic offenders could therefore mean that they have impairments in the modulation of gamma oscillations which might explain worse working memory performance. As such, high frequency rTMS could be beneficial for individuals in whom aggression and antisocial behavior is linked to a lack of cognitive control and poor emotion regulation related to DLPFC dysfunction.

In the first chapter of the cerebellum part (**§4.1**), cerebellar contributions to emotion, cognition and neuropsychiatric disorders were explored. Given the extensive connections of the cerebellum with the spinal cord, brain stem, septum, amygdala, (hypo)

thalamus and cerebral cortex it is no wonder the cerebellum contributes to the functions that these brain structures underlay (65, 327, 486). As such, involvement of the cerebellum in neuropsychiatric disorders is to be expected. Based on this literature review we concluded that particularly data of patients with schizophrenia and autism suggests a pathological role for the cerebellum. Also, in line with suggestions made by Jeremy Schmahmann (65, 71, 73, 486), pathological functioning of the cerebellum may result in dysregulated behavior, including oppositionality, irritability and aggression. As described above, stimulation of the cerebellum could help alleviate these symptoms (68, 69). In addition, we proposed TMS as a means to measure the functional connectedness of the cerebellum to the cerebral cortex. In addition, repetitive TMS (rTMS) was used to modify cerebellar functioning which could be therapeutically beneficial in for instance major depressive disorder (MDD) (**§4.2**) (413). Taken together, future studies are advised to seriously take into account the strong influence of cerebellar (dys)function on neuropsychiatric disorders but also on the regulation of impulsivity and aggression. Particularly damage to vermal regions of the cerebellum may induce affective changes including oppositionality, irritability or aggression. Therefore, in the final chapter of this thesis (**§4.2**), we sought to directly test whether the medial cerebellum is involved in emotion and affect. High frequency rTMS was employed targeting the medial cerebellum to show that vermal regions of the cerebellum are indeed associated with emotional responding. Whereas the cerebellar hemispheres appear involved in cognition, the cerebellar vermis is more associated with emotion (70, 443). Specifically, lobules VI and VII of the posterior lobe constitute the cognitive part of the cerebellum whereas the posterior vermis has been termed the limbic cerebellum (487). rTMS targeted at the vermis induced an increase in attention for happy facial expression, whereas cerebellar sham rTMS and rTMS administered over the occipital lobe did not induce this effect. It was concluded that vermal rTMS induces increased emotional responses to masked happy facial expressions. In addition to the idea that magnetic stimulation of the cerebellar hemispheres could potentiate cognitive processing, this finding suggests that magnetic stimulation of the cerebellar vermis could have a beneficial influence on emotional responding. It has for instance been argued that cerebellar rTMS could help patients with MDD (413). Similarly, one could speculate that in aggressive patients, rTMS over the medial cerebellum might increase the regulatory function of the cerebellum (68, 69, 277, 488). The cerebellar vermis has dopaminergic projections to the ventral tegmental

area, suggesting that the cerebellum could influence the mesolimbic reward pathway. As was also suggested (**§4.2**), electrical stimulation of the cerebellum, specifically Purkinje cells in the cerebellar cortex, modulates dopamine activity in the prefrontal cortex (363). As we showed that psychopathic offenders have structural deficits in precisely this pathway, one may speculate that magnetic or electrical stimulation of the cerebellar vermis could influence, and potentially normalize, dopaminergic neurotransmission in the mesolimbic reward pathway in antisocial populations.

In closing

On a final note, aggression is present in all species and is often very adaptive behavior. In developing societies such as ours, the acceptance of aggression is however quickly diminishing. While aggressive behavior often serves a purpose (e.g., defense of oneself or one's family, competition over food), nowadays it has become largely maladaptive. In this thesis we endeavoured to unravel some of the neurobiological underpinnings of aggressive and antisocial behavior. To this end a group of extremely violent psychopathic offenders was tested. It is easy to think of psychopaths as monstrous creatures, eager to abuse their peers and to defy the social order. From a psychiatric point of view however, they are just as ill as the paranoid schizophrenic patient that believes the world has plotted a conspiracy against him. The psychopath is indeed at extreme risk of getting involved in antisocial and criminal behavior but, as he is inept of regular attachment and affective experience, he struggles to understand why anyone would care about him doing so. Indeed, we have seen that the brain structures and processes that should allow for flexible avoidance of potential punishments are affected in psychopathic offenders (**§3.1**, **§3.2** and **§3.3**). These findings also showed that subcortical areas that are highly involved in emotion, such as the amygdala, show structural damage. In this regard, the psychopath is a lonely unfeeling soloist, unable to steer clear of danger. It is the atrocity of their crimes that prevents us from seeing psychopaths as victims of a severely debilitating illness. The psychopath may not care about his affliction –he is indeed incapable of doing so- and his narcissism may even lead him to think he is better than others. However, one need but see the course of their lives to understand that they have drawn a blank and will not be able to comprehend what part of the human experience is secluded from them. One does not need to have sympathy for them to want to them to lead better lives- not only for ourselves, but also for them. Once these patients reach adulthood treatment will be extremely difficult. Therefore, it is key that these patients with strong aggressive tendencies and psychopathic traits, are reached early in life. Although personalities develop until later age, already in early life, children with psychopathic traits show signs of a warped personality. This is reflected in conflicts with parents, teachers and the law as young psychopaths will break moral and social rules without consideration of potential negative outcomes. They will get into contact with drugs and crime and will subsequently get jailed upon which their social development largely comes to a halt. In parallel, the frontal cortex develops until adolescence and is

shaped by environmental experiences and challenges. At this point adolescents with psychopathic traits are often already in youth detention and will not benefit from normal moral development. One could argue that adolescents with psychopathic traits will not learn these moral and societal rules since they do not possess the brain architecture to do so. In fact, in this thesis we highlighted some potentially neurodevelopmental deficits associated with psychopathy, i.e., interhemispheric connectivity deficits (**§3.1**). On the other hand, one could also argue that especially in these cases, extra efforts should be undertaken to impose upon them the benefits, for themselves, of functioning properly in society. We are far from 'curing' psychopathic patients and therefore I would argue that we are only left with the option to focus on preventing that a neurodevelopmental arrest mimics societally stunted progress. In other words, we cannot allow poor psychological therapy and isolation from society (i.e., prison) to further shape the young psychopath's brain into one that easily allows for escalated aggression and cold exploitation of others.

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Nederlandse Samenvatting

Deel 1.

De maatschappelijke kosten van antisociaal gedrag zijn immens, zowel financieël als emotioneel. Slachtoffers ervaren nog lange tijd de gevolgen van misbruik, afpersing, extreme agressie of moord op een naaste. De ernst van dit soort delicten verhindert ons vaak te zien dat de motivatie van de delict pleger pathologisch kan zijn, en er sprake kan zijn van psychiatrische problematiek bij de dader. Deze kan bestaan uit persoonlijkheidsproblematiek of problemen in de controle van impulsen, het reguleren van emotie, overmatig alcoholgebruik of het missen van sociale emoties zoals liefde, empathie of gevoelens van schuld. In dit proefschrift is gekeken naar mogelijke verstoringen in hersenconnectiviteit en hoe deze aggressief en antisociaal gedrag zouden kunnen veroorzaken. In het kort behelst connectiviteit de functionele en structurele communicatie tussen bepaalde hersendelen. De centrale techniek waarmee we deze connectiviteit in kaart hebben gebracht is transcraniële magnetische stimulatie (TMS).

Deel 2

Het eerste deel van deze thesis bestaat uit een fundamentele verkenning van connectiviteit in het brein en hoe deze in relatie kunnen staan tot sociaal gedrag. Sommige mensen zijn socialer dan anderen en een deel van deze socialiteit wordt gevangen met de term Agreeableness. Mensen die deze karaktereigenschap in sterke mate bezitten zijn gericht op samenwerking, hechten aan aangename omgang en zijn invoelend. In het eerste empirische hoofdstuk is gekeken naar het persoonlijkheidskenmerk Agreeableness en of dit kenmerk samenhangt met interhemisferische connectiviteit. De trek Agreeableness hebben we gemeten via een persoonlijkheidsvragenlijst genaamd de NEO-FFI welke naast *Agreeableness* nog 4 andere overkoepelende persoonlijkheidstrekken onderscheidt, te weten *Neuroticism*, *Extraversion, Openneness to Experience* en *Conscientiousness*. Door een combinatie van TMS en electroencefalografie (EEG) is de signaaloverdracht van de linker motor cortex naar de rechter motor cortex en van de linker prefrontaal kwab naar de rechter prefrontaal kwab gemeten. Deze signaaloverdracht wordt interhemisferische signaal propagatie (ISP) genoemd. De resultaten tonen dat prefrontale ISP positief correleert met Agreeableness. Dat wil zeggen dat mensen die hoog scoren op de persoonlijkheidstrek

agrreableness een sterkere signaaloverdracht hebben van de linker naar de rechter hemisfeerHiermee tonen we voor de eerste keer aan dat neurofysiologische indices van interhemisferische connectiviteit samenhangen met persoonlijkheidskenmerken.

Alcohol vermindert responsinhibitie en de cognitieve controle over gedrag. Het is daarom niet verwonderlijk dat bij veel misdaden alcohol in het spel is. In §2.2 is gekeken naar het effect van alcohol op interhemisferische connectiviteit in mannen en vrouwen. Om interhemisferische connectiviteit te meten is een ander TMS-paradigma gebruikt, namelijk een zogeheten paired pulse paradigm waarbij een conditionerende stimulus wordt gegeven over de ipsilaterale motor cortex gevolgd door een test stimulus over de contralaterale motor cortex. De contralaterale motor cortex induceert een beweging van bijvoorbeeld de duim- deze beweging wordt de motor evoked potential genoemd (MEP). De grootte van de MEP wordt (ongeveer) gehalveerd als de contralaterale test stimulus vooraf wordt gegaan door een ipsilaterale conditionerende stimulus. Dit fenomeen heet interhemisferische inhibitie (IHI). Om het effect van alcohol op IHI te meten is een groep van 22 gezonde vrijwilligers (12 vrouwen) getest. Zij kregen eenmaal een placebo en eenmaal een alcohol-houdende vloeistof te drinken waarna IHI gemeten werd. De resultaten tonen aan dat bij vrouwen IHI vermindert na inname van alcohol. Een belangrijk punt is dat zowel mannen als vrouwen hetzelfde promillage alcohol in hun bloed hadden wat suggereert dat vrouwen gevoeliger zijn voor de effecten van alcohol.

Het laatste hoofdstuk van deel 2 (§2.3) bevat een methodologisch intermezzo waarin de relatie tussen IHI en ISP wordt onderzocht. Beide technieken indiceren interhemisferische connectiviteit maar de precieze samenhang tussen IHI en ISP is nog niet duidelijk. Daarom is in een groep van 16 mannen IHI en ISP in beide richtingen gemeten, i.e., van de linker naar de rechter motor cortex en vice versa. Op basis van het veronderstelde model van interhemisferische connectiviteit werd een negatieve correlatie tussen IHI en ISP verwacht. Deze correlatie werd inderdaad gevonden voor signaaloverdracht van de rechter naar de linker motor cortex. Tegen de verwachting in werd een positieve correlatie tussen IHI en ISP gevonden voor signaaloverdracht van de linker naar de rechter motor cortex. Deze bevindingen suggereren dat de samenhang tussen IHI en ISP afhangt van de richting van interhemisferische connectiviteit. Tevens zou dit kunnen betekenen dat de mechanismen van interhemisferische connectiviteit niet identiek zijn voor signaaloverdracht in beide richtingen.

Deel 3.

Het derde deel van deze thesis bestaat uit 3 hoofdstukken waarin de hersenen van mensen met psychopathie onder de loep wordt genomen. Psychopathie is een persoonlijkheidsstoornis waarin de cognitieve vermogens over het algemeen intact zijn. In tegenstelling, psychopathische individuen hebben weinig sociale emoties zoals empathie, liefde of loyalitiet en hebben grote moeite hun emoties te reguleren en hun gedrag in toom te houden. Deze patienten zijn impulsief en sterk geneigd te handelen op basis van wat het moment hen ingeeft, waardoor ze vaak in aanraking komen met de rechterlijke macht. Psychopathie wordt over het algemeen gemeten met de Psychopathy Checklist-revised edition (PCL-R). De PCL-R meet 2 factoren, te weten een 'affectieve/ interpersoonlijke'-factor en een 'antisociale levensstijl'-factor.

In het eerste hoofdstuk van deel 3 (§3.1) is gekeken naar interhemisferische connectiviteit in een groep psychopathische criminelen en een groep gezonde controles. Eerdere gedragsdata heeft aangetoond dat er bij psychopathische patienten inderdaad sprake is van problemen in interhemisferische communicatie. Het lijkt evenwel zo te zijn deze problemen met name bestaan in signaal overdracht van de rechter naar de linker prefrontaal kwab. Daarom hebben we interhemisferische connectiviteit in psychopathische patienten in kaart gebracht door ISP en IHI in psychopaten en controles te meten. In overeenkomt met de bovengenoemde gedragsdata verwachtten we dat psychopathische patienten met name problemen hebben in signaaloverdracht van de rechter naar de linker frontaal kwab. Inderdaad, ISP van de rechter naar de linker frontal kwab was significant hoger in psychopaten dan in controles. In andere woorden, magnetische stimulatie van de rechter frontaal kwab resulteert in de contralaterale hemisfeer in een corticale respons die ongeveer even groot is als die in de gestimuleerde hemisfeer. Dit suggereert dat de linker frontaal kwab van psychopathische patienten input van de rechter frontaal kwab niet goed verwerkt.

In het tweede hoofdstuk van deel 3 (§3.2) is magnetic resonance imaging (MRI) gebruikt om de integriteit van witte stof banen te bekijken. Dit is gedaan middels diffusion tensor imaging (DTI). Door middel van deze techniek wordt de diffusie van watermoleculen gemeten. Deze diffusie is in verschillende weefsels of vloeistoffen anders: in bloed verspreiden watermoleculen zich in alle richtingen. In de buurt van witte stofbanen hebben watermoleculen de neiging zich te verspreiden langs de as van deze witte stofbanen.

In DTI wordt diffusie in alle richtingen weergegeven met een '0' terwijl perfecte diffusie langs één as de waarde '1' krijgt. In dit hoofdstuk zijn 11 psychopathische criminelen en 11 gezonde controles gescand middels DTI. De hypothese was dat psychopaten verslechterde integriteit van witte stofbanen zouden hebben, te weten die tussen de amygdala en orbitofrontale cortex en die in het mesolimbische beloningssysteem. Dit laatste systeem loopt van het striatum via de thalamus naar de prefrontaal kwab en is sterk betrokken bij impulsief en antisociaal gedrag. In overeenstemming met de hypotheses lieten psychopaten verslechterde integriteit van amygdalo-frontaal en striato-thalamo-frontaal connecties zien. De afwijkingen in witte stof in het amygdalo-frontale netwerk correleerde met de 'affectieve/interpersoonlijke'-factor van de PCL-R terwijl de afwijkingen in het mesolimbische beloningscircuit samenhingen met de 'antisociale levensstijl'-factor van de PCL-R. Hoewel dit kleine sample niet toestaat harde conclusies te trekken, lijkt het er op dat psychopathie het resultaat zou kunnen zijn van disfunctie in een amygdalo-frontaal en in een striato-thalamo-frontaal netwerk.

In het laatste hoofdstuk van deel 3 (§3.3) is wederom de combinatie van TMS en EEG gebruikt maar ditmaal niet om connectiviteit te meten. In dit hoofdstuk is corticale inhibitie gemeten in psychopathische patienten en controles, waarvoor een paired pulse paradigm is gebruikt dat long interval intracortical inhibition (LICI) meet. Corticale inhibitie is het proces waarbij corticale interneuronen de activiteit van corticale output neuronen (e.g., pyramidal cells) verminderen. Onlangs is aangetoond dat LICI gemeten van de dorsolaterale prefrontale cortex (DLPFC) samenhangt met werkgeheugen. Zeker bij psychopathische criminelen die keer op keer worden opgepakt is de kans aanwezig dat zij cognitieve problemen hebben, zoals werkgeheugen-problemen. Om deze redenen hebben we in een groep psychopathische criminelen en gezonde vrijwilligers LICI van de motor cortex en DLPFC gemeten. Daarnaast is werkgeheugen gemeten middels de number letter sequencing test van de WAIS-III. We verwachtten dat psychopathische criminelen verslechterde corticale inhibitie in de DLPFC zouden hebben maar niet in de motor cortex. Daarnaast was de hypothese ook hun werkgeheugen aangedaan zou zijn en dat zit samen zou hangen met corticale inhibitie gemten van de DLPFC. In vergelijking met gezonde vrijwilligers hebben psychopathische criminelen verminderde corticale inhibitie in de DLPFC maar niet in de motor cortex. Tevens was hun werkgeheugen slechter wat verklaard werd door verminderde cortical inhibitie. Een mogelijke implicatie van deze bevinding

zou kunnen zijn dat psychopaten door deze prefrontale en cognitieve problemen slecht in staat zijn hun gedrag te reguleren.

Deel 4.

In deel 4 is de invloed van het cerebellum op emotie en cognitie onderzocht. Cerebellum staat voor 'kleine hersenen' welke zich onderaan de achterzijde van de hersenen bevinden. Van oudsher denk met dat het cerebellum voornamelijk betrokken is bij fijne motoriek. Studies van Jeremy Schmahmann hebben echter laten zien dat schade aan het cerebellum ook kan resulteren in affectieve en cognitieve problemen. In het eerste hoofdstuk van deel 4 (§4.1) is de betrokkenheid van het cerebellum bij psychiatrische problematiek onderzocht. Dat wil zeggen cerebellaire neuropathologie bij onder andere autisme spectrum stoornissen, schizofrenie, stemmings- en angststoornissen en ADHD is onderzocht. Eerst is echter de anatomie van het cerebellum besproken waaruit tevens bleek dat het cerebellum connecties heeft met bijzonder veel andere hersengebieden, zij het direct of indirect. Deze hersengebieden ondersteunen cognitieve functies zoals werkgeheugen, taal of executief functioneren. Op basis van deze constateringen lijkt het al waarschijnlijker dat het cerebellum inderdaad bij een groter scala aan cognitieve en affectieve processen betrokken is, dan voorheen werd gedacht. De beschikbare data over cerebellaire betrokkenheid bij neuropsychiatrische stoornissen suggereert in weze hetzelfde. Met name bij schizofrenie wordt het cerebellum veelvuldig geïmpliceerd. Het cerebellum staat via de thalamus in contact met de cerebrale cortex en het is, onder andere door Nancy Andreasen, gepostuleerd dat dit netwerk sterk betrokken is bij een zeer basaal cognitief proces. Als dit verstoord raakt, zoals het bij schizofrenie verstoord is geraakt, dan zou dit kunnen resulteren in de verscheidenheid aan psychiatrische symptomen die bij schizofrenie wordt geobserveerd. Bij autisme lijken deze connecties ook beschadigd te zijn. Tevens vindt men degeneratie van Purkinje-cellen wat, aangezien dit de voornaamste output-cellen van het cerebellum zijn, zou kunnen wijzen op een disconnectie van het cerebellum van andere delen van de hersenen. Andere psychiatrische stoornissen zoals ADHD en depressie vertonen ook cerebellaire schade.

Om te onderzoeken of het cerebellum daadwerkelijk een rol speelt in emotie hebben we in het laatste empirische hoofdstuk van deze thesis (§4.2) repetitive TMS (rTMS) gebruikt. Bij rTMS worden treinen van magnetische pulsen toegediend aan bijvoorbeeld

de motor cortex of het cerebellum. Waar de cerebellaire hemisferen meer in verband worden gebracht met cognitie, wordt het mediale cerebellum (het vermis) meer gezien als het affectieve deel van het cerebellum. Daarom hebben we in onze studie middels rTMS getracht het vermis te stimuleren. Ter controle hebben we in één sessie ook de occipitaal kwab gestimuleerd en eenmaal hebben we een nep (sham)-stimulatie gedaan. Na stimulatie moesten de proefpersonen een Strooptaak doen waarbij ze de kleur van een bepaald masker moesten benoemen. Echter, voordat dit masker verscheen werd er kort een emotioneel gezicht getoond. Dit gezicht kon een neutrale, angstige of blije expressie hebben. Naar aanleiding van eerdere onderzoeksbevindingen verwachtten we dat proefpersonen een meer aandacht voor blije gezichten zouden hebben na rTMS over het cerebellum. Hier wordt 'meer aandacht' gekwantificeerd als een langere reactietijd van het benoemen van de kleur van een masker na aanbieding van een blij gezicht. Dit is inderdaad wat we vonden: na rTMS over het vermis, maar niet occipitaal kwab of sham stimulatie, hadden proefpersonen inderdaad meer aandacht voor blije gezichten. Dit suggereert dat het mediale cerebellum inderdaad een belangrijke rol speelt in affectieve processen.

Dankwoord

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Dankwoord.

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Lieve Haike, opeens was jij daar. Ik hoop dat ik je ooit kan vertellen hoe blij ik daar mee ben.

Dankwoord

Curriculum Vitae

Sylco Hoppenbrouwers was born in Maastricht, The Netherlands, on September 8th 1982. After graduating from secondary school at the 'Onze Lieve Vrouw Lyceum' he went on to study Philosophy for two years. After this he switched to Psychology in which he obtained his Bachelor's degree. During undergraduation he became highly interested in research. After obtaining his Master's degree, for which he conducted various studies together with Dennis Schutter, he did a research internship at the Centre for Addiction and Mental Health. He then started his PhD-research with Dennis Schutter at Utrecht University, Department of Experimental Psychology. During this period he developed a strong interest in forensic psychology. He currently works at Forensic Psychiatric Centre Oldenkotte where he conducts research and risk assessments.

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