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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2012

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):
Meffert, H. (2012). *Empathy under arrest? functional and structural neural correlates of empathy in psychopathy*. s.n.

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EMPATHY UNDER ARREST?

FUNCTIONAL AND STRUCTURAL NEURAL CORRELATES OF
EMPATHY IN PSYCHOPATHY

HARMA MEFFERT

Paranimfen: Jojanneke Bastiaansen
 Marleen Schippers

The research in this thesis was supported by a VIDI (452-4-305) and an open competition grant (400-8-89) from the Nederlandse Organisatie voor Wetenschappelijk Onderzoek (NWO) and a Marie Curie Excellence Grant of the European Commission to Prof. dr. C. Keyzers . FPC Dr. S. van Mesdag partially funded salary costs and costs related to security.

Publication of this thesis was financially supported by the University of Groningen and the Graduate School for Medical Sciences of the University Medical Center Groningen and FPC Dr. S. van Mesdag.

Cover design: Matty Postma, ideatelier

Printed by: Wöhrmann Print Service

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EMPATHY UNDER ARREST?

Functional and structural neural correlates of empathy in psychopathy

Proefschrift

ter verkrijging van het doctoraat in de

Medische Wetenschappen

aan de Rijksuniversiteit Groningen

op gezag van de

Rector Magnificus, dr. E. Sterken,

in het openbaar te verdedigen op

maandag 21 mei 2012

om 16.15 uur

door

Harma Meffert

geboren op 10 februari 1977

te Groningen

Promotores: Prof. dr. C. Keyzers
Prof. dr. J.A. den Boer

Beoordelingscommissie: Prof. dr. A. Aleman
Prof. dr. R.J.R. Blair
Prof. dr. E.A.M. Crone

ISBN printed version: 978-90-367-5495-8

ISBN digital version: 978-90-367-5494-1

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1

GENERAL INTRODUCTION

Criminal psychopathy can at the same time seem both repulsive and fascinating, as illustrated by the number of books and movies that have been inspired by this topic. It is also an odd observation: although society is often quick in expressing their loathing of serious criminality, be it murder, rape, paedophilia or other horrific offences, many of us cannot resist watching chilling thrillers, cop reality shows or movies about the war. However, psychopathy is a specific disorder with clear-cut diagnostic features and the stories told in books and movies can easily give the wrong impression, especially given characters like Hannibal Lecter (*Silence of the Lambs*), Patrick Bateman (*American Psycho*) or Jack Torrance (*The Shining*). It is important to realize that the main characters of these movies might display some overlap with official psychopathic traits, but that the syndrome as a whole is usually not captured by their images. Criminal psychopathy is a personality disorder characterized by a constellation of symptoms of which deficits in the emotional and interpersonal domain (Coid et al., 2009; Hare & Neumann, 2009), and a considerable reduced emotional empathy (Blair, Peschardt, Budhani, Mitchell, & Pine, 2006) are at the core of the disorder (Blair, 1995). A developmental model by James Blair (1995; 2006), the Violence Inhibition Model (VIM, Blair, 1995), tries to explain why moral transgressions are easier to commit for individuals with psychopathy, by linking inadequate moral development to an early deficit in responding to the emotions of others. However, it is not only important to see how an empathy deficit can lead to amoral behaviour, but also why psychopathic individuals respond less to emotions of others. In this respect, a very promising framework has emerged within the neuroscience literature over the past two decades, which generally states that understanding others relies (partly) on triggering neural states in the self, similar to those in others (e.g. Bastiaansen, Thioux, & Keysers, 2009; Gallese, Keysers, & Rizzolatti, 2004; Iacoboni & Dapretto, 2006; Keysers, Kaas, & Gazzola, 2010; Pineda, 2008; Preston & de Waal, 2003; Rizzolatti & Craighero, 2004). The neural network associated with these responses is referred to as a shared circuit. In this thesis, we will examine the integrity of shared circuits in forensic patients diagnosed with psychopathy, by comparing their neural responses to emotional laden movies with a control group and by investigating the structural integrity of shared circuits compared to a control group and two additional psychiatric disorders associated with empathy deficits: Autism Spectrum Disorder (ASD) and schizophrenia. This chapter will introduce psychopathy and its relation to empathy, briefly review research on shared circuits and assess the history of this type of research within the psychiatric populations included in this thesis. It will end with a short description of the challenging recruitment part of this research and an outline of the thesis.

1.1 PSYCHOPATHY

The golden standard to diagnose psychopathy within forensic settings is the Psychopathy Checklist - Revised (Hare, 2003; Hare, Vertommen, Brink, & Ruiters, 2001). This instrument was developed by Robert Hare in 1980 (Hare, 1980) based on the descriptions of Harvey Cleckley. Through years of clinical work with psychiatric patients, Cleckley had put together a list of 16 characteristic points, which together describe the typical psychopath (see Box 1.1, 1982). However, not all of the original Cleckley criteria were retained in the PCL-R. As the instrument was intended to measure a unitary construct and was validated on criminal samples rather than non-incarcerated subjects, items of the original Cleckley list indexing positive adjustment were dropped (e.g. Patrick, Fowles, & Krueger,

2009). The focus on criminal samples during the construction phase makes the PCL-R an instrument most suitable for forensic populations.

Box 1.1: 16 items of Harvey Cleckley (Cleckley, 1982)

1. Superficial charm and good “intelligence”
2. Absence of delusions and other signs of irrational thinking
3. Absence of “nervousness” or psychoneurotic manifestations
4. Unreliability
5. Untruthfulness and insincerity
6. Lack of remorse and shame
7. Inadequately motivated antisocial behavior
8. Poor judgment and failure to learn by experience
9. Pathologic egocentricity and incapacity for love
10. General poverty in major affective reactions
11. Specific loss of insight
12. Unresponsiveness in general interpersonal relations
13. Fantastic and uninviting behavior with drink and sometimes without
14. Suicide rarely carried out
15. Sex life impersonal, trivial, and poorly integrated
16. Failure to follow any life plan

The PCL-R currently contains a list of 20 character descriptions which are scored 0 (no indication), 1 (some indication) or 2 (indication) by a trained diagnostician (see Table 1). The items are completed using file information, preferably extended with a semi-structured interview. A maximum score of 40 can be obtained and the manual recommends using a cut-off score of 30 for a diagnosis of psychopathy to be given. This threshold was based on North-American samples. As PCL-R scores tend to be slightly lower in European countries (Cooke, Michie, Hart, & Clark, 2005), a slightly lower cut-off score (26) was used as inclusion criterion throughout this thesis, a common practise in European studies on psychopathy (e.g. Grann, Långström, Tengström, & Kullgren, 1999; Rasmussen, Storsæter, & Levander, 1999; Sjöstedt & Långström, 2002).

Factor 1: Interpersonal/affective	Factor 2: Social deviance
1. Glibness/superficial charm	3. Need for stimulation/proneness to boredom
2. Grandiose sense of self-worth	9. Parasitic lifestyle
4. Pathological lying	13. Lack of realistic, long-term goals
5. Conning/manipulative	15. Irresponsibility
6. Lack of remorse or guilt	14. Impulsivity
7. Shallow affect	10. Poor behavioural control
8. Callous/lack of empathy	12. Early behaviour problems
13. Failure to accept responsibility for own actions	18. Juvenile delinquency
	20. Criminal versatility
	19. Revocation of conditional release
Do not load	
11. Promiscuous sexual behavior	
17. Many short-term marital relationships	

Table 1: Psychopathy Checklist-Revised items. The two columns represent the original division into two factors, although the item criminal versatility was only added to Factor 2 in the second edition of the manual (Hare, Neumann, & 2006). A two-factor, four facet model is recommended by the manual (Hare, 2003). These four facets are named: affective (red font), interpersonal (blue), lifestyle (green) and antisocial (purple).

Because the criminal lifestyle encompasses a significant portion of the PCL-R and collateral information is needed, the instrument is not very suitable as a diagnostic tool for the non-forensic control group included in this thesis. To overcome this problem, we used an additional measure of psychopathy, developed by Lilienfeld and collaborators (Lilienfeld & Andrews, 1996). The

Psychopathy Personality Inventory is an extensive self-report questionnaire which consists of 187 items that are answered on a 4-point Likert scale (1 = false, 2 = mostly false, 3 = mostly true, 4 = true). The instrument was designed to apply equally well to criminal and non-criminal populations. Since the Cleckley criteria also served as the theoretical basis for this instrument, the PPI is moderately comparable to the PCL-R. However, rather than searching for a unitary construct, the developers allowed their subscales to be uncorrelated (Lilienfeld & Andrews, 1996; Patrick, et al., 2009, see Table 2 for a list of the subscales of the PPI).

Main subscales	Factor	Description
Machiavellian Egocentricity	II	A ruthless willingness to manipulate and take advantage of others
Social Potency	I	Interpersonal impact and skill at influencing others
Fearlessness	I	A willingness to take physical risks and an absence of anticipatory anxiety
Coldheartedness		Callousness, guiltlessness and absence of empathy
Impulsive Nonconformity	II	A flagrant disregard for tradition
Blame Externalization	II	A tendency to attribute responsibility to one's mistakes to others
Carefree Nonplanfulness	II	An insouciant attitude toward the future
Stress Immunity	I	Sanguine and absence of tension in anxiety-provoking situations
Validity subscales		Description
Unlikely Virtues		Positive impression management
Variable Response Inconsistency		Malingering
Deviant Responding		Careless or random responding

Table 2: Subscales of the PPI (Lilienfeld & Fowler, 2006). Coldheartedness does not load on either factor but might be considered as a third factor (Benning, Patrick, Hicks, Blonigen, & Krueger, 2003).

In this thesis we will focus on the literature specifically dealing with subjects diagnosed with psychopathy and not with the more heterogeneous Antisocial Personality Disorder (APD). Psychopathy is not listed in the current manual of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2000), but shares many characteristics with APD (see Box 1.2). Consequently, many patients diagnosed with psychopathy according to the PCL-R, also satisfy the criteria of APD. However, the reverse is usually not the case (Hare & Neumann, 2009). The base rate of APD is very high in forensic psychiatric clinics, as it is characterized by (antisocial) behaviours that are very common in this type of institutions. Lykken therefore wrote that 'Identifying someone as "having APD" is about as non-specific and scientifically unhelpful as diagnosing a sick patient as having a fever or an infectious or neurological disorder' (Lykken, 2006, page 4). The added value of the psychopathy concept over APD lies in the additional focus on problems within the affective and interpersonal domain.

1.2 THE ASSOCIATION BETWEEN EMPATHY AND PSYCHOPATHY

A few early accounts have distinguished primary from secondary psychopathy. These two subtypes are believed to originate from different underlying causes: where primary psychopathy is more related to a congenital affective deficit, secondary psychopathy emerges in response to environmental stressors (Poythress, Skeem, & 2006). Although the PCL-R measures a unitary construct, factor analyses have shown that its items also split into two subordinate factors (see Table 1), which are loosely related to this notion of primary and secondary psychopathy (e.g. Levenson, Kiehl, & Fitzpatrick, 1995). The first factor of the PCL-R taps into affective and interpersonal deficiencies, whereas the second factor is related to antisocial behaviour and an impulsive lifestyle (Hare, 2003; Hare, et al., 2001). Interestingly, the subscales of the PPI can also be divided into two factors, which seem to some extent to mirror the two factors of the PCL-R (see Table 2, Benning, et al., 2003). The two factors of the PCL-R have distinct patterns of correlations

with external criterion measures (Patrick, et al., 2009) and it is Factor 1 that captures the empathy deficit seen in psychopathy (Hare, 2003; Hare, et al., 2001).

The description of the empathy deficit in the PCL-R manual gives the impression of someone who understands others, but does not feel or care for them. It describes a person who has the ability to put himself in the shoes of others in a cognitive sense, but shows no affective response to this. Similarly, the empathy deficit in the PPI is described as a propensity toward callousness, guiltlessness and unsentimentality (Lilienfeld & Andrews, 1996). In both instruments, the lack of empathy seems therefore to apply mostly to an emotional component, which fits with the empathy literature in general, where the subdivision of empathy in cognitive and affective components is a recurring theme (see for example Davis, 1996).

Box 1.2: Antisocial personality disorder (APD)

The Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM IV-TR), defines antisocial personality disorder (in Axis II Cluster B) as:

- 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:
 - a. failure to conform to social norms with respect to lawful behaviors as indicated by repeatedly performing acts that are grounds for arrest;
 - b. deception, as indicated by repeatedly lying, use of aliases, or conning others for personal profit or pleasure;
 - c. impulsiveness or failure to plan ahead;
 - d. irritability and aggressiveness, as indicated by repeated physical fights or assaults;
 - e. reckless disregard for safety of self or others;
 - f. consistent irresponsibility, as indicated by repeated failure to sustain consistent work behavior or honor financial obligations;
 - g. 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.

Cognitive empathy is closely related to the concept of Theory of Mind and refers to the process by which we make inferences about the mental states of other people. Fitting with the descriptions in both the PCL-R and the PPI, there is not much evidence that individuals with psychopathy show pronounced deficits in this area, as a few studies indicate that they perform normal on various tests of Theory of Mind (Blair et al., 1996 ; Dolan & Fullam, 2004; Richell et al., 2003 ; Sommer et al., 2010), although Dolan et al. (2004) did observe some difficulties with detecting a faux pas¹. There is more evidence for a deficit in responses to the emotions of others, as indicated by psychophysiological research. For example, male adults with psychopathy show diminished autonomic responses to photographs depicting people experiencing distressing emotions (Blair,

¹ an embarrassing or tactless act or remark in a social situation (<http://oxforddictionaries.com/>)

Jones, Clark, & Smith, 1997) and when observing others receiving electrical shocks (Aniskiewicz, 1979). In addition, psychopathic individuals display a less potentiated startle reflex when they are instructed to watch pictures containing negative or thrilling content (Levenston, Patrick, Bradley, & Lang, 2000; Patrick, Bradley, & Lang, 1993).

The word empathy has been used to indicate many different, although not unrelated, phenomena. Batson (2009) attributed this to the different questions researchers can ask within the various fields in which empathy is a topic of interest. Where some investigators may be more interested in how people understand what others are thinking or feeling, others may find the mechanisms that lead people to respond with sensitivity to the needs of others more fascinating. As Batson puts it, researchers interested in the first question are interested in explaining “a particular form of knowledge”, whereas researchers interested in the second question are interested in explaining “a particular form of action” (Batson, 2009, page 4). In the field of psychopathy, both questions are very relevant. The significance of the second question becomes evident when looking at the characteristics of objectively measurable behaviour in psychopathy. It has been shown that psychopathy is not only related to an elevated risk for reactive aggression, but also for instrumental aggression (Blair, 2006; Cornell et al., 1996). The difference between these two is that reactive aggression is triggered by a perceived threat or provocation, whereas instrumental aggression is defined as the use of violence with the intent to achieve a goal (Cornell, et al., 1996). Previous research has shown that Factor 1 items of the PCL-R are not only associated with a considerable lower empathy (Hare, 2003; Hare, et al., 2001), but also with a heightened risk for instrumental aggression (Patrick & Zempolich, 1998; Porter & Woodworth, 2006).

The relationship between moral behaviour and empathy has been incorporated into a developmental model by James Blair (1995; Blair). The Violence Inhibition Model (VIM, Blair, 1995) tries to explain why moral transgressions² are easier to commit for individuals with psychopathy, by linking inadequate moral development to an early deficit in responding to the emotions of others. This early affective deficit is consistent with the notion of primary psychopathy. The VIM holds that individuals become aroused when they perceive someone in the vicinity experiencing distressing emotions, like fear or sadness. If these emotions occur within the context of a moral transgression, the two become paired. Eventually, this pairing gets internalized so that even the imagination of a moral transgression will increase the arousal of an individual and decrease the likelihood of an actual transgression. Critically, the VIM predicts that the early affective deficit of individuals with psychopathy interferes with this pairing process and as such with their moral development. The model therefore tries to explain how an empathy deficit can lead to behaviour which is less sensitive to the needs of others.

The other question Batson identified within the general literature on empathy (2009) is equally relevant with respect to the research on psychopathy; not only is it important to see how an empathy deficit can lead to amoral behaviour, but also why psychopathic individuals respond less to the emotions of others. In this respect, a very promising framework has emerged within the neuroscience literature over the past two decades, which generally states that understanding others

² a violation of a moral principle

relies (partly) on triggering neural states in the self similar to those in others (e.g. Bastiaansen, et al., 2009; Gallese, et al., 2004; Iacoboni & Dapretto, 2006; Keysers, et al., 2010; Pineda, 2008; Preston & de Waal, 2003; Rizzolatti & Craighero, 2004). In this thesis we will refer to these neural responses as vicarious responses and they will form the basis of the neuroscientific research presented in this thesis.

1.3 VICARIOUS RESPONSES

According to de Vignemont and Singer (2006), empathy occurs when the imagination or perception of the affective state of another triggers an affective state in the self which resembles the state of the other, without confusion about the source. This definition is in harmony with neuroscientific studies showing that observing emotions of others triggers neural activations in insular and cingulate (see Bastiaansen, et al., 2009` for a review) cortices normally associated with experiencing emotions yourself. In addition, studies investigating action observation suggest that the premotor cortex is also recruited both when we perform actions, and when we observe others performing similar actions (Caspers, Zilles, Laird, & Eickhoff, 2010; Keysers & Gazzola, 2009) and that somatosensory aspects of the experiences of other people are likewise able to trigger parts of the somatosensory cortex usually involved in sensing this ourselves (Keysers, et al., 2010; Pineda, 2008). This suggests that this mechanism of mirroring others is not restricted to emotions, but also applies to action performance and somatosensation. We will therefore extend the definition of de Vignemont and Singer to include sensations and actions. However, as our research was not intended to investigate whether there is any confusion about the source while sharing experiences of others, we will further simplify our working definition to: ***embodied empathy occurs when the imagination or perception of the affective state, sensation or action of another triggers a representation of this affective state, sensation or action in the self which resembles that of the other.*** As stated above, we will refer to these spontaneous neural responses as vicarious responses³ and the brain circuits that are re-activated as shared circuit (as they are shared between the first and second person perspective). This sharing mechanism appears to provide observers with an embodied feeling of the experiences of others. Indeed, in typical individuals, inter-individual differences in self-report measures of trait empathy correlate with the strength of these vicarious activations (Gazzola, Aziz-Zadeh, & Keysers, 2006; Jabbi, Swart, & Keysers, 2007; Singer et al., 2004).

1.4 THE GENERAL PARADIGM

Vicarious responses are by definition the activation of one's own neural repertoire for actions, sensations and emotions, upon the perception of similar actions or experiences of someone else. Paradigms designed to study this response often include both an experience condition and an observation condition. The experience condition then serves as a localizer condition to identify the neural substrates a participant uses to control his own actions and experience his own sensations and emotions. For example, the neural representation of a hand action differs slightly from that of a mouth action. The easiest way to establish whether subjects observing hand actions also truly recruit regions normally involved in hand actions is by overlaying their pattern of neural activation

³ 'experienced in the imagination through the feelings or actions of another person' (<http://oxforddictionaries.com/>)

during the observation of hand actions with the neural pattern during the execution of similar hand actions. The same rationale holds true for observing specific emotions and touch. For example, to know whether the observation of disgusted facial expressions recruits regions that are also used when you smell something disgusting, one would not only ask people to observe disgusted facial expressions, but also to smell disgusting odours. This is exactly what Wicker and colleagues (2003) did in a seminal study on the observation of disgust.

In this thesis we used magnetic resonance imaging (MRI) as an investigative tool. An MR scanner can take measurements from the brain while the subject is performing a task and provides information about the involvement of brain regions. Scanning the brain while the subject is performing a task is called functional magnetic resonance imaging (fMRI) and it is used to measure the blood-oxygen-level-dependent (BOLD) effect, or hemodynamic response, which is related to neural activity in brain regions. It is not possible with fMRI to measure the absolute level of 'brain activity' in a certain region. Instead, 'activity' during one condition is always subtracted from that during another condition. We therefore always speak of a relative increase or decreases in the hemodynamic response compared to, for example, a baseline condition or a control condition. In addition, functional signals measured by fMRI are comparatively weak, which means that subjects often have to perform the same task over and over again in order to achieve an acceptable signal-to-noise-ratio.

1.5 VICARIOUS RESPONSES IN PSYCHOPATHY AND OTHER PSYCHIATRIC DISORDERS

Although the empathy deficit in psychopathy has been related to inadequate neural sharing of emotions, with a special emphasis of the importance of this lack of affective sharing for the ability for instrumental aggression (Decety & Moriguchi, 2007), to date no fMRI study of criminal psychopathy has directly investigated whether psychopathy is indeed related to diminished vicarious responses. There are some indications that shared circuits are differentially activated compared to control groups (Deeley et al., 2006; Müller et al., 2003). In addition, of the five studies reporting whole-brain analyses of structural differences in psychopathy, four (de Oliveira-Souza et al., 2008; Schiffer et al., 2011; Tiihonen et al., 2008; Yang, Raine, Colletti, Toga, & Narr, 2009a) actually observed abnormalities in shared circuits. However, the amount of available neuroimaging data is still small. To date only 14 studies have used fMRI to study criminal psychopathy, using the PCL-R or the screening version as a diagnostic instrument. This includes one case study (Hoff, Beneventi, Galta, & Wik, 2009), eight studies including ten or less subjects per group (Birbaumer et al., 2005; Deeley, et al., 2006; Kiehl et al., 2001; Kiehl et al., 2004; Müller et al., 2008; Müller, et al., 2003; Veit et al., 2002; Veit et al., 2009) and only three studies with more than ten subjects (Dolan & Fullam, 2009; Harenski, Harenski, Shane, & Kiehl, 2010; Sommer, et al., 2010). This relative paucity is somewhat surprising given that the estimated point prevalence of psychopathy (0.006, Coid, et al., 2009; 0.012 Neumann & Hare, 2008) is higher than that of autism (0.0013, Fombonne, 2005) or schizophrenia (0.0046, Bhugra, 2005). In addition, as illustrated above, the sample sizes are often smaller than what is often considered the bare minimum for fMRI to lead to reliable results ($n > 15$, Thirion et al., 2007). This state of affairs likely reflects the incredible logistical challenge related with recruiting a large group of criminal subjects diagnosed with psychopathy.

Other psychiatric disorders that have been linked to deficient vicarious responses include both ASD (Iacoboni & Dapretto, 2006) and schizophrenia (Gallese, 2003; Salvatore, Dimaggio, & Lysaker,

2007). Disorders that fall within the spectrum of autism are related to problems with social relationships and communication and a display of stereotyped behaviours and interests. Autistic symptoms start to emerge during infancy or early childhood and the disorder is therefore listed under the Pervasive Developmental Disorders of the DSM-IV-TR (American Psychiatric Association, 2000). Neuroimaging studies on the association between shared circuits and ASD have generally focused on the role of the premotor cortex during the observation of actions and facial expressions of others. Findings have been rather inconsistent with some studies observing abnormal activity in motor regions or in muscle-specific motor responses (Bookheimer, Wang, Scott, Sigman, & Dapretto, 2008; Dapretto et al., 2006; Greimel et al., 2010; Grèzes, Wicker, Berthoz, & de Gelder, 2009; Hadjikhani, Joseph, Snyder, & Tager-Flusberg, 2007; Martineau, Cochin, Magne, & Barthelemy, 2008; Oberman et al., 2005; Oberman, Ramachandran, & Pineda, 2008; Uddin et al., 2008) and others not (Ashwin, Baron-Cohen, Wheelwright, O'Riordan, & Bullmore, 2007; Ilan Dinstein et al., 2010; Fan, Decety, Yang, Liu, & Cheng, 2010; Marsh & Hamilton, 2011; Pierce, Haist, Sedaghat, & Courchesne, 2004; Raymaekers, Wiersema, & Roeyers, 2009; Williams et al., 2006). However, the degree to which motor responses are triggered by the perception of others seems to relate to symptom severity (Dapretto, et al., 2006; Fan, et al., 2010) or social functioning (Bastiaansen et al., 2011).

Schizophrenia is listed on the first axis of the DSM-IV under the header of psychotic disorders. Manifestation of symptoms usually occurs between adolescence and early adulthood. This relative late onset stands in contrast to ASD, where symptoms are by definition present during the first three years of life and psychopathy, where behavioural problems usually manifest at an early age (before 12). Despite this late onset of active symptoms, schizophrenia is more and more viewed as a neurodevelopmental disorder, where subtle precursors of the illness might already be present during the first year of life (Insel, 2010). The DSM-IV recognizes positive and negative symptoms, which refer respectively to the presence of active symptoms like delusions and hallucinations and symptoms representing loss of function, such as flattened affect or catatonic behaviour (American Psychiatric Association, 2000). The observed signs of psychosis are the most obvious to spot and many forms of medication exist that are used to treat these symptoms. Although periods of psychosis can be very distressing, the remaining negative symptoms, can be just as debilitating (Kaneda, Jayathilak, & Meltzer, 2009). In addition, individuals with schizophrenia and negative symptoms show many of the same social deficits as adults with autism (Bastiaansen et al., 2010; Frith & Frith, 2003; Sheitman, Kraus, Bodfish, & Carmel, 2004).

Similarly to psychopathy, the integrity of shared circuits has not been intensively investigated in schizophrenia, although contrary to psychopathy, this is not due to a general lack of neuroscientific interest in this disorder. Using various tasks and techniques in relatively small samples, studies on schizophrenia have suggested that there might be more extensive activation in (pre)motor regions during the observation of simple facial diagrams (Quintana, Davidson, Kovalik, Marder, & Mazziotta, 2001), reduced motor responses during the observation of hand actions (Enticott et al., 2008), and decreased emotional resonance related to negative symptoms in small pre-defined regions in the anterior cingulate, orbitofrontal, and medial prefrontal cortex (Fahim et al., 2004). However, in a recent study, no group differences were observed between schizophrenia, ASD, and a control group

during face perception in a predefined region of the ventral premotor cortex that has been extensively studied in autism (Bastiaansen, et al., 2011).

The link between both ASD and schizophrenia and deficits in shared circuits makes them very interesting candidates to study alongside psychopathy. We have therefore also included ASD subjects and schizophrenic subjects in part of the experimental work of this thesis (Chapter 3 and 4).

1.6 AND SO, FINALLY...

In the Netherlands a convicted criminal can be sentenced to a ‘maatregel van Ter Beschikking Stelling’ (TBS-order) when the offence results in a sentence of at least four years of imprisonment and the defendant was deemed to have diminished responsibility for his or her acts due to a serious mental and / or personality disorder. The system was established to protect society from this type of offenders in two ways: directly by involuntary admission of the offender to a forensic psychiatric hospital and indirectly by reducing the risk of recidivism through treatment. The case of the offender is reviewed by an independent court at least once every two years to determine whether the risk of recidivism has sufficiently diminished. The psychopathic subjects included in the experimental part of this thesis were recruited from two forensic psychiatric clinics in the Netherlands that carry out this TBS-order. This process already began in late 2004 and has taken many years to complete, due to all the additional measures that were necessary in order to ensure safety throughout the project. These measures also affected the main subjects of this thesis, the inhabitants of the forensic clinics. Where most participants can enter our neuroimaging facilities on their own terms, they had to go through a lot to come to the centre. I therefore want to take this opportunity to thank the subjects for their involvement in this project. This work could not have been completed without their effort and willingness to cooperate.

1.7 AIMS AND OUTLINE OF THE THESIS

In this thesis, we will investigate the integrity of shared circuits in forensic patients diagnosed with psychopathy. In **chapter 2** we compare brain activity of psychopathic individuals with healthy control subjects while they observe short movies of hand interactions. In order to locate brain regions involved in these hand interactions, we additionally asked our subjects to experience similar interactions themselves with the researcher. The movies were developed in our own lab and always displayed two hands interacting with each other. We used a range of interactions with different valences to test whether group differences are specific for (particular) emotions or whether they also apply to emotionally neutral stimuli. The presented emotions were love (two hands caressing each other), pain (one hand hitting the other) and social rejection (one hand pushing away the other friendly hand). In addition, a neutral movie started with one hand touching the other, so as to attract attention, to which the second hand then responded non-emotionally. We included hand interactions instead of the more often used facial expressions because hand interaction show clear goal directed actions, sensations and emotions, and can thereby induce vicarious activations in all three of the systems associated with empathy at once (Bastiaansen, et al., 2009; Keysers & Gazzola, 2009). In **chapter 3**, we investigate the structural integrity of shared circuits, not only in psychopathy, but also in ASD and schizophrenia. We approach this matter by first performing a structured meta-analysis over the available literature on psychopathy, ASD and schizophrenia and

then compare the results from this meta-analysis to our own experimental dataset. This experimental dataset consists of T1 weighted anatomical images, which are analyzed using voxel-based morphometry. In **chapter 4**, we examined the quality of social interactions in psychopathy, ASD and schizophrenia, compared to a healthy control group, using the Autism Diagnostic Observation Schedule (ADOS, Lord, et al., 2000; Lord, Rutter, & Couteur, 1994; Lord, et al., 1999). The ADOS adopts a semi-structured interview setting to judge the quality of social interaction, communication, and imagination with an examiner and was administered to the psychopathy group in order to rule out any overlap with autistic symptoms. Because of the paucity of data on the validity of the ADOS in this population, especially in forensic settings, we decided to use the data from our three psychiatric groups to gain more knowledge about the selectivity and sensitivity of this instrument in diagnosing ASD and additionally examine how much of the behavioural characteristics of ASD truly overlap with psychopathy. **Chapter 5** reviews the literature on psychopathy and vicarious responses and suggests a possible mechanism by which the vicarious response might be regulated in the psychopathy group. In **chapter 6** we will then briefly summarize the chapters in this thesis and provide a general discussion.



VICARIOUS REPRESENTATIONS IN PSYCHOPATHY

Submitted as:

Reduced spontaneous but relatively normal deliberate vicarious representations of other people's experiences in psychopathy

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ABSTRACT

Psychopathy is a personality disorder associated with a profound lack of empathy. Neuroscientists have associated empathy and its variation with how strongly participants activate brain regions involved in their own actions, emotions and sensations while viewing those of others. Here we compared brain activity of 18 psychopathic offenders with 26 control subjects while viewing movie clips of hand interactions and while experiencing similar interactions. Brain regions involved in *experiencing* these interactions were not spontaneously activated as strongly in the patient group while *viewing* movie clips. However, this group difference was markedly reduced when we specifically instructed participants to feel with the actors in the movies. Our results suggest that psychopathy is not a simple incapacity for vicarious activations but rather reduced *spontaneous* vicarious activations co-existing with relatively normal *deliberate* counterparts.

2.1 INTRODUCTION

Psychopathy, as diagnosed using the Psychopathy Checklist-Revised (PCL-R) (Hare, 2003; Hare, et al., 2001) is a personality disorder that affects about 1% of the general population and about 10% of the male prison population (Coid, et al., 2009). Offenders diagnosed with psychopathy pose a significant threat to society because they are more likely to harm other individuals and to do so again after being released (Coid, et al., 2009). Psychopathy is characterized by poor behavioural control, a disregard for the rights of other people, deficits in the emotional and interpersonal domain (Coid, et al., 2009; Hare & Neumann, 2009) and in particular, a considerably reduced emotional empathy (Blair, et al., 2006), i.e. a reduced tendency to share the emotions of others. It has been argued that this reduced emotional empathy may disinhibit aggression (Feshbach & Feshbach, 1982; Miller & Eisenberg, 1988) and therefore facilitate antisocial behaviour. If a typically developing child punches another and sees it cry, the vicarious experience of pain is likely to discourage future violence. On the other hand, a child with psychopathic tendencies may not share this emotion as much and may therefore have less reason to refrain from further violence.

In the normal population, observing the actions, sensations and emotions of others triggers activations in premotor (Caspers, et al., 2010; Keysers & Gazzola, 2009), somatosensory (Keysers, et al., 2010), insular (Bastiaansen, et al., 2009; Jabbi, et al., 2007; Lamm, Decety, & Singer, 2011; Singer, et al., 2004; Singer et al., 2006; Wicker, 2003) and cingulate (Bastiaansen, et al., 2009; Singer, et al., 2004) cortices normally associated with programming similar actions and feeling similar sensations and emotions. This suggests that vicarious representations of the observer's own actions, sensations and emotions are spontaneously triggered when viewing those of others. These vicarious activations are thought to represent a neural foundation for empathy in general, and emotional empathy in particular (Bastiaansen, et al., 2009; Iacoboni & Dapretto, 2006; Keysers & Gazzola, 2009; Singer, et al., 2004). In typical individuals, inter-individual differences in self-report measures of trait empathy correlate with the strength of these vicarious activations (Gazzola, et al., 2006; Jabbi, et al., 2007; Singer, et al., 2004). Additionally, when participants are asked to consciously attribute thoughts and beliefs to others (mentalizing), rather than simply perceive their actions, emotions and sensations, they recruit a different network of brain regions including the medial prefrontal cortex, precuneus and temporo-parietal junction (Amodio & Frith, 2006; Van Overwalle & Baetens, 2009). This mentalizing network is seldom co-activated with regions related to vicarious activations, suggesting that spontaneous empathy and mentalizing are distinct mental operations, that can however complement each other (de Lange, Spronk, Willems, Toni, & Bekkering, 2008; Keysers & Gazzola, 2007; Schippers, Roebroek, Renken, Nanetti, & Keysers, 2010; Zaki, Ochsner, Hanelin, Wager, & Mackey, 2007).

Understanding whether the lack of empathy characterizing psychopathy is associated with reduced vicarious activations would have wide ranging implications. First, it would inform clinicians and legal practitioners, helping them to optimize the diagnosis and treatment of psychopathy thereby reducing the societal risks of this disorder (Koenigs, Baskin-Sommers, Zeier, & Newman, 2010). Second, it would help assess the hotly debated idea that dysfunctions in vicarious activations could underlie psychiatric disorders (Dapretto, et al., 2006; Dinstein, Thomas, Behrmann, & Heeger, 2008; Iacoboni & Dapretto, 2006; Minio-Paluello, Lombardo, Chakrabarti, Wheelwright, & Baron-Cohen,

2009; Smith, 2009). So far this idea has mainly been tested in Autism Spectrum Disorders (ASD), but it remains unclear whether autistic individuals have reduced emotional empathy (Minio-Paluello, et al., 2009; Smith, 2009). Instead, some argue that social difficulties in autism may primarily derive from impaired mentalizing (Blair, 2005; Smith, 2009). In contrast, adults with psychopathy present with a relatively pure deficit in emotional empathy coexisting with normal mentalizing skills (Blair, 2005). Accordingly, measuring vicarious activations in psychopathy might be a direct test if abnormal vicarious activations can be a feature of certain psychiatric disorders of empathy. Third, psychopathy has often been studied as a deficit model to understand the development of morality (Blair, 1995, 2007; de Oliveira-Souza, et al., 2008), and a better estimate of vicarious activations in psychopathy could therefore inform our understanding of the neural basis of morality. Unfortunately, measuring vicarious activations in psychopathy has been hindered by the unavailability of high-field magnetic resonance imaging (MRI) in the high security forensic institutions in which convicted psychopathic offenders reside. Only two fMRI studies so far included a psychopathic offender group that was rigorously diagnosed (PCL-R) and large enough (>10 subjects) to reliably measure brain activity in this population (Harenski, et al., 2010; Sommer, et al., 2010), but none of them used paradigms designed to reveal abnormal vicarious activations.

To test the hypothesis that the lack of emotional empathy in psychopathy can be partly attributed to reduced vicarious activations, we developed short movie clips of two hands interacting with each other in either a loving (hands caressing each other), painful (one hand hitting the other), neutral (one hand touching the other to get attention) or rejecting way (one hand pushing away the other friendly hand; Figure 1A). We used the interactions of hands because they involve goal directed actions, sensations and emotions, and can thereby induce vicarious activations in all three of the systems associated with empathy at once (Bastiaansen, et al., 2009; Keysers & Gazzola, 2009). We used a range of interactions with different valences to test whether group differences are specific for (particular) emotions or whether they also apply to emotionally neutral stimuli. Because of their deficits in empathy, we expected the psychopathy group to show reduced vicarious activations, i.e. that brain regions involved in performing/experiencing hand interactions would be hypoactive in the psychopathy group (compared to healthy controls) while viewing these hand interactions. In addition, we hypothesized that explicitly encouraging psychopathic individuals to empathize with the actors in the screen might reduce this difference, because previous studies have shown that deliberate social cognition is relatively preserved in subjects diagnosed with psychopathy (Blair, et al., 1996; Dolan & Fullam, 2004; Richell, et al., 2003; Sommer, et al., 2010). Accordingly, in the first, Observation experiment, we mapped regions spontaneously recruited by the vision of these stimuli by instructing subjects to simply watch the movies. During the second, Empathy experiment, we examined if group differences might be reduced if participants deliberately attempt to empathize, by instructing subjects to feel with one of the hands in the screen. In the third, Experience experiment, we localized brain areas involved in executing/experiencing these interactions by letting subjects perform similar interactions (Figure 1B) with one of the authors (HM). The design of the three experiments is depicted in Figure 1C. In accordance with the recently recommended guidelines (Koenigs, et al., 2010) we analyzed a group of 18 incarcerated offenders satisfying the European psychopathy cut-off of PCL-R \geq 26, with 15 of them also satisfying the high American cut-off of 30.

2.2 METHODS

2.2.1 PARTICIPANTS

We recruited 20 convicted male offenders diagnosed with psychopathy and 26 matched controls. The offenders were recruited from two forensic psychiatric hospitals in the Netherlands (Forensic Psychiatric Clinic Dr. S. van Mesdag and Veldzicht). The male patient list was screened for possible suitable candidates with the help of the research departments within both clinics. We invited all patients with a Psychopathy Checklist-Revised (PCL-R; (Hare, 2003; Hare, et al., 2001)) ≥ 26 (see description below), no prior diagnoses of Schizophrenia, other Psychotic Disorders or Autistic Spectrum Disorders and age 18 - 60 years to participate in the study. It was stressed that participation would not influence their treatment in any way. Two patients had to be excluded from further analyses, one because of technical difficulties during scanning and one because of drug abuse on the day of scanning. All results presented in this paper are of the remaining 18 patients.

None of the controls had been treated for or diagnosed with a neuropsychiatric disorder and they were matched as a group with the patient group on age, gender and IQ. It was not possible to match the groups on both education level and IQ, since the criminal history of the psychopathic group interfered with their formal education, leading to atypically low levels of education for their IQ. However, only control subjects were included with an education level below bachelor degree.

This study was approved by the Research and Ethics Committee of the University Medical Center Groningen. Signed informed consent was obtained from all subjects. Head of treatment of each patient also gave permission for participation in the study and reported that the patient was able to understand written and spoken Dutch language. The Ministry of Justice gave permission for the study and evaluated the status of each individual patient separately for safety issues. All subjects received €7,50 per hour for participation in this study.

2.2.2 SPECIFIC ASSESSMENT OF THE PSYCHOPATHY GROUP

The DSM-IV diagnosis of each patient was established prior to arrival at the clinic by a forensic psychiatrist and psychologist commissioned by court or during a stay at a national forensic-psychiatric observation and diagnostics centre, as organized by the Netherlands Institute for Forensic Psychiatry and Psychology (NIFP). This initial diagnosis is adjusted based on additional or extended psycho diagnostic and psychiatric investigation at the clinic itself.

The golden standard for establishing psychopathy in psychiatric patients is the PCL-R (Hare, 2003; Hare, et al., 2001), which is administered as part of the standard clinical procedure within these forensic institutions. The PCL-R consists of 20 items which are scored 0 (no indication), 1 (some indication) or 2 (indication) and can lead to a maximum sum score of 40. The items are completed using file information extended with, if necessary, a semi-structured interview. Although the traits of psychopathy are considered to be dimensional, the manual recommends using a cut-off of 30. This cut-off was determined through studies in North America. However, in Europe a more lenient cut-off (PCL-R ≥ 26) is often used (Grann, et al., 1999; Rasmussen, et al., 1999; Sjöstedt & Långström, 2002), which seems consistent with a lower mean PCL-R score recently found in a large Dutch forensic sample across three institutions (Spreen, ter Horst, Lutjehuis, & Brand, 2008) compared to the one reported in the manual. The diagnosis of psychopathy was established by two

trained diagnosticians of the clinic, who independently scored the PCL-R for every patient and reached consensus about each item through discussion.

2.2.3 GENERAL ASSESSMENT

All subjects completed questionnaires about their health, age, handedness, education and fMRI compatibility. Subjects' reported education level was converted to a standard rating using the method of the Central Bureau of Statistics in the Netherlands. The education level is expressed by a number ranging from zero to nine, where a level of one stands for primary school and a level of 9 is reached when participants obtain a master degree from a university. Years of education is the summation of years attending school, not including short courses.

The Raven's Standard Progressive Matrices (Raven; (Raven, Raven, & Court, 2003)) and the abbreviated Groninger Intelligentie Test (GIT-2; (Luteijn & Barelds, 2004)) were used as measures of IQ. The abbreviated GIT-2 is a Dutch validated ~35 minutes IQ test for adults between 16 and 90 years of age with normative data from a sample of 1514.

Because the PCL-R cannot be used on the general population for lack of collateral information, all subjects filled out the Psychopathic Personality Inventory (PPI; (Jelicic, Merckelbach, Timmermans, & Candel, 2004; Lilienfeld & Andrews, 1996)), a 187 item self-report measure designed to apply to criminal and noncriminal populations. All subjects were screened using the Autism Diagnostic Observation Schedule (ADOS; (Lord, et al., 1999)).

All subjects provided a list of their medication. The list of the patients was checked against their official record. The medication list was reviewed by one of the authors (JdB, psychiatrist) for psychoactive medication.

Three measures of self-reported trait empathy were administered to all subjects. The Interpersonal Reactivity Index (IRI, Davis, 1980), the Balanced Emotional Empathy Scale (BEES; (BEES, Mehrabian, 1997)) and the Empathy Quotient (EQ; (EQ, Baron-Cohen & Wheelwright, 2004)).

Independent t-tests were performed to assess the difference between the groups on age, education level, years of education, handedness, IQ scores (Raven and GIT2), and on the scores of the PPI and empathy questionnaires, using SPSS 16.0 for Windows. Two tailed tests were used for most measures (Age, GIT2-IQ, Raven, Handedness, Years of education, Education level) but one tailed t-tests were used for those in which the patient group was a-priori expected to show reduced scores (i.e. the IRI, EQ and BEES) or augmented scores (i.e. the PPI).

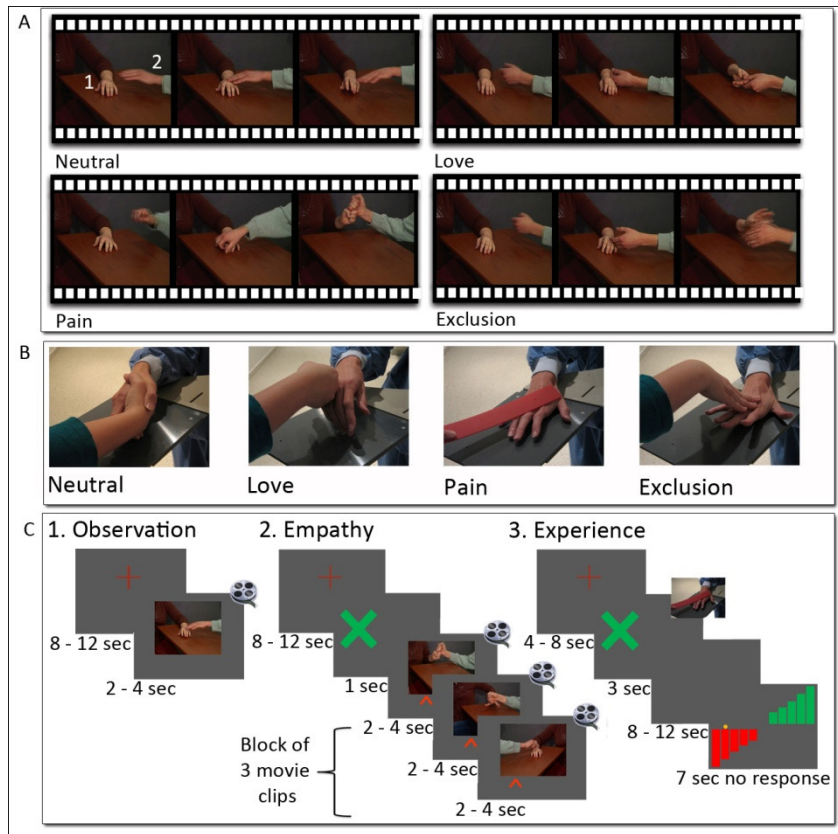


Figure 1: Experimental paradigm. **A:** Three still frames from example movies of each condition. Each movie included a receiving (white number 1) and an approaching (white number 2) hand. **B:** Photo of hand interactions during the Experience experiment. **C:** Design of the three experiments (always performed in this order). **1. Observation experiment:** Event related display of movie clips separated by fixation cross. **2. Empathy experiment:** A fixation cross in the middle of the screen was followed by a green cross on the left or right side of the screen. This indicated the hand in the screen with which the subjects were instructed to ‘feel’, thereby directing their empathy towards the receiving or approaching hand. Subjects then saw three short movie clips of the same category (either 3 painful or 3 loving hand interactions) separated by 500 ms of black screen. During the movies, a red arrow reminded the subjects of the hand they were instructed to feel with. **3. Experience experiment:** A fixation cross was presented in the middle of the screen, followed by a green cross on the left or right side of the screen. This indicated the start of the interaction with the experimenter (HM). At that point subjects initiated the interaction by lifting their hand towards the experimenter. The experimenter immediately responded with a caress, a handshake, and three slaps on the back of the hand or by pushing the hand of the subject away. Subjects then rated the interaction using a 2-button response box. Subjects had 7 seconds to start moving the dot. If no rating was given within 7 seconds, the experiment would continue without a score. Before the Experience experiment, every interaction was practiced with the subjects until they understood how they should perform. During the Observation experiment, eye-gaze was tracked (see for an example of an eye gaze density plot Figure S2). Movies were rated post scanning using in-house questionnaire (Figure S1).

2.2.4 EXPERIMENTAL PARADIGM

All subjects performed three separate fMRI experiments: Observation, Empathy and Experience. During the Observation experiment, subjects watched short (2, 3 or 4s) movie clips depicting emotional or neutral hand interactions (Figure 1A). The represented emotions were love (two hands caressing each other), pain (one hand hitting the other) and social rejection (one hand pushing away the other friendly hand). A neutral movie started with one hand touching the other, as to attract attention. The second hand then responded non-emotionally. Each movie contained a receiving hand, already visible at the beginning of the movie, and an approaching hand (Figure 1A, respectively white numbers 1 and 2), entering the screen to initiate the interaction and was left-right mirrored using movie editing software to ensure that approaching hands would enter just as

often from the left as the right side of the screen. Subjects were instructed to watch the movies as if they were watching one of their favourite movies. They were told that a question would be asked about the movies later and that they could answer this question if they had watched (not memorized) the movies carefully. Movies were randomly assigned to two ~8 minutes' event-related functional runs, each of which consisted of 36 movies (9 repetitions of each of the 4 movie types) separated by a fixation cross for about 8-12s (Figure 1C). Subjects' gaze was recorded, during the Observation experiment, using an infrared video camera (SMI, iView). The camera was mounted onto the feet end of the scanner bed and tracked the movements of the left eye of the subject through a mirror mounted on the head coil. Sample frequency was 50 Hz. Before each run the eye tracker was calibrated using 9 points within the part of the screen on which the movies were later displayed.

Only the love and pain conditions were used for the Empathy experiment, due to the time constraint of the total paradigm, and presented in a block design (12 blocks for the love and 12 for the pain condition; ~9 minutes in total). Each block was composed of three different movies from the same category (Figure 1C). In half of the blocks, subjects were instructed to feel with the receiving, in the other half with the approaching hand (Figure 1A, respectively white numbers 1 and 2).

During the Experience experiment, participants interacted with one of the authors (HM) in a way similar to the interactions shown in the movies (Figure 1B). In particular, subjects offered their left or right hand to the experimenter, who in turn caressed, hit, shook or rejected the subject's hand. The 24 interactions (6 repetitions for each of the 4 conditions) were split in two runs. Subjects used the left hand in one run, the right in the other run. The run order was then counterbalanced across subjects (Figure 1C). This experiment was added to our paradigm as a localizer condition, to identify the neural substrates a participant uses to perform similar hand interactions himself.

2.2.5 MOVIE RATING

After finishing the three MR experiments, subjects were asked to rate all the movies presented during the Observation and Empathy experiment by means of an in-house questionnaire. To build the questionnaire, 60 undergraduate students, not participating in the MR study, were asked to watch all the stimuli and come up with the word that would best describe the emotion behind the two interacting hands. The most frequently used words were then chosen as emotion descriptors for the questionnaire. The questionnaire, shown in Figure S1, consisted of three parts. First, separately for each of the two hands, subjects had to choose the category that best described the emotion (Question 1a) and rate the intensity of that emotion on a Likert scale (Question 1b). Second, subjects were asked to indicate the hand with which they spontaneously empathized most strongly (Question 2). Finally, subjects had to indicate how negative or positive the movie made them feel (Question 3). The data of Question 1a and Question 2 were transformed into frequency scores. For Question 1a this meant that the frequency for each answer category (Pain/Hurt, Annoyed/Anger or Love/Affection) was calculated per movie type and hand (approaching or receiving). For Question 2a frequency for each answer category (Approaching hand, receiving hand, both of the hands and none of the hands) was calculated per movie type. A repeated measures linear mixed model was then used with movie type as repeated measures to analyze both questions. For Question 1b and 3 we

used a repeated measures linear mixed model on the average rating per subject per movie type and hand category. Mixed models (linear mixed-effects models) were used to deal with the correlated nature of the data and were calculated using SPSS 16.0 for Windows.

2.2.6 FMRI ACQUISITION, PREPROCESSING AND GENERAL LINEAR MODEL ANALYSIS

Brain activity was measured using a Philips Intera 3T Quaser with an 8Ch synergy SENSE head coil (32 axial gradient-echo slices, 3 mm thickness, no gap, single shot EPI, echo time = 30 ms, repetition time = 1.5) to cover the entire brain and cerebellum. Slices were aligned to the AC-PC line. The first 5 scans were discarded for each run to adjust for T1 equilibration. A T1 weighted image was acquired for anatomical co-registration with 160 slices (TR: 7.55 ms, TE: 3.5 ms, flip angle, FoV: 224; 160; 256, matrix 256x229, voxel size: 1 x 1 x 1 mm). The duration of fMRI experiment scan time was about 47 minutes.

Images were processed and analyzed using the Statistical Parametric Mapping software (SPM5; Wellcome Department of Cognitive Neurology, London, UK), running on Matlab (Version 7.1; MathWorks Inc., Natick, MA, USA). All EPIs of a subject were aligned to each other; the T1 scan was co-registered to the mean EPI and segmented into grey, white and CSF. Normalization parameters were calculated based on the grey-matter segment of the co-registered T1 image and applied to all EPI volumes. Images were then normalized with a resolution of 3x3x3mm and analyzed using SPM5. The data was spatially smoothed using a 9 mm Gaussian kernel. Time series were high-pass filtered at 300s to remove low-frequency noise and slow drifts in the signal. Analysis of the individual imaging data was carried out using separate general linear models for each experiment.

At the first level of analysis, we modelled the Observation experiment using separate predictors for the four movie types (Love, Pain, Exclusion and Neutral) as boxcar functions convolved with the hemodynamic response function. The same was done for the Experience experiment, with the addition of a fifth predictor that modelled the rating phase of all the trials. For the Empathy experiment, separate regressors were used for empathizing with the receiving or approaching hand in both the Love and the Pain conditions. Beta values for the same predictors during the Observation experiment were summed across runs to create a summary volume per condition and subject. For the Experience experiment the two runs were first analysed separately at the first level. These separate volumes for the left and the right hand were then pooled together and analyzed at the second, population level. Unless otherwise specified, all analyses were performed within a mean grey matter mask and thresholded using $p_{unc} < 0.001$ and $p_{FDR} < 0.05$, whatever was more stringent. The mean grey matter mask was constructed by taking the average of all normalized grey matter segments and thresholding this mean image at 0.3.

First, we explored group differences during any of the experiments separately, starting out with the Experience experiment. We generated a general linear model ANOVA, including eight columns, four for each interaction type (Love, Pain, Exclusion and Neutral) in the psychopathic group, and four for each interaction type in the control group. As a manipulation check, we first examined the main effect of interaction type, followed by post hoc tests within significant voxels to determine the direction of the differences. We then tested the null hypothesis that for each interaction type, the two groups had the same BOLD signal in each voxel, using a contrast of [1 0 0 0 -1 0 0 0; 0 1 0 0 0 -1

0 0; 0 0 1 0 0 0 -1 0; 0 0 0 1 0 0 0 -1]. Given that we found significant differences, we then explored if the differences between the groups depended on interaction type, with group as between subjects variable and movie type as repeated measure (using an F-contrast of [1 -1 0 0 -1 1 0 0; 0 1 -1 0 0 -1 1 0; 0 0 1 -1 0 0 -1 1]). As we had included the Experience experiment as a localizer experiment, we then used this condition to build a Vicarious-Experience mask (see subsection 2.2.7).

Secondly, we examined differences between the two groups during the Observation experiment, again using a general linear model ANOVA including eight columns, four for each movie type in the psychopathic group, and four for each condition in the control group. To examine whether our different categories of visual stimuli had been able to activate different brain networks, we first assessed the main effect of movie type. Given that there was an effect of movie type, we performed post hoc tests between all movie types inclusively masked by the main effect of movie type to determine the direction of these effects (similar to the analysis of the Experience experiment). We then assessed the group differences and the interaction between movie type and group in a similar manner to the analyses conducted on the Experience experiment. We repeated this analysis by explicitly masking the results (pre-threshold) with our Vicarious-Experience mask (see subsection 2.2.7) in order to localize these effects to voxels that had also been activated by similar interactions during the Experience experiment.

Thirdly, we looked at group differences during the Empathy experiment. This was again done by using a general linear model ANOVA, with group as between subjects factor and the factor movie type (Love, Pain) and hand (receive, approach) as two within subjects factors. We first tested whether there were main effects of movie type and hand. Given that there were any differences, these were followed up with post hoc tests, inclusively masked with the corresponding main effect. We then tested the null hypothesis that the two groups had the same BOLD signal in every voxel for each movie type-hand combination (Love approach, Love receive, Pain approach, Pain receive). Given that we found significant differences, we then explored if the difference between the groups depended on the displayed emotion or on the hand they had to attend to. As with the Observation experiment we redid these analyses within the Vicarious-Experience mask (subsection 2.2.7) in order to localize these effects.

Finally we wanted to assess whether the additional instructions to empathize at the start of the second experiment had significantly changed the group differences. We therefore performed an interaction analysis between group (psychopathic vs. control participants) and experiment (Observation and Empathy). Only two of the emotions were tested in both experiments (Pain and Love). Given that we found no interactions between group and emotion in either experiment, we created summary parameter estimate images separately for both experiments. For Observation, parameter estimates for Pain and Love movies were summed over the two sessions and the two movie types for each participant. For Empathy, parameter estimates were summed over Pain receive, Pain approach, Love receive and Love approach. This resulted in one summary parameter estimate y per subject i for the Observation experiment ($y_{i,obs}$) and one for the Empathy experiment ($y_{i,emp}$). An interaction analysis was performed using a full factorial ANOVA in SPM, with groups being independent and experiment being dependent, to account for the repeatedness of the data. The

interaction was calculated over the entire gray matter mask. A subsequent small volume correction using the Vicarious-Experience mask was used to check whether significant changes also involved empathy regions.

2.2.7 ROI ANALYSES

To examine whether group differences during the Observation and Empathy experiments fell inside brain areas associated with vicarious responses, we used a regions of interest (ROI) approach in addition to our whole brain analyses. Vicarious responses are by definition the activation of one's own neural repertoire for actions, sensations and emotions, upon the perception of similar actions or experiences of someone else. Since the literature on neural representations of experiencing hand interactions similar to ours is scarce, we decided to run our own separate experiment (Experience experiment) to localize regions recruited by our specific hand interactions. However, because not all voxels, which are recruited during this Experience experiment, are likely to be vicarious (as we don't know whether they are also activated during the perception of others, we intersected these results with a very general anatomical parcellation of the brain, including regions that have previously been associated with vicarious responses. This was implemented by adopting a three step approach.

During the first step, we created a large anatomical ROI, containing brain regions known to exhibit vicarious properties. Review studies indicate that the premotor cortex (Caspers, et al., 2010; Gazzola & Keysers, 2009), the somatosensory cortices (Keysers, et al., 2010), the insula (Bastiaansen, et al., 2009; Lamm, et al., 2011) and the ACC (Bastiaansen, et al., 2009; Lamm, et al., 2011) all contain voxels that have vicarious properties. We therefore created ROIs containing these regions, using the Anatomy Toolbox (Eickhoff et al., 2007) for SPM and, for regions not available in the Anatomy toolbox, the AAL atlas of the WFU Pickatlas (Maldjian, Laurienti, Kraft, & Burdette, 2003). We then combined these separate ROIs using a logical 'OR' into a single composite anatomical ROI (Figure 2, red transparent regions).

In the second step, we used the independent data from our localizer experiment (Experience) to select voxels that were significantly activated by one of our conditions, by either one of the groups using Marsbar (<http://marsbar.sourceforge.net/>). Specifically, we first performed eight separate one-sample random effect t-tests comparing the four summary volumes (Love, Pain, Neutral, Exclusion) of the controls and those of the patients against zero ($p_{unc} < 0.001$). We then combined these eight functional maps with a logical 'OR'. This composite functional ROI thus contained voxels that were significantly activated by at least one of the conditions for at least one of the groups (Figure 2, blue transparent regions).

In the third step we combined the composite functional ROI with the composite anatomical ROI using a logical 'AND' between the two (Figure 2, purple transparent regions).

2.2.8 BASELINE ANALYSIS

Because the BOLD measure during all experiments was established relative to baseline, differences in baseline activation between the two groups could also account for the differences found between the groups. We therefore assessed whether the groups differed during baseline by testing separately

for every experiment, using two sample t-tests, if the global parameter in the GLM differed across groups.

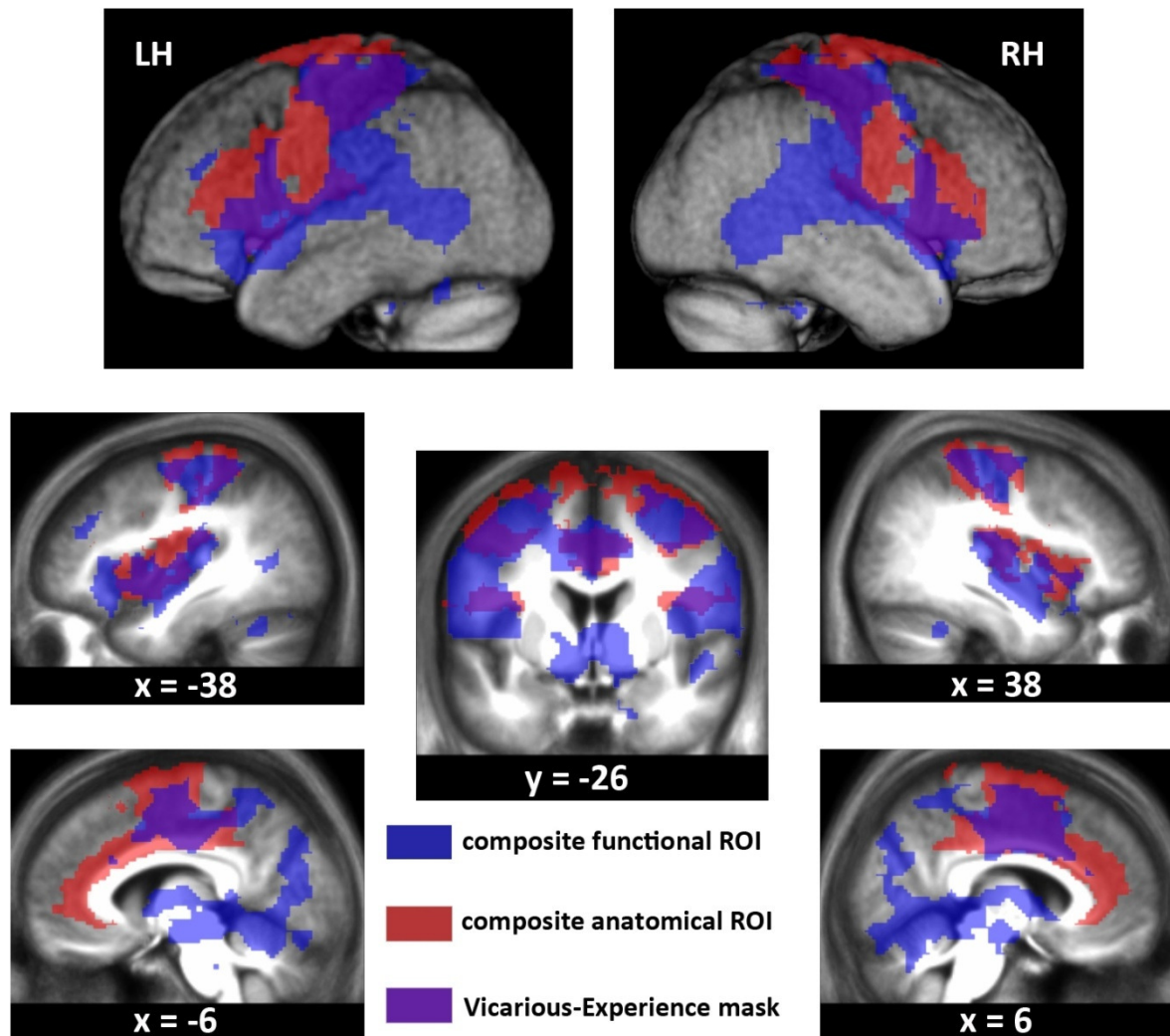


Figure 2: Vicarious-Experience mask. A voxel was included in this mask if it was significantly activated during one of the interactions of the Experience experiment (for the patients or the controls, composite functional ROI) and if it belonged to anatomically defined brain regions the literature has associated with motor, somatosensory or affective aspects of tactile experiences (composite anatomical ROI). This is indicated by the purple regions, which indicate the overlap between the red and blue regions.

2.2.9 INFLUENCE OF EXPERIENCE ON PERCEPTION

It could be argued that the lack of sensitivity to other people's experiences in psychopathic individuals might be due to the reduced intensity with which they experience similar situations themselves. We were interested in seeing whether the differences between the groups during Observation could be explained by differences in brain activity during Experience. Because group differences did not significantly depend on movie type for Observation, we first calculated a summary contrast image per subject for the Observation experiment by adding the beta values for the four movie types. The same was done for the four types of interactions during the Experience experiment. We then fitted a linear regression, voxel-by-voxel, such that $observation(i) = a * experience(i) + b + residual(i)$, where $observation(i)$ and $experience(i)$ represent the

summed parameter estimates for all Observation and Experience conditions, respectively, for participant *i*. We then compared the residual(*i*) across the two groups to test if there was a group difference between the activity during Observation after removing the variance that can be accounted for by differences in Experience.

2.2.10 ANALYSIS OF THE EYE TRACKER DATA

Differences during the Observation experiment between the two groups could also be driven by differences in where (gaze location) and how long (gaze duration) subjects looked at the videos. We therefore examined the eye tracking data during the Observation experiment. We first removed artefacts, then blinks and saccades. Saccades were defined as samples between which the eye gaze velocity relative to the last sample changed by more than 30 deg/s, and blinks as values where the *x* and *y* coordinates were zero. To remove slow frequency drift from the data due to head movements, the data was de-trended using a third-degree polynomial. To do this, we reasoned that while a fixation cross was presented in the middle of the screen during the Observation experiment, the average gaze position of the participant should be constant over time. Accordingly, we calculated the mean eye gaze position for each period of fixation cross of the Observation experiment. We then fitted a third order polynomial as a function of time (one for the *x*-axis and one for the *y*-axis), separately for each functional run to these average fixation periods. These regressions were then used to detrend all eye gaze measurements by subtracting the expected (*x*,*y*) coordinates over time from all (*x*,*y*) measurements.

To check if patients and controls looked at different regions of the screen while watching the movies, we pooled the data from all movie types and generated eye gaze density plots (Figure S2) for each subject, representing the relative time a subject spent looking at each possible coordinate while movies were being presented. This was done by counting how often each pixel of the screen had been a point of fixation (i.e. the number of 50Hz frames during which the point of regard was in this position after exclusions of saccades and blinks) while participants looked at the movies, and dividing this by the total amount of fixations measured during the movies. This two dimensional matrix was then smoothed using an 8x8 pixel HWFM Gaussian kernel. The eye gaze density pattern of the two groups was then compared pixel-by-pixel using a 2-sample t-test at $p_{FDR} < 0.05$. This was done by transforming the matrix into a single slice Nifti Volume, and analyzing it using SPM as if it were fMRI data. To assess for group differences in the amount of time subjects spend looking at the movies we calculated the ratio of samples per movie that fell inside the part of the screen where the movie was displayed during each event. We then calculated the average ratio across the movies for each subject and performed a 2-sample t-test ($p < 0.05$) to assess for differences between the groups.

2.3 RESULTS

Groups did not differ from each other on age, IQ and handedness (Table 1). The patient group was significantly lower-educated. Mean PCL-R score for the patient group was 32.3 (SE 0.85; Figure S3). As expected, the control group scored lower on the Psychopathy Personality Inventory (PPI). However, groups did not differ from each other on the three measures of self-reported trait empathy we used (Table 1). Diagnostic and Statistical Manual of Mental Disorders - IV (DSM-IV) diagnoses of the included patients are summarized in Table S1. None of the participants scored

above the cut-off for ASD. Two patients were taking medication classified as psychoactive (one subject took citalopram 20 mg per day and one received amitriptyline daily 7 tablets of 25 mg). None of the control subjects reported using medication that was classified as psychoactive.

	Mean control (n = 26)	Mean patient (n = 18)	p-value t-test
Age	36.96 (1.62)	39.17 (2.41)	$p_{2\text{-tailed}} = 0.434$
GIT2-IQ	98.77 (2.79)	93.65 (4.00)	$p_{2\text{-tailed}} = 0.283$
Raven-IQ	115.08 (2.05)	106.62 (5.30)	$p_{2\text{-tailed}} = 0.101$
Handedness	10.08 (0.38)	9.67 (0.83)	$p_{2\text{-tailed}} = 0.623$
Education level	4.88 (0.54)	2.00 (0.47)	$p_{2\text{-tailed}} < 0.001$
Years of education	11.96 (0.34)	7.39 (0.40)	$p_{2\text{-tailed}} < 0.001$
PCL-R	n/a	32.3 (0.85)	n/a
IRI	53.80 (2.95)	56.44 (3.04)	$p_{2\text{-tailed}} = 0.273$
EQ	60.28 (8.06)	60.72 (8.39)	$p_{2\text{-tailed}} = 0.431$
BEES	26.08 (4.74)	39.00 (8.11)	$p_{2\text{-tailed}} = 0.076$
PPI Total	398.92 (7.61)	422.39 (9.48)	$p_{2\text{-tailed}} = 0.030$

Table 1: Assessment data. Numbers in brackets represent standard errors of the means. T-tests were used to compare the means of the groups (p values were not corrected for multiple comparisons). As indicated in the last column, p-values are based on two-tailed testing except where directed hypotheses existed. Data for the PCL-R is not available for the control group. Abbreviations as described in the Assessment sections of the Methods. Further detail can be found in the Supplemental Information: Supplemental Figure 1 is a histogram of the PCL-R scores for the patient group and Supplemental Table 1 lists the clinical diagnosis for each patient separately.

We first assessed the main effect of interaction type during the Experience experiment as a manipulation check for the different emotions we had included. We found a main effect of interaction type ($p_{\text{unc}} < 0.001$ at $F(3,168) = 5.68$, also survives $p_{\text{fdr}} < 0.05$). We then assessed the directionality of these effects using post hoc tests on the voxels that showed a main effect of interaction type (Table S2). We assessed group differences during the Experience experiment by testing the null hypothesis that for each interaction type, the two groups had the same BOLD signal. An analysis of variance (ANOVA) did not reveal any significant group differences ($p_{\text{FDR}} > 0.05$), nor interactions between hand interaction type and group ($p_{\text{FDR}} > 0.05$), despite the fact that we had found a significant main effect of interaction type. We therefore combined the activation maps from the Experience experiment from all participants with anatomically defined *a priori* regions to build our Vicarious-Experience mask (Figure 2), which we used to identify areas involved in empathy for both groups (i.e. areas activated by the execution/experience and observation of similar emotional hand interactions).

We then analyzed the Observation experiment. We found a main effect of movie type ($p_{\text{unc}} < 0.001$ at $F(3,168) = 5.68$, also survives $p_{\text{fdr}} < 0.05$). We assessed the directionality of these effects using post hoc tests on the voxels that showed a main effect of movie type (Table S3). Ventral parts of the medial prefrontal cortex, including the orbitofrontal cortex and the anterior cingulate gyrus, respond stronger to Love compared to Neutral and Pain, whereas more dorsal regions respond more to Painful movies compared to all other conditions. A few voxels in the medial prefrontal cortex also respond more to Exclusion compared to Pain. More dorsal parts of the premotor cortex were relatively more recruited by the non-negative stimuli (Neutral and Love), whereas more ventral parts were found to be more active for the Pain and Exclusion movies. Primary somatosensory cortex was most extensively activated by the Love movies compared to all other conditions, probably reflecting the relative large amount of touch in this condition. Secondary somatosensory cortex (right) was least activated by the Exclusion movies. The Neutral condition activated a

bilateral region more than Love that was located at approximately the temporo-parietal junction. An ANOVA on the Observation data revealed no significant interaction between group and movie

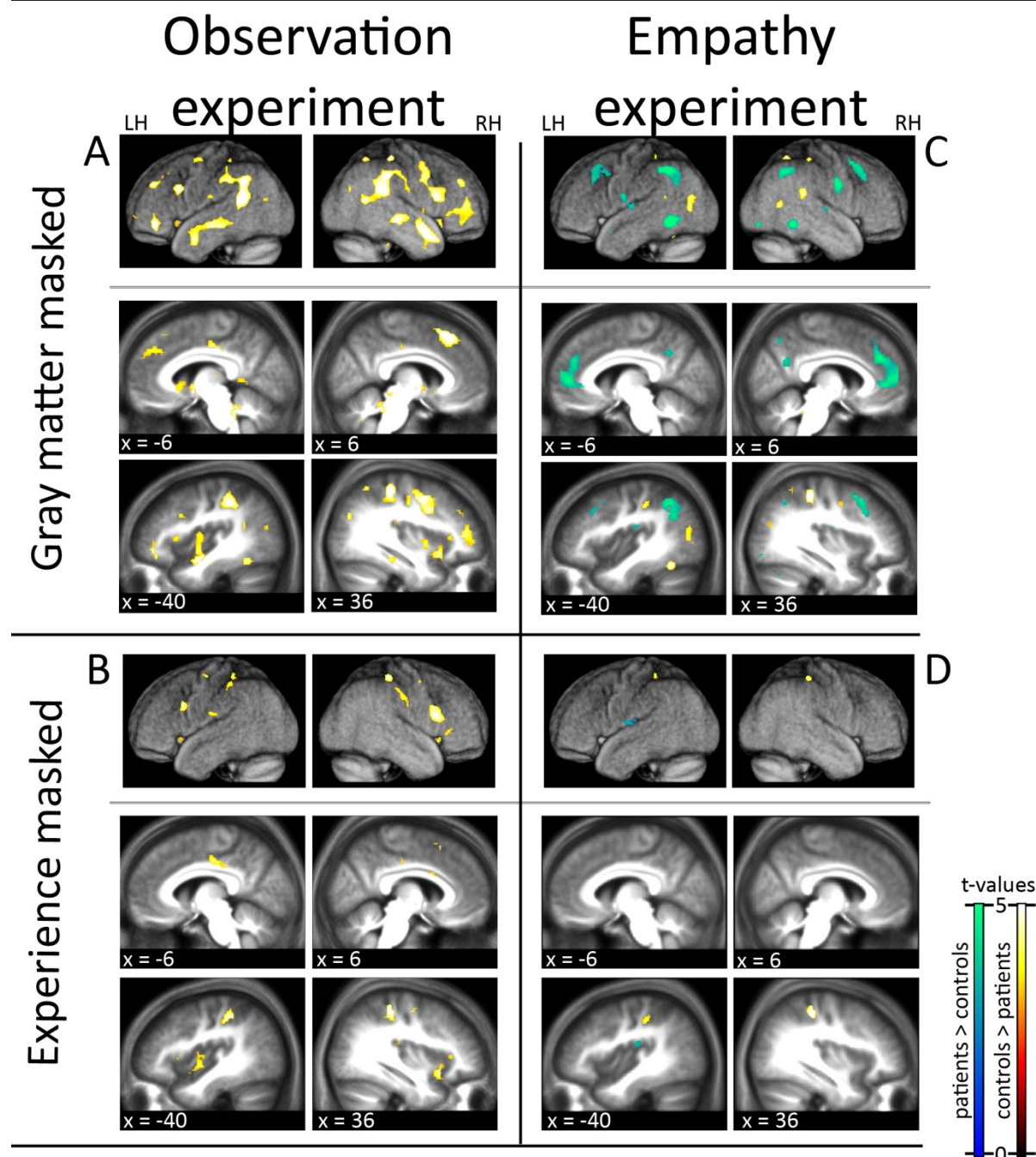


Figure 3: Results of Observation and Empathy experiment. A, B: group differences during the Observation experiment. C, D: group differences during the Empathy experiment. A, C: results within the gray matter mask (viewing depth of 16 voxels; $p_{\text{unc}} < 0.001$. All clusters also survive $p_{\text{FDR}} < 0.05$, minimal cluster size of 10 voxels, Supplemental Tables 2 and 3). B, D: same as A, C, but masked inclusively with the Vicarious-Experience (Tables 2 and 3). Hot colors: BOLD response control > psychopaths, cold colors: psychopaths > controls. RH = right hemisphere, LH = left hemisphere. x: MNI coordinate of sagittal plane. Slices and renders are taken from the mean normalized anatomy of all subjects.

type ($p_{\text{FDR}} > 0.05$). We therefore summed the activations in the four movie types to look at the main effect of group and reveal an extended network of brain regions in which the blood oxygen level dependent (BOLD) signal differed between the groups ($p_{\text{unc}} < 0.001$ at $F(1,168) = 11.22$); Fig. 3A and

Table S4, all differences also survive $p_{FDR} < 0.05$). All of these regions showed higher BOLD for the control subjects. We then repeated this analysis, explicitly masking our results (pre-threshold) with regions falling inside our Vicarious-Experience mask to localize these effects. Results indicate that group differences during the Observation experiment indeed include a significant number of voxels of this mask (Figure 3B and Table 2).

Cluster size	T	MNI coordinates			Hemi-sphere	Macro anatomical location of peak voxel	Overlap with cytoarchitectonic regions
		x	y	z			
Controls larger patients							
173	6,26	36	-33	54	R	Postcentral Gyrus	BA2, BA3ab
	4,25	51	-24	42	R	Supramarginal Gyrus	
	3,87	60	-15	27	R	Supramarginal Gyrus	
242	6,20	-33	-36	45	L	Postcentral Gyrus	BA2, BA3ab SPL (5L)
	4,68	-9	-18	42	L	Midcingulate Gyrus	
	4,33	-12	-42	48	L	Precuneus	
35	5,64	21	-3	54	R	Superior Frontal Gyrus	BA6
	4,80	6	18	54	R	pre-SMA	
	4,04	12	6	57	R	pre-SMA	
84	5,41	60	15	18	R	Inferior Frontal Gyrus (p.	BA44, BA45
	3,87	48	12	24	R	Inferior Frontal Gyrus (p.	
85	5,15	-36	-6	-12	L	Insula	Insula (Id)
	3,89	-36	-3	12	L	Insula	
72	5,08	27	-12	48	R	Precentral gyrus (dPM)	BA6
20	4,87	-51	15	27	L	Inferior Frontal Gyrus (p.	BA44
45	4,86	30	15	-18	R	anterior Insula	
	4,72	36	18	-12	R	anterior Insula	
67	4,80	-27	-21	51	L	Precentral gyrus (dPM)	BA 6
	4,24	-27	-9	54	L	Precentral gyrus (dPM)	
	4,06	-33	-6	60	L	Precentral gyrus (dPM)	
72	4,38	-33	15	3	L	anterior Insula	
	4,07	-27	21	6	L	anterior Insula	
35	4,25	9	-21	39	R	Midcingulate Gyrus	
30	4,14	42	-33	15	R	Superior Temporal Gyrus	OP1, OP2
	4,00	45	-24	18	R	Rolandic Operculum	
49	4,07	45	-3	-9	R	Superior Temporal Gyrus	
	3,99	42	3	0	R	middle Insula	
14	4,03	54	30	0	R	Inferior Frontal Gyrus (p.	BA45
27	3,86	-54	-15	21	L	Postcentral Gyrus	OP1, OP4 BA3b
	3,25	-54	-15	33	L	Postcentral Gyrus	
16	3,83	9	9	27	R	Midcingulate Gyrus	
	3,52	3	15	21	R	Midcingulate Gyrus	
14	3,82	36	30	6	R	anterior Insula	
Patients larger controls							

Table 2: Main effect of group, Observation experiment within Vicarious-Experience mask. Differences in brain activity between the psychopathy and control group ($p < 0.001$ uncorrected, cluster extend threshold of ten voxels, all clusters survive FDR correction at $p = 0.05$) within the Vicarious - Experience mask (see Supplemental Table 2 for the results within the gray matter mask). The table specifies the size of each cluster, then, for its peak, the T-value, MNI coordinates, hemisphere and macro anatomical location based on the groups mean anatomy. Finally, the table specifies cytoarchitectonic brain regions that the cluster overlaps with according to the Anatomy Toolbox.

We then analyzed the results from the Empathy experiment. We found a main effect of movie type ($p_{unc} < 0.001$ at $F(1,168) = 11.22$, also survives $p_{fdr} < 0.05$) but no main effect of hand (approach, receive) at $p_{unc} < 0.001$ ($F(1,168) = 11.22$). Post hoc tests for the main effect of movie type, inclusively masked by the main effect of movie type are presented in Table S5. Amongst these differences were that the Love movies triggered a relative higher BOLD response in primary somatosensory

areas, whereas the Pain movies were related to a higher response in areas such as the anterior insula, anterior cingulate cortex and ventral premotor cortex. We then tested for group differences during the Empathy experiment. An ANOVA revealed a main effect of group (Fig. 3C, $p_{\text{unc}} < 0.001$ at $F(1,168)=11.22$; all clusters also survive $p_{\text{FDR}} < 0.05$), but no interaction between group and movie type. Some areas were more activated for the controls, but fewer than during the Observation experiment. Importantly, in contrast to the Observation experiment, the instruction to feel with the hands in the movies now led to a number of brain regions being more activated in the *patients*, including the medial and dorsolateral prefrontal cortex and the angular gyrus (Fig. 3C and Table S6). Repeating the analysis, explicitly masked with the Vicarious-Experience mask, revealed only a few group differences: the control group only had higher BOLD in bilateral primary somatosensory cortex; the patient group in bilateral secondary somatosensory cortex (both $p_{\text{unc}} < 0.001$ at $T=3.14$; Fig. 3D and Table 3, all clusters also survive $p_{\text{FDR}} < 0.05$).

Cluster size	T	MNI coordinates			Hemi-sphere	Macro anatomical location of peak voxel	Overlap with cytoarchitectonic regions
		x	y	z			
Controls larger patients							
53	6,64	36	-33	51	R	Postcentral gyrus	BA2, BA3
48	4,87	-33	-36	45	L	Postcentral gyrus	BA2, BA3
Patients larger controls							
33	4,63	42	-15	18	R	Parietal Operculum	OP1-4
48	3,89	-57	-12	9	L	Parietal Operculum	OP1-4

Table 3: Group differences, Empathy experiment within Vicarious - Experience mask. Table lists areas that were more activated for the controls (positive effect of controls) and areas that were more activated for the patients (positive effect of patients) within the Vicarious - Experience mask (see Supplemental Table 3 for differences between the two groups within the gray matter mask) at $p_{\text{unc}} < 0.001$, cluster extend threshold of ten voxels, all clusters survive FDR correction at $p=0.05$). Conventions as in Table 2.

To test if group differences are significantly smaller after the instruction to empathize with one of the hands in the movies, we examined the interaction effect between the Observation and Empathy experiments and the variable group. We first tested for which voxels the differences between the patients and controls had been smaller or larger during the Observation experiment compared to the Empathy experiment. The results indicate that brain activation in many regions normalizes (relatively more similar to the control group) after the instruction to empathize ($p_{\text{unc}} = < 0.001$, $T=3.19$, also survives $p_{\text{fdr}} < 0.05$), but that there are no regions where the difference in BOLD response between the two groups becomes significantly larger. Brain normalization occurs in regions such as the medial and anterior left insula, left hippocampus, bilateral thalamus, left caudate, left anterior cingulate cortex, bilateral angular gyrus, see Table 4. After a small volume correction with the Vicarious-Experience mask it turns out the left anterior insula within this mask significantly normalizes with the instruction to empathize (see Table 4, see asterisk). We repeated this analysis with z-transformed data but the results were very similar (data not shown).

Before discussing the implications of these findings in terms of differences in empathy, several alternative explanations for the extended hypoactivation of the patient group relative to the control group during the Observation experiment have to be excluded. First, the patients might not have been looking at the movies as much as the controls. We examined eye-tracking data collected during the Observation experiment. Because of technical challenges, stable eye gaze data was obtained for 13 patients and 19 control subjects. Since we found no significant interaction effect between movie type and group in the fMRI data, we tested for differences in average eye gaze

patterns towards all the movies (see Figure S2 for an example eye gaze pattern). No significant differences were found between the two groups in spatial eye gaze pattern ($p_{FDR} > 0.05$) or in time spent looking at the movies ($p > 0.05$). Second, differences between the groups while viewing the movie types might have been caused by differences in baseline activation, rather than differences in activity during the actual movies. However, we found no differences in baseline activation

Cluster size	T	MNI coordinates			Hemi-sphere	Macro anatomical location of peak voxel	Overlap with cytoarchitectonic regions
		x	y	z			
59	5.69	-21	-33	-3	L	Thalamus, Hippocampus	Hipp (FD, SUB, CA)
30	5.19	-42	42	-12	L	Inferior Frontal Gyrus (p.	
59	4.91	-48	0	-27	L	Middle Temporal Gyrus, Temporal Pole	
137	4.53	-48	-54	39	L	Inferior Parietal Lobe	hIP1, IPC (PGa, PF, PFm)
11	4.49	36	39	-12	R	Inferior Frontal Gyrus, Middle Orbital Gyrus	
207	4.39	33	15	45	R	Middle Frontal Gyrus	
49	4.36	9	30	48	R	Superior Medial Gyrus, Anterior Cingulate Gyrus	
49	4.33	-9	39	33	L	Superior medial Gyrus, Anterior Cingulate Gyrus	
36	4.24	-48	21	30	L	Inferior Frontal Gyrus	BA44, BA45
12	4.16	-21	57	-3	L	Superior Orbital Gyrus	
31	4.04	-30	24	45	L	Medial Frontal Gyrus	
63*	3.99	-36	3	-6	L	Insula Lobe	
45	3.99	45	-42	24	R	Inferior Parietal Cortex	IPC (PFm, PGa)
16	3.87	-21	36	33	L	Superior Frontal Gyrus	
13	3.87	-15	15	0	L	Caudate	
13	3.83	21	-33	3	R	Hippocampus	Hipp (FD)
12	3.48	-33	-15	-24	L	Hippocampus	Hipp (CA, SUB, EC)

Table 4. Regions normalized after empathy instruction. Table represents results within the gray matter mask. Analysis is based on raw values. *Also survives after SCV with the Vicarious-Experience mask (31 voxels). Only peak voxels are included in the table. Conventions as in Table 2.

between the groups using a 2-sample t-test on the global parameters of the GLM during Observation, Empathy and Experience ($p_{FDR} > 0.05$). Third, group differences can arise because the movies were appraised in a different way by both groups. To examine this possibility we analyzed the rating of the movies provided by all participants after the experiment (Figure S1). We found no significant main effect of group for any of the movie ratings questions. Fourth, it has been argued that reduced empathy in psychopathy might result from a flattening of the emotions of psychopathic individuals themselves (Hare, 1993). Translated to our experiment, one might therefore ask whether differences in brain activity during Experience might account for the group difference during Observation. Although we did not find any group differences in the analysis of the Experience experiment (see above), we used a linear regression analysis to further investigate this question. We therefore removed, separately for each voxel of the brain, the variance in BOLD activity across participants during the Observation experiment that could be predicted/explained by that during the Experience experiment. We then repeated the initial ANOVA on the residual, unexplained variance in Observation within those regions that were hypoactivated for the patient group during the Observation experiment. Some of the brain regions that demonstrated group differences in our initial analysis still showed significant group differences after removing the variance that could be explained by differences in Experience (Table 5).

2.4 CONCLUSIONS

In this study we analyzed vicarious activations in a group of incarcerated subjects with a diagnosis of psychopathy by having them experience and observe emotional hand interactions while being scanned. We then compared these activations with those of age and IQ matched healthy controls. During passive observation, individuals with psychopathy showed, compared to controls, a hypoactivated network that included parts of bilateral superior temporal gyrus, bilateral middle

Cluster size	T	MNI coordinates			Hemi-sphere	Macro anatomical location of peak voxel	Overlap with cytoarchitectonic regions		
x	y	z							
Controls larger patients									
21	4,44	-18	-33	0	L	Thalamus	Hippocampus (SUB, FD)		
27	4,30	48	-27	-3	R	Superior temporal gyrus			
10	3,95	48	-42	24	R	Supramarginal gyrus	IPC (PFm)		
12	3,82	6	27	48	R	Superior frontal gyrus	BA6		
12	3,76	21	-33	3	R	Thalamus	Hippocampus (FD, CA,		
10	3,74	-48	-48	15	L	Superior temporal gyrus			
12	3,60	-33	-36	42	L	Supramarginal gyrus	BA2		
Patients larger controls									

Table 5. Results of regression analysis. Differences in average brain activity while viewing movies after variance related to experiencing similar interactions has been regressed out. Analysis is restricted using a regions of interest approach using the areas that were found to be differentially activated for the groups during the Observation experiment (based on the F-test). Only clusters of at least 10 voxels with $p_{unc} < 0.001$ are shown (all clusters also survive FDR correction at $p = 0.05$). No areas were hyperactive for the patients compared to the control group (not even at $p = 0.05$ uncorrected). Conventions as in Table 2.

temporal gyrus, bilateral hippocampus extending into amygdala, bilateral inferior parietal cortex, bilateral prefrontal and frontal regions, bilateral thalamus and left caudate nucleus and brainstem clusters. A subset of these regions was also involved in performing/experiencing similar interactions. In particular, by using the independent data from our Experience experiment, we show that areas associated with vicarious responses to actions (premotor and posterior parietal cortices (Caspers, et al., 2010; Gazzola & Keysers, 2009)), sensations (SI/SII, (Keysers, et al., 2010)) and emotions (Insula (Bastiaansen, et al., 2009; Jabbi, et al., 2007; Lamm, et al., 2011; Singer, et al., 2004; Singer, et al., 2006; Wicker, 2003)) were hypoactivated in the psychopathy compared to the control group. We further show that these differences in visually triggered responses go beyond what can be explained by differences in the experience of similar interactions. These significantly reduced vicarious activations were measured despite the fact that the (i) looking pattern (from eye-tracking), (ii) rating of the movies (from post-scanning ratings), and (iii) baseline brain activation (from the global parameter estimate in the general linear model) did not significantly differ across groups. Additionally, these group differences were markedly reduced when we specifically instructed participants to feel with the actors in the movies.

Because there is a significant security risk associated with bringing incarcerated offenders to our scanning facility, we do not have a control group of incarcerated not-psychopathic offenders. Accordingly, our results should be interpreted with awareness of the possibility that secondary factors that are linked to the psychopathic life-style may have contributed to the differences we observe: unusually low level of education, history of drug abuse and length of incarceration. As high-field neuroimaging facilities may become available within forensic institutions, it will become essential to compare psychopathic offenders against two control groups, forensic and non-forensic

individuals, to isolate the contribution of psychopathy proper from those associated with a criminal life-style. Unfortunately, as these variables are highly correlated with the factor group in our study, we are not able to correct for them using nuisance covariates in our analyses (G. A. Miller & Chapman, 2001). With this caveat in mind, our results shed new light on the neural basis of psychopathy in two ways.

First, they point to reduced vicarious activity in regions involved in performing actions, feeling touch and experiencing emotions as a likely neural basis for the reduced empathy, so central to psychopathy (Blair, et al., 2006; Hare, 2003; Hare & Neumann, 2009; Hare, et al., 2001). For most of us, seeing someone hurt another triggers vicarious activity in pain related areas including the somatosensory (Keysers, et al., 2010), insular and anterior cingulate cortices (Lamm, et al., 2011). This vicarious pain activation essentially gives us an egoistic reason to refrain from antisocial behaviour: do not hurt others because it (vicariously) hurts you. The fact that electrical stimulation of the insula can make monkeys discontinue actions they are currently engaged in (e.g. biting an apple or threatening others (Caruana, Jezzini, Sbriscia-Fioretti, Rizzolatti, & Gallese, 2011)) provides causal evidence for the notion that insular activity (as triggered during the vision of our stimuli) can influence goal directed actions in powerful ways. In the case of psychopathy, the reduced vicarious representations could relax these constraints on antisocial behaviour and help explain why they can use antisocial behaviour more often than other individuals to achieve their goals (Frick, Stickle, Dandreaux, Farrell, & Kimonis, 2005). Because we found the deficits in vicarious activations to be independent of movie type, these deficits seem to extend to the pleasure of other individuals and their emotionally neutral actions. When we help others, their happiness could vicariously reward our actions and promote prosocial behaviour. Reduced vicarious activations for pleasure could then also explain why individuals with psychopathy fail to help others.

This hypo-vicarious view of psychopathy, suggested by our data, integrates with models where the amygdala plays an important role (Blair, 2007). According to these models, the amygdala of normal children helps them associate their instrumental aggressive behaviour, which is originally neutral, with negative emotions triggered by the distress of their victims (Blair, 2007). These negative associations discourage the normal child from future aggression. In children with psychopathic tendencies, a hypo-functioning amygdala impairs this process. An open question in these models remains how the distress of others acquires a negative valence to be associated with the action. The burgeoning literature on vicarious activations (e.g. (Bastiaansen, et al., 2009; Gallese, et al., 2004; Keysers, et al., 2010; Lamm, et al., 2011; Singer, et al., 2004; Wicker, 2003) suggests that the distress of others is associated with personal distress because it triggers activity in regions involved in our own experience of these sensations and emotions. Indeed, in the normal population, people experiencing more personal distress and empathic concern show stronger vicarious activations (Jabbi, et al., 2007; Lamm, et al., 2011; Singer, et al., 2004; Singer, et al., 2006). Combining our findings with the amygdalar view leads to a more comprehensive vision of psychopathy: reduced vicarious activations lead to reduced personal distress while harming others and reduced amygdalar function leads to reduced associations between aggression and the (reduced) personal distress. This combination could then explain why individuals with psychopathy fail to distinguish moral transgressions involving the distress of others from conventional transgressions that do not (Blair,

1995). In support of this view, we also measured reduced activation in the bilateral amygdala of our psychopathy compared to our control group during passive observation (Observation experiment).

Second, our results show that an explicit instruction to feel with the actors in the movies had a profound impact on the group differences we observed. Psychopathic brain activity changes, compared to controls, from none of the voxels being more active during the Observation experiment (Table 2, Table S4) to slightly more than half being more active in the Empathy experiment (Table 3, Table S6). Without instructions to empathize, individuals with psychopathy therefore show reduced vicarious activations, while when encouraged to deliberately empathize, they boost their brain activity in response to the stimuli in a number of ways. Their medial prefrontal and precuneal activity increases beyond that of typically developing individuals. Both of these regions have been associated with conscious mentalizing (Amodio & Frith, 2006; Van Overwalle & Baetens, 2009) but not with spontaneous empathy (Van Overwalle & Baetens, 2009). Psychopathic individuals also boost their dorsolateral prefrontal cortex and angular gyrus activity relative to control individuals - two regions involved in emotional reappraisal (Ochsner et al., 2004). At the same time, in the Vicarious-Experience mask, the instruction to empathize made most of the group differences during Observation disappear: premotor, insular and cingulate regions now show similar levels of vicarious activations in the two groups. Only a small region of SI continues to show more vicarious activation in the control participants whilst part of bilateral SII is now more strongly activated for the psychopathy group. Altogether, this pattern of changes between Observation and Empathize suggests that when instructed to empathize, psychopathic individuals may deploy voluntary social cognition and emotional reappraisal more than controls and that this is accompanied by an almost complete normalization of their vicarious activation. Accordingly, combining the findings of the Observation and Empathize experiment, our data characterizes psychopathy as a reduced *propensity* for, rather than an incapacity to, generate vicarious activations.

Situational factors and personal characteristics can influence the strength of spontaneous vicarious responses (de Vignemont & Singer, 2006). For example, it has been shown that, compared to their female counterparts, male participants show equally strong vicarious activity in response to the pain of fair victims but weaker responses when these victims had previously been unfair to them (Hein & Singer, 2008b; Singer, et al., 2006). We show that vicarious activations are more affected by instructions in male psychopathic than male control participants. In the light of these observations, the evolutionary pressure that may have equipped males with mechanisms to modulate their empathy may have equipped subjects with psychopathy with an exceptional capacity to do so. One might speculate that this capacity to modulate vicarious activations is an evolutionary advantage: they could use vicarious activations when trying to understand what makes others 'tick' to con them, but when aggression serves their purpose, their capacity to refrain from spontaneous empathy would loosen the bounds of conscience and give them a competitive edge. Interestingly, psychopathy is also more frequent in males than females (Cale & Lilienfeld, 2002).

In conclusion, our study has three core implications. First, it sheds light on the neural basis of psychopathy by suggesting that it is not so much an *incapacity* to vicariously activate representations of the actions, sensations and emotions of others but a lacking *propensity* to do so spontaneously. This may have important implications for therapies: therapies may not need to focus

on the capacity for empathy but on the propensity to do so spontaneously. That said, motivating them to do so might be the biggest challenge of all. Second, our study provides support for the idea that deficits in vicarious activations may be an important feature of at least some psychiatric disorders of empathy. Finally, in line with seeing psychopathy as a deficit model for morality, our data invites the speculation that normal *spontaneous* vicarious activations, rather than the *capacity* for vicarious activations, are necessary for the development of care-based morality.



2.5 SUPPLEMENTAL FIGURES

Look carefully at the designated hand and report the emotion ‘behind’ that hand



	No	Weak	Clear	Strong
Annoyed / Anger	0	1	2	3
Pain / Hurt	0	1	2	3
Love / Affection	0	1	2	3

	No	Weak	Clear	Strong
Annoyed / Anger	0	1	2	3
Pain / Hurt	0	1	2	3
Love / Affection	0	1	2	3

Which of the two hands matters the most to you, personally?  

Circle none if you don't feel clear empathy, both if you empathize with both and one (right or left) if you only empathize with one hand.

How do you *yourself* feel while watching the movie?

Tickmark the most appropriate box.

-5	-4	-3	-2	-1	0	1	2	3	4	5
<i>very bad</i>					<i>no emotion</i>					<i>very good</i>

Figure S1: Movie rating questionnaire. This questionnaire was used to rate an instance of every movie shown to the subjects during the Observation experiment, translated in English.



Figure S2: Example eye gaze density plot. A frame from a loving movie is displayed in the background. The white dots on top of the movie frame represent the relative amount of time this subject spent looking at that particular location. The whiter a dot, the more time that location was looked at.

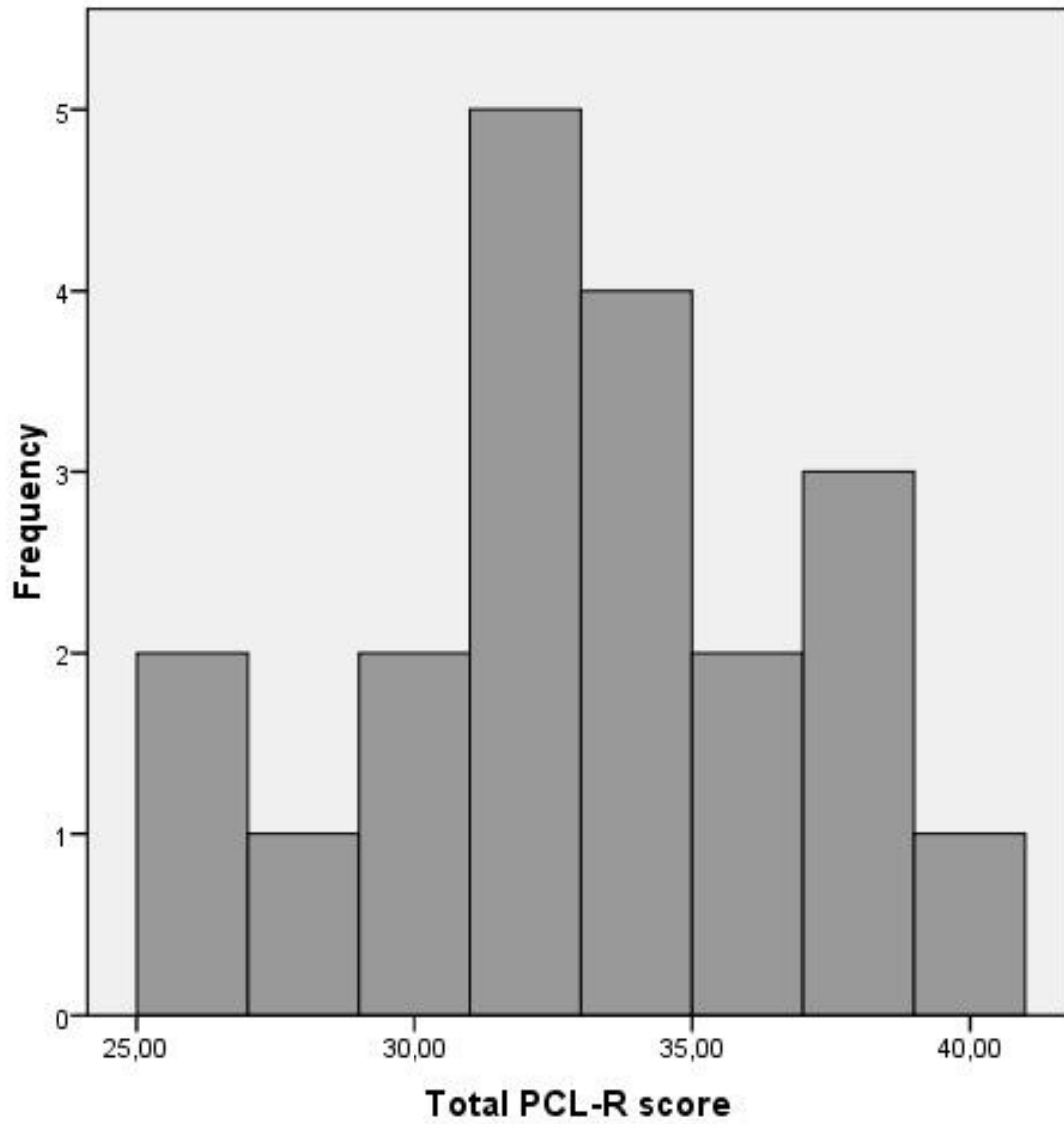


Figure S3: PCL-R assessment in patient group. A histogram of the PCL-R scores of all analyzed patients.

2.6 SUPPLEMENTAL TABLES

Subject	Axis I	Drug History	Axis II		Current Medication
1	305.20 305.10 305.70 304.20 305.50	Cannabis Abuse Nicotine Dependence Amphetamine Abuse Cocaine Dependence Opioid Abuse	301.7 301.81	Antisocial PD Narcissistic PD	
2	305.00 305.60 305.20	Alcohol Abuse Cocaine Abuse Cannabis Abuse	301.7	Antisocial PD	
3	305.00 302.81 302.84	Alcohol Abuse Fetishism Sexual Sadism	301.7 301.83 301.81	Antisocial PD Borderline PD Narcissistic PD	citalopram 20 mg per day
4	312.31	Pathological Gambling	301.7	Antisocial PD	
5	303.90 314.01	Alcohol Dependence Attention-Deficit /	301.83	Borderline PD	
6	304.80	Polysubstance	301.7	Antisocial PD	amitriptyline 25 mg daily 7
7	302.2 305.00	Pedophilia Alcohol Abuse	301.9	PD NOS	
8	305.00 300.23	Alcohol Abuse Social Phobia	301.9	PD NOS	
9	305.00 305.60 305.20	Alcohol Abuse Cocaine Abuse Cannabis Abuse	301.81 301.7 301.83	Narcissistic PD Antisocial PD Borderline PD	
10	V71.09	No Diagnosis or Condition on Axis I	301.81 301.7	Narcissistic PD Antisocial PD	
11	304.30	Cannabis Dependence	301.9	PD NOS	
12	V71.09	No Diagnosis or Condition	301.7	Antisocial PD	
13	304.80 302.70	Polysubstance Sexual Dysfunction NOS	301.7 301.81	Antisocial PD Narcissistic PD	
14	305.60 305.50	Cocaine Abuse Opioid Abuse	301.9	PD NOS	
15	V61.21 302.2 303.90	Sexual Abuse of Child Pedophilia Alcohol Abuse	301.7	Antisocial PD	
16	V61.1 V61.1 304.30 305.00 312.31	Sexual Abuse of Adult Physical Abuse of Adult Cannabis Dependence Alcohol Dependence Compulsive Gambling	301.7	Antisocial PD	
17	304.20 304.30	Cocaine Dependence Cannabis Dependence	301.7 301.83	Antisocial PD Borderline PD	
18	302.2 V61.21 305.20	Pedophilia Sexual Abuse of Child Cannabis Abuse	301.9	PD NOS	

Table S1: Assessment of clinical diagnosis of patient group. The table lists DSM-IV diagnosis and psychoactive medication per patient. Subjects were given arbitrary number to preserve their anonymity. PD = Personality Disorder.

Cluster size	T	MNI			Macro anatomical location of peak voxel
		x	y	z	
Love > Pain					
539	10,93	-45	-21	51	Precentral gyrus, Postcentral gyrus, Superior parietal lobe
870	10,82	51	-18	48	Precentral gyrus, Postcentral gyrus, Superior parietal lobe
117	8,46	24	-51	-30	Cerebellum
123	7,46	-21	-51	-27	Cerebellum
161	6,33	-6	6	48	Mid cingulate gyrus
284	6,28	-9	45	-3	Mid orbital gyrus, Anterior cingulate gyrus
24	4,98	57	9	30	Precentral gyrus
39	4,89	24	3	0	Putamen, Pallidum
13	4,87	-30	42	27	Middle frontal gyrus
47	4,81	51	-60	0	Medial temporal gyrus, Inferior temporal gyrus (posterior)
55	4,76	-18	9	3	Putamen
17	4,05	3	6	-3	Caudate
Pain > Love					
847	7,16	-60	-36	9	Medial / Superior temporal gyrus, Heschls gyrus, Insula lobe, Rolandic operculum
150	7,08	66	-24	3	Superior temporal gyrus
150	6,28	54	-51	42	Inferior parietal lobe, Angular gyrus
46	5,29	-48	-51	45	Inferior parietal lobe, Angular gyrus
12	4,92	6	33	39	Superior medial gyrus
Love > Neutral					
87	5,51	-57	-18	33	Postcentral gyrus
73	5,17	24	-9	60	Superior frontal gyrus, Precentral gyrus
80	5,06	-33	-42	54	Inferior parietal lobe
233	5,05	-3	21	27	Anterior / Mid cingulate gyrus, Superior Medial Gyrus
47	4,92	-27	-9	63	Superior frontal gyrus, Precentral gyrus
136	4,83	60	-15	27	Supramarginal gyrus, Superior temporal gyrus
17	4,72	6	6	-3	Caudate
108	4,70	33	-36	42	Postcentral gyrus, Superior parietal lobe, Precuneus
35	4,61	-3	3	45	Mid cingulate gyrus / Superior frontal gyrus
54	4,52	-30	-45	-36	Cerebellum
39	4,08	27	-48	-30	Cerebellum
26	3,92	3	3	45	Mid cingulate gyrus / Superior frontal gyrus
13	3,81	27	0	0	Putamen
Neutral > Love					
76	6,79	-33	-69	42	Angular gyrus, Inferior parietal lobe
53	5,47	-39	48	-3	Middle and Superior orbital gyrus
21	5,21	51	12	-24	Medial temporal pole
83	5,21	42	-63	39	Angular gyrus, Inferior parietal lobe
64	5,01	-57	-45	-6	Middle temporal gyrus
41	4,54	-39	27	36	Middle frontal gyrus
18	4,45	12	-54	12	Precuneus
10	4,15	18	-27	57	Posterior bank of the precentral gyrus
Love > Exclusion					
622	9,855585	-48	-27	45	Postcentral gyrus, Inferior parietal lobe, Precentral gyrus
774	9,374331	45	-24	39	Postcentral gyrus, Superior parietal lobe
436	7,427135	-3	57	-3	Mid orbital gyrus, Superior medial gyrus, Anterior cingulate cortex
158	5,710973	3	0	48	Medial frontal gyrus
90	5,66759	-21	-54	-27	Cerebellum
70	5,304406	24	-54	-30	Cerebellum
56	5,23458	-24	-3	3	Putamen
53	5,211216	27	0	-3	Putamen
49	4,745509	3	-51	21	Precuneus
18	4,738404	6	6	-3	Caudate
25	4,709366	57	9	30	Precentral gyrus
10	4,507574	-24	0	-15	Amygdala

Cluster size	T	MNI			Macro anatomical location of peak voxel
		x	y	z	
22	4,138065	54	-60	3	posterior Middle temporal gyrus
Exclusion > Love					
837	8,07	-54	-39	18	Middle / Superior temporal gyrus, Heschls gyrus, Insula
305	6,87	66	-24	3	Superior temporal gyrus, Heschls gyrus, Insula
31	6,19	18	-27	57	Posterior bank of the precentral gyrus
60	5,86	6	-33	57	Paracentral lobule
65	5,37	-3	-33	57	Paracentral lobule
123	5,31	57	-42	42	Supramarginal gyrus, Angular gyrus
43	4,79	-51	-48	42	Angular gyrus
14	4,46	18	-51	9	Precuneus
22	4,24	-9	-39	-15	Cerebellum
20	4,01	-45	15	36	Middle frontal gyrus
Pain > Neutral					
729	7,18	-60	-36	12	Superior temporal gyrus, Rolandic operculum, Insula
195	6,21	66	-30	9	Superior temporal gyrus
25	4,32	57	-48	39	Inferior parietal lobe
Neutral > Pain					
450	10,61	51	-15	48	Precentral gyrus, Postcentral gyrus
183	8,39	-45	-18	51	Precentral gyrus, Postcentral gyrus
60	5,70	-18	-51	-27	Cerebellum
38	5,26	24	-51	-30	Cerebellum
37	5,09	24	-51	60	Superior parietal lobe
14	4,63	51	36	9	Inferior frontal gyrus (pars Triangularis)
26	4,61	51	-51	-9	posterior Inferior temporal gyrus
26	4,36	-6	57	-3	Mid orbital gyrus, Anterior cingulate gyrus
24	4,15	51	9	-24	Medial temporal pole
11	4,12	-39	48	-6	Middle orbital gyrus
17	4,08	3	-60	21	Precuneus
Pain > Exclusion					
17	4,28	-57	3	-3	Superior temporal gyrus, Temporal pole
29	4,05	-42	-12	9	Insula, Rolandic operculum
42	3,83	-57	-21	39	Supramarginal gyrus, Postcentral gyrus
20	3,54	-36	-42	45	Inferior parietal lobe, Postcentral gyrus
Exclusion > Pain					
28	5,67	18	-30	60	Posterior bank of the precentral gyrus
130	5,18	42	-27	18	Rolandic operculum, Supramarginal gyrus
77	5,11	9	-36	57	Paracentral lobule
35	5,04	-21	-39	-27	Cerebellum
49	4,85	-3	-30	57	Paracentral lobule
70	4,36	51	-9	51	Precentral gyrus/ Postcentral gyrus
38	4,34	12	-57	-18	Cerebellum
Neutral > Exclusion					
297	8,11	-48	-27	45	Inferior / Superior parietal lobe
359	7,26	51	-15	48	Precentral gyrus, Postcentral gyrus, Superior frontal gyrus
23	5,20	-6	57	-3	Superior medial gyrus, Mid orbital gyrus
73	4,94	6	-45	21	Posterior cingulate gyrus, Precuneus
18	4,71	48	33	3	Superior parietal lobe, Postcentral gyrus
22	4,42	54	0	-24	Medial temporal gyrus (temporal pole)
29	4,21	9	57	0	Superior medial gyrus, Mid orbital gyrus
18	3,87	24	-51	60	Inferior frontal gyrus (pars Triangularis)
Exclusion > Neutral					
708	8,69	-60	-36	18	Superior temporal gyrus, Insula
439	8,05	63	-27	15	Superior temporal gyrus, Rolandic operculum, Supramarginal gyrus
26	5,33	-3	-39	-12	Cerebellum
44	4,71	-18	-30	57	Central sulcus
56	4,41	12	-42	54	Precuneus, Paracentral lobule, Mid cingulate gyrus

Table S2: Post hoc tests main effect of interaction type during Experience experiment. Differences in brain activity between the four interaction types ($p < 0.001$ uncorrected, cluster extend threshold of ten voxels), inclusively masked by the main effect of interaction type. The table specifies the size of each cluster, then, for its peak, the T-value, MNI coordinates, and macro anatomical location of the cluster, based on the groups mean anatomy.

Cluster size	T	MNI			Macro anatomical location of peak voxel
		x	y	z	
Love > Pain					
192	5.66	-33	-39	54	Inferior (Supramarginal gyrus) / Superior parietal lobe
66	5.38	-24	-12	60	Superior frontal gyrus
341	5.30	21	-60	60	Inferior (Angular gyrus) / Superior parietal lobe
174	4.67	24	18	51	Superior / Middle frontal gyrus, Precentral gyrus
16	3.83	-3	57	-6	Superior frontal gyrus
Pain > Love					
169	5.35	3	-78	0	Linual gyrus, Cuneus
95	4.62	-57	-48	27	Supramarginal gyrus
90	4.15	-51	18	0	Inferior frontal gyrus (pars Triangularis / Orbitalis)
11	4.12	3	-33	-6	Brainstem
10	4.00	-33	24	-18	Inferior frontal gyrus (pars Opercularis)
Love > Neutral					
69	4.87	-3	63	0	Superior medial gyrus, Mid orbital gyrus
10	4.36	3	60	-3	Superior medial gyrus, Mid orbital gyrus
Neutral > Love					
150	4.88	-57	-48	18	Superior temporal gyrus, supramarginal gyrus
70	4.51	63	-27	30	Superior temporal gyrus, supramarginal gyrus
73	4.42	-42	9	21	Inferior frontal gyrus (pars Triangularis / Opercularis)
14	4.22	60	-45	3	Middle temporal gyrus
37	4.14	54	24	21	Inferior frontal gyrus (pars Triangularis)
19	3.92	39	9	48	Middle frontal gyrus
10	3.88	-33	6	54	Middle frontal gyrus
10	3.67	12	-39	60	Postcentral gyrus
Love > Exclusion					
741	7.57	42	-33	57	Postcentral gyrus, Superior parietal lobe, Rolandic operculum
200	5.30	-42	-33	51	Postcentral gyrus, Superior parietal lobe
43	5.07	18	-90	0	Calcarine gyrus
104	5.05	45	-66	-9	Inferior temporal gyrus, Middle occipital gyrus
46	4.89	-21	-90	-3	Inferior occipital gyrus
24	4.09	-27	-12	60	Precentral gyrus
14	4.09	27	-84	6	Middle occipital gyrus
32	4.06	27	-6	60	Superior frontal gyrus
19	3.99	-39	-78	0	Middle occipital gyrus
10	3.47	-3	57	-6	Mid orbital gyrus
Exclusion > Love					
509	6.84	-60	-48	18	Superior / Middle temporal gyrus
263	5.70	-45	21	21	Inferior frontal gyrus (pars Triangularis)
Pain > Neutral					
27	4.93	-6	57	12	Superior medial gyrus
11	4.90	-6	30	54	Superior frontal gyrus
11	4.26	-3	54	30	Superior frontal gyrus
11	4.18	-33	24	-18	Inferior frontal gyrus (pars Opercularis)
55	3.85	3	-75	18	Cuneus
12	3.79	-57	-51	33	Supramarginal gyrus, Angular gyrus
18	3.68	6	-72	-3	Linual gyrus
Neutral > Pain					
511	6.68	27	6	54	Inferior / Middle / Superior frontal gyrus, Precentral gyrus
680	6.11	39	-66	33	Middle occipital gyrus, Inferior / superior parietal lobe, Postcentral gyrus
110	5.12	-24	-6	60	Superior frontal gyrus
47	4.89	-15	-60	54	Superior parietal lobe
27	4.72	12	-27	42	Mid cingulate gyrus
45	4.34	-30	-36	57	Postcentral gyrus
14	4.25	-48	0	30	Precentral gyrus
10	4.25	60	-45	-12	Inferior temporal gyrus

Cluster size	T	MNI			Macro anatomical location of peak voxel
		x	y	z	
10	3.62	18	-57	24	Precuneus
Pain > Exclusion					
328	6.90	60	-21	30	Supramarginal gyrus, Rolandic operculum, Postcentral gyrus
119	5.47	45	-66	-6	Inferior temporal gyrus
66	3.90	3	-81	3	Linual gyrus
Exclusion > Pain					
98	5.57	39	-69	42	Angular gyrus
12	4.27	18	-57	21	Superior / Middle frontal gyrus
65	4.16	24	18	51	Cuneus
10	3.83	9	-57	42	Middle frontal gyrus
Neutral > Exclusion					
955	7,77	48	-30	51	Postcentral gyrus, Supramarginal gyrus, Superior parietal lobe
147	6,02	45	-66	-9	Inferior temporal gyrus
52	5,25	18	-87	-9	Linual gyrus
283	4,69	51	12	27	Inferior / Middle / Superior frontal gyrus, Precentral gyrus
45	4,20	-27	-87	-12	Inferior occipital gyrus, Linual gyrus
21	4,09	-36	-78	-6	Inferior occipital gyrus
14	4,08	27	-84	9	Middle occipital gyrus
17	3,95	12	-24	39	Mid cingulate gyrus
29	3,81	-27	0	57	Middle frontal gyrus
28	3,56	-51	-27	48	Inferior parietal lobe
Exclusion > Neutral					
10	3.45	-51	30	3	Inferior frontal gyrus (pars Triangularis)

Table S3: Post hoc tests main effect of movie type during Observation experiment. Differences in brain activity between the four movie types ($p < 0.001$ uncorrected, cluster extend threshold of ten voxels), inclusively masked by the main effect of movie type ($p < 0.001$ uncorrected). The table specifies the size of each cluster, then, for its peak, the T-value, MNI coordinates, and macro anatomical location of the cluster, based on the groups mean anatomy.

Cluster size	T	MNI coordinates			Hemisphere	Macro anatomical location of peak voxel	Overlap with cytoarchitectonic regions
		x	y	z			
Controls larger patients							
1561	7,70	-21	-33	-3	L	Thalamus	Hipp (CA, SUB, FD) BA2, BA3b, BA17, BA18 IPC (PFt, PGa, hIP1 hIP3, Amyg (LB))
	6,87	-48	-48	15	L	Middle Temporal Gyrus	
	6,50	-33	-54	-15	L	Fusiform Gyrus	
2168	7,47	48	-27	-3	R	Middle Temporal Gyrus	hIP2 IPC (PFm, PF, PFt, PGa, FFcm, PFop) BA2, BA3ab, BA44, BA45, BA4p Hipp (FD, CA, SUB)
	6,99	48	-42	24	R	Supramarginal Gyrus	
	6,83	21	-33	6	R	Hippocampus	
76	6,21	-42	42	-12	L	Inferior Frontal Gyrus (p. Orb.)	BA45
	4,09	-33	42	6	L	Inferior Frontal Sulcus	
	3,42	-48	42	3	L	Inferior Frontal Gyrus (p. Tri.)	
154	6,03	-21	39	30	L	Superior Frontal Sulcus / Gyrus	
	4,66	-9	39	33	L	Superior Medial Gyrus	
	4,19	-12	27	30	L	Midcingulate Gyrus	
146	5,95	-3	-39	-27	L	Cerebellum	bil. Lobules I-IV(Hem)
	5,85	6	-39	-24	R	Cerebellum	
	4,61	3	-33	-12	R	Cerebellum	
37	5,60	30	-60	57	R	Superior Parietal Lobe	SPL (7A)
69	5,44	-45	15	27	L	Inferior Frontal Gyrus (p. Tri.)	BA44
223	5,22	27	54	-3	R	Superior Orbital	BA45
	4,66	36	42	6	R	Middle Frontal Gyrus	
	4,45	42	42	-12	R	Middle Frontal Gyrus	
40	5,20	-15	63	-3	L	Mid Orbital Gyrus	
133	5,04	-12	15	-3	L	Caudate	
	4,62	-3	-3	-3	L	Caudate	
	4,24	-18	12	-15	L	Caudate	
161	4,97	33	15	-15	R	Insula/ Amygdala	Amyg (LB)
	3,96	15	12	6	R	Caudate	
	3,94	21	18	-9	R	Putamen	
19	4,79	39	-75	24	R	Middle Occipital Gyrus	
	4,27	33	-78	30	R	Middle Occipital Gyrus	
64	4,74	42	-30	9	R	Superior Temporal Gyrus	TE 1.1 OP1, OP2
	4,00	45	-24	18	R	Rolandic operculum	
	3,97	33	-24	21	R	Insula	
121	4,67	-9	-18	42	L	Midcingulate Gyrus	BA6 SPL(5Ci, 5M)
	4,45	-12	-45	48	L	Precuneus	
	3,58	-6	-30	36	L	Midcingulate Gyrus	
128	4,66	-27	-15	54	L	Precentral Gyrus	BA6
	4,63	-27	0	51	L	Middle Frontal Gyrus	
	4,06	-33	-6	60	L	Precentral Gyrus	
11	4,41	-24	-24	51	L	Anterior bank central sulcus / Precentral Gyrus	BA6
114	4,38	-33	15	3	L	Insula	
	4,08	-27	21	6	L	Insula	
	3,49	-30	18	-9	L	Insula	
12	4,28	24	-36	-33	R	Cerebellum	Lobule V
26	4,25	9	-21	39	R	Midcingulate Gyrus	
30	4,24	12	-48	54	R	Precuneus	SPL (5M)
	3,28	15	-51	36	R	Precuneus	
19	4,04	-36	-78	18	L	Middle Occipital Gyrus	IPC(PGp)
15	4,02	-3	30	51	L	Superior Medial Gyrus	BA6
47	3,98	18	-66	21	R	Cuneus	BA17
	3,57	12	-54	9	R	Precuneus	
11	3,97	9	-60	-36	R	Cerebellum	Lobule IX (Vermis) Lobule VIIIa (Vermis)
	3,34	-3	-60	-36	L	Cerebellum	
29	3,86	-54	-15	21	L	Postcentral Gyrus	OP1, OP4
	3,32	-63	-9	27	L	Postcentral Gyrus	

Cluster size	T	MNI coordinates			Hemisphere	Macro anatomical location of peak voxel	Overlap with cytoarchitectonic regions
		x	y	z			
	3,24	-54	-15	33	L	Postcentral gyrus	
Patients larger controls							
No suprathreshold voxels							

Table S4: Any group differences during Observation experiment (grey matter masked). Differences in brain activity between the psychopathy and control group ($p < 0.001$ uncorrected, cluster extend threshold of ten voxels, all clusters survive FDR correction at $p = 0.05$) within the grey matter mask (see also Figure 3A). Rows filled with grey indicate clusters without overlap with those reported in Table 2. Conventions as in Table 2.

Cluster size	T	MNI			Macro anatomical location of peak voxel
		x	y	z	
Love > Pain					
74	6,20	-21	-9	57	Precentral gyrus, Superior frontal gyrus
112	5,53	-33	-39	57	Postcentral gyrus, Superior parietal lobe
92	4,93	33	-36	51	Postcentral gyrus
72	4,80	27	-9	57	Superior frontal gyrus, Precentral gyrus
38	4,46	-54	-18	36	Postcentral gyrus, Inferior parietal lobe
55	4,00	27	-54	60	Superior parietal lobe
51	3,90	30	-87	6	Middle occipital lobe, Linal gyrus, Inferior occipital gyrus
Pain > Love					
186	6,86	-54	-45	27	Supramarginal gyrus, Inferior parietal lobe
371	5,80	3	-75	-3	Linal gyrus, Calcarine gyrus, Cerebellum
96	5,59	-51	15	0	Inferior frontal gyrus (pars Opercularis)
146	5,42	42	21	-12	Inferior frontal gyrus (pars Orbitalis), anterior Insula
184	4,97	3	27	48	Anterior cingulate gyrus, Mid cingulate gyrus, Superior frontal gyrus
67	4,88	-3	21	30	Anterior cingulate gyrus, Superior medial gyrus
45	4,77	-45	42	15	Inferior frontal gyrus (pars Triangularis)
13	3,72	-6	-12	6	Bilateral Thalamus

Table S5: Posthoc tests main effect of movie type during Empathy experiment. Differences in brain activity between the two movie types ($p < 0.001$ uncorrected, cluster extend threshold of ten voxels), inclusively masked by the main effect of movie type. The table specifies the size of each cluster, then, for its peak, the T-value, MNI coordinates, and macro anatomical location of the cluster, based on the groups mean anatomy.

Cluster size	T	MNI coordinates x y z	Hemi-spher	Macro anatomical location of peak voxel	Overlap with cytoarchitectonic regions
Controls larger patients					
71	6,5	36 -33 51	R	Postcentral gyrus	BA2, BA3b, BA4p, BA3a
50	5,7	27 -57 57	R	Superior parietal lobe	SPL (7A, 7PC, 5L)
63	5,4	-39 -54 -21	L	Fusiform gyrus	Lobule VI (Hem)
88	4,9	-33 -36 45	L	Postcentral gyrus	BA2, IPC (PFt)
	4,8	-30 -39 57	L	Superior parietal lobe	
	4,3	-39 -30 42	L	Postcentral gyrus	
54	4,8	63 -39 21	R	Superior temporal gyrus	IPC (PF, PFm, PFcm)
115	4,8	-45 -75 6	L	Middle occipital gyrus	hOC5(V5)
	4,7	-36 -78 18	L	Middle occipital gyrus	
	4,5	-21 -78 30	L	Superior occipital gyrus	
39	4,6	51 -63 9	R	Middle temporal gyrus	hOC5(V5)
	3,6	48 -72 0	R	Middle temporal gyrus	
40	4,6	-27 -72 -15	L	Fusiform gyrus	hOC4v(V4)
20	4,4	21 -9 54	R	Precentral gyrus	BA6
14	4,3	39 0 42	R	Medial frontal gyrus	
20	4,1	-48 -48 15	L	Superior temporal gyrus	
17	4,0	9 -39 -30	R	Pons	Lobules I-IV (Hem)
11	3,9	33 -75 -18	R	Fusiform gyrus	hOC4v(V4)
21	3,9	21 -60 -12	R	Parahippocampal gyrus	Lobule VI (Hem), hOC3v(V3v)
12	3,8	39 -75 18	R	Middle occipital gyrus	
	3,3	33 -78 24	R	Middle occipital gyrus	
Patients larger controls					
86	7,2	-54 -57 -9	L	Middle temporal gyrus	
247	5,5	-45 -51 48	L	Supramarginal gyrus	hIP1, IPC (Pga, PFm), hIP3
	4,6	-33 -57 42	L	Supramarginal gyrus	
	4,6	-39 -57 30	L	Supramarginal gyrus	
173	5,5	24 18 54	R	Superior frontal gyrus	
	5,3	33 12 54	R	Superior frontal gyrus	
	4,7	36 21 48	R	Middle frontal gyrus	
64	5,5	60 -3 33	R	Precentral gyrus	BA6, BA3b, BA3a, BA4p
	3,2	54 -9 45	R	Precentral gyrus	
51	5,4	57 -48 -9	R	Middle temporal gyrus	
463	5,2	-3 57 12	L	Superior frontal gyrus	
	5,1	9 48 6	R	Anterior Cingulate Gyrus	
	5,1	6 39 30	R	Superior frontal gyrus	
30	4,9	30 -84 -9	R	Lingual gyrus	hOC3v (V3v), hOC4v (V4)
76	4,9	3 -57 24	R	Precuneus	
93	4,9	45 -60 45	R	Angular gyrus	IPC (Pga, PFm)
	4,7	51 -51 48	R	Angular gyrus	
	3,7	27 -60 42	R	Angular gyrus	
76	4,6	42 -15 18	R	Parietal operculum	OP3, TE 1,0
	4,0	60 -18 6	R	Temporal operculum	
	3,4	51 -12 9	R	Parietal operculum	
96	4,5	-60 -6 18	L	Postcentral gyrus	OP4, OP2, OP1, BA3b, TE1.2
	4,0	-54 -15 6	L	Temporal operculum	
	3,9	-36 -27 18	L	Parietal operculum	
24	4,4	9 -69 45	R	Precuneus	SPL (7A)
184	4,4	-15 18 60	L	Superior frontal gyrus	
	4,3	-27 24 48	L	Middle frontal gyrus	
	4,2	-36 24 36	L	Middle frontal gyrus	
36	4,1	27 -69 -30	R	Cerebellum	Lobule VI (Hem), Lobule VIIa
10	3,9	21 -30 69	R	Postcentral gyrus	BA4a, BA6
16	3,6	-12 -72 -24	L	Cerebellum	
11	3,5	-24 12 -9	L	Putamen	
10	3,4	-48 3 -24	L	Superior temporal gyrus	

Table S6: Group differences during Empathy experiment (gray matter masked). Table lists areas that were more activated for the controls (positive effect of controls) and areas that were more activated for the patients (positive effect of patients). Only clusters of at least 10 voxels with $p < 0.001$ uncorrected are shown

(all clusters also survive FDR correction at $p = 0.05$). Results are displayed in Figure 3C. Rows filled with gray indicate clusters without overlap with those reported in Table 3. Conventions as in Table 2.

Acknowledgements

We thank A.J. Sibeijn-Kuiper for scanning the subjects and her help in setting up the specific safety protocol for this study. We thank R. Renken for his help with the data-analysis. We also want to thank all the participants for their cooperation. C.K. and the research were supported by a VIDI , V.G. by a VENI grant, both from the Dutch Science Foundation (NWO). The Forensic Psychiatric Clinic Dr. S van Mesdag paid for transport and security costs and partially funded HM. None of the authors have conflicts of interest regarding this work.

3

STRUCTURAL DEFICITS IN SHARED CIRCUITS

A version of this manuscript is being submitted as:

Structural differences in brain regions involved in vicarious responses in schizophrenia, autism, and psychopathy

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ABSTRACT

Context Impairments or qualitative differences in empathy are reported in neurodevelopmental disorders characterized by impaired social functioning such as autism, schizophrenia, and psychopathy. Empathy may rely on vicarious responses in “shared circuits”; brain regions that are activated when performing actions, experiencing sensations and feeling emotions, but also when observing (or imagining) others performing similar actions.

Objective To directly compare grey matter volumes in brain regions related to vicarious responses in subjects diagnosed with schizophrenia, autism and psychopathy and compare this to the location of abnormalities found in previous studies.

Design First, a meta-analysis of published studies investigating volumetric differences in any of the patient groups compared to a control group using Activation Likelihood Estimation. Second, comparing structural brain images (T1, voxel-based) of the aforementioned patient groups with a control group in- and outside brain regions associated with shared circuits.

Setting All subjects were tested at the BCN Neuroimaging Center of the University of Groningen and the University Medical Center Groningen.

Patients or Other Participants 20 subjects with schizophrenia, 21 subjects with autism spectrum disorder, 20 subjects with psychopathy and 26 healthy controls.

Results Shared circuits were disproportionately affected in schizophrenia and in psychopathy. In contrast to the broad impairments in schizophrenia, abnormalities in psychopathy were restricted to sensorimotor regions of the shared circuits. In ASD, both the meta-analysis and experimental data revealed significantly more volumetric differences outside shared circuits, including regions involved in mentalizing tasks.

Conclusions Regions related to empathic responses were relatively more affected compared to regions outside the mask. This was particularly true for subjects diagnosed with schizophrenia, warranting more investigation into the neural underpinnings of empathy in this disorder.

3.1 INTRODUCTION

Autism Spectrum Disorder (ASD), schizophrenia, and psychopathy are distinct diagnostic entities each having unique characteristics and different developmental trajectories, but deficits in the social domain (empathy in particular) exist in all three disorders. Indeed, some of the social abnormalities displayed by individuals with schizophrenia, including impaired shared enjoyment, directing of facial expressions, and commenting on other people's emotions, can be difficult to distinguish from similar social behaviours displayed by individuals with ASD during a semi-structured interview (Bastiaansen, et al., 2010). In this controlled setting, abnormalities in social behaviours were not as apparent for individuals with psychopathy. Deficits in the emotional and interpersonal domain (Coid, et al., 2009; Hare & Neumann, 2009) are, however, considered to be hallmarks of this personality disorder, which separate it from the DSM-IV classification of antisocial personality disorder. Social inadequacy may be fuelled by empathy deficits by reducing prosocial behaviour (Miller & Eisenberg, 1988) and/or increasing various displays of aggression (Jolliffe & Farrington, 2004; Lovett & Sheffield, 2007). With impairments or qualitative differences in empathy suggested to be central to ASD (Baron-Cohen & Wheelwright, 2004; Blair, 2008; Gillberg, 1992), schizophrenia (Emre Bora, Gökçen, & Veznedaroglu, 2008), and psychopathy (Blair, et al., 2006; Decety & Moriguchi, 2007) it becomes important to directly compare the deficits between these groups. This is, however, complicated by the existence of many different definitions of empathy (e.g. Batson, 2009).

De Vignemont and Singer (de Vignemont & Singer, 2006) have proposed that empathy occurs when the imagination or perception of the affective state of another triggers an affective state in the self, which resembles the state of the other, without there being confusion about the source. This definition is in harmony with recent neuroscientific observations that brain regions implicated in performing actions, experiencing sensations and feeling emotions are also partly (vicariously) activated when observing (or imagining) others performing actions, experiencing sensations and feeling emotions (Bastiaansen, et al., 2009; Jabbi, et al., 2007; Keysers & Gazzola, 2009; Keysers, et al., 2010; Pineda, 2008; Singer, et al., 2004). Regions with these properties have been called 'shared circuits', and include premotor (Keysers & Gazzola, 2009), posterior parietal (Keysers & Gazzola, 2009), somatosensory (Keysers, et al., 2010), insular (Bastiaansen, et al., 2009; Jabbi, et al., 2007; Singer, et al., 2004) and cingulate (Bastiaansen, et al., 2009; Singer, et al., 2004) cortices. Importantly, the strength of vicarious activations in shared circuits has been related to inter-individual differences in self-report measures of empathy (Gazzola, et al., 2006; Jabbi, et al., 2007; Singer, et al., 2004; Singer, et al., 2006). This has led to the notion that this kind of empathy may emerge as a consequence of vicarious activations and encompasses sharing of not only affective, but also somatosensory and motor states of others. This raises the question whether the reported abnormalities of empathy in ASD, schizophrenia, and psychopathy may be related to structural or functional abnormalities in these regions.

In recent years, this question has been most extensively investigated for ASD with a focus on simulation of the actions and facial expressions of others in premotor regions associated with the putative Mirror Neuron System (MNS). Findings have been rather inconsistent with some studies finding abnormal activity in motor regions or in muscle-specific motor responses (Bookheimer, et

al., 2008; Dapretto, et al., 2006; Greimel, et al., 2010; Grèzes, et al., 2009; Hadjikhani, et al., 2007; Martineau, et al., 2008; Oberman, et al., 2005; Oberman, et al., 2008; Uddin, et al., 2008) and others not (Ashwin, et al., 2007; Ilan Dinstein, et al., 2010; Fan, et al., 2010; Marsh & Hamilton, 2011; Pierce, et al., 2004; Raymaekers, et al., 2009; Williams, et al., 2006). A review of the current literature suggests that at the very least, observation of the actions and emotional expressions of others can trigger motor responses, even though they are not reported as consistently as in typically developing individuals (insert: for a review see Thioux, Bastiaansen, & Keysers, in revision). The degree to which motor responses are triggered by the perception of others seems to relate to symptom severity (Dapretto, et al., 2006; Fan, et al., 2010) or social functioning (Bastiaansen, et al., 2011). Many neuroimaging studies on emotion perception in ASD have additionally reported abnormalities in somatosensory regions and regions involved in emotional experience such as the insula, amygdala, and anterior cingulate cortex (e.g. Ashwin, et al., 2007; Hadjikhani, et al., 2007).

Schizophrenia has also been hypothesized to relate to abnormal vicarious responses (Gallese, 2003; Salvatore, et al., 2007), but only a small amount of studies have been specifically designed to answer this question. Subjects with schizophrenia display less contagious laughing and yawning (Haker & Rössler, 2009) in response to video clips, which might indicate a lack of vicarious response in the corresponding regions. Using various tasks and techniques in relatively small samples, studies on schizophrenia have suggested that there might be more extensive activation in (pre)motor regions during the observation of simple facial diagrams (Quintana, et al., 2001), reduced motor responses during the observation of hand actions (Enticott, et al., 2008), and decreased emotional resonance related to negative symptoms in small pre-defined regions in the ACC, orbitofrontal, and medial prefrontal cortex (Fahim, et al., 2004). However, in a recent study, we did not find group differences between schizophrenia, ASD, and a control group during face perception in a predefined region of the ventral premotor cortex that has been extensively studied in autism (Bastiaansen, et al., 2011).

No neuroimaging studies have been published yet on vicarious activations in criminal psychopathy. However, one study shows that criminal subjects with psychopathy display decreased neural activity in right secondary somatosensory cortex, right insula and anterior cingulate cortex when viewing neutral faces during the acquisition phase of a fear conditioning paradigm (Birbaumer, et al., 2005). Another study found premotor and primary somatosensory hypoactivation when observing faces in a gender discrimination task (Deeley, et al., 2006). Counter intuitively, Fecteau and colleagues (Fecteau, Pascual-Leone, & Theoret, 2008) observed that during the observation of needles penetrating human hands, the motor responses of healthy control subjects were positively correlated with the Coldheartedness subscale of the Psychopathic Personality Inventory (PPI) but it has been argued that differences in the general population are not necessary predictive of the deficits in clinical groups (Koenigs, et al., 2010).

To summarize, although abnormalities in shared circuits have been implicated in all three psychiatric groups, the functional evidence for reduced brain activations in shared-circuits is mixed in ASD and scarce for schizophrenia and psychopathy. Moreover, the use of different neuroimaging methods, paradigms and stimulus sets hinder a direct comparison of functional deficits across

groups. In contrast, structural deficits can be compared more easily across studies, because they are not bound to a particular experimental paradigm. Therefore, we will investigate structural brain differences inside and outside brain regions associated with shared circuits (which we will simply refer to as ‘shared circuits’ for brevity’s sake) using two complementary approaches. First, we will conduct a quantitative meta-analysis of studies on brain morphometry differences between healthy control groups and the above mentioned patient groups using an activation likelihood estimation (ALE). This allows us to examine to what extent the deviations that have been reported in these patient groups, compared to healthy controls, are located in shared circuits for actions, sensations and emotions. Second, we will directly investigate similarities and differences in regional brain volume between these three patient groups and controls by means of Voxel-Based Morphometry (VBM) performed on structural MRI images collected in our lab, and compare this to the results of the meta-analysis. This will be the first time that regional brain volumes are directly compared in these patient groups within a single study.

3.2 METHODS

3.2.1 EMPATHY AND GREY MATTER MASK

Because of our interest in empathy from the perspective of shared circuits (Bastiaansen, et al., 2009; Caspers, et al., 2010; Keysers, et al., 2010; Lamm, et al., 2011), we created a Shared Circuit mask by combining these cytoarchitectonic regions that have consistently been associated with shared circuits for actions (Anatomy Toolbox: BA6, BA44 or BA45), for somatosensation (Anatomy Toolbox OP1-4, BA3a, BA3b, BA1 or BA2) and affective regions (WFU Pickatlas: bilateral Insula, bilateral Anterior Cingulate Cortex, bilateral Amygdalae). Whole-brain analyses for our experimental data were performed within a grey matter mask which was constructed by taking the average of all normalized grey matter segments of our participants and thresholding this mean image at 0.3.

3.2.2 PART I: META-ANALYSIS

In brief, we conducted a systematic search for studies published between January 1999 and June 2011 that reported whole-brain, voxel-wise morphometric grey-matter comparisons between a healthy control group on the one hand, and a schizophrenia, ASD and / or psychopathy group on the other hand. We performed an activation likelihood estimation (ALE) procedure on this literature. Roughly, an ALE is a coordinate-based meta-analysis approach that can be used to detect convergence between reported peak coordinates (i.e. foci) from different studies (Simon B. Eickhoff et al., 2009; Peter E. Turkeltaub et al., 2011). Due to the limited amount of studies for psychopathy, we could only perform these analyses for ASD and schizophrenia. We performed within group ALE analyses as well as a between group comparison. In addition, we examined per group which proportion of volumetric differences across studies within the whole-brain also fell inside the Empathy mask and subsequently analyzed whether this proportion was significantly larger than could have occurred by chance alone using a chi-square test. The exact procedure of the literature search and the subsequent analyses are described in detail in the supplemental methods.

3.2.3 PART II: EXPERIMENTAL DATA

Participants

In total, 87 structural images were obtained from subjects that gave written informed consent to partake in one of two neuroimaging studies into the neural basis of empathy conducted at the Social Brain Laboratory (www.socialbrainlab.org). Both neuroimaging studies were approved by the Institutional Review Board of the University Medical Center Groningen (METc). Participants belonged to a psychopathy group (20), a schizophrenia group (20) or an ASD group (21), which are described below or to a group of control subjects (26), without any type of neuropsychiatric disorder. Group characteristics are reported in Table 1.

The psychopathy group was recruited from two forensic psychiatric hospitals in the Netherlands. We invited males between 18 and 60 years to participate in the study if they did not have a prior diagnosis of Schizophrenia, other Psychotic Disorder or Autistic Spectrum Disorder, but did have a Psychopathy Checklist-Revised (PCL-R) (Hare, 2003; Hare, et al., 2001) score of at least 26 (in accordance with the reported lower total scores in the Netherlands (Spren, et al., 2008) and other European countries (Cooke, et al., 2005)). Of the recruited 20 subjects, two subjects had to be excluded from further analyses due to movement artefacts and one subject due to normalization problems. Of the remaining 17 subjects, 15 fulfilled the official (American) cut-off score of 30 or higher.

Twenty-one adult males with ASD were recruited via local mental health institutions (Autism Team North Netherlands, Lentis) and through mailing lists. All subjects were diagnosed with autism (n=7), Asperger Syndrome (n=9), or PDD-NOS (n=5) by a clinical psychologist or psychiatrist according to DSM-IV-TR criteria (American Psychiatric Association, 2000). Clinical diagnoses were verified by the administration of the Autism Diagnostic Observation Schedule (ADOS, Lord, et al., 2000) by a trained and certified psychologist. One of the subjects scored below the cut-off of the communication subscale, but his diagnosis was confirmed by the administration of the Autism Diagnostic Interview Revised (ADI-R, Lord, et al., 1994). The subjects were considered to be high-functioning by their clinicians.

Twenty adult males with schizophrenia were recruited through a specialized mental health organization (Psychosencircuit, GGZ Drenthe, Assen, the Netherlands). Individuals with schizophrenia were selected by experienced clinicians on the basis of predominant negative symptomatology. Diagnoses were confirmed by the administration of the Dutch version of the Schedules of Clinical Assessment in Neuropsychiatry (SCAN 2.1, Giel & Nienhuis, 1996). Current symptomatology was assessed by the Positive and Negative Syndrome Scale (PANNS, Kay, Fiszbein, & Opler, 1987).

MRI data acquisition and preprocessing

All images were acquired using a Philips Intera 3T Quaser, a synergy SENSE head coil, 30 mT/m gradients and a standard single shot EPI with time echo = 3.5 ms, echo time = 7.567 ms, 160 transcranial slices of 1 mm thickness aligned with ac-pc, no slice gap and a 1 1 mm in plane resolution (256 x 229) acquired to cover the entire brain and cerebellum. Images were processed and analyzed with SPM5 (Wellcome Department of Cognitive Neurology, London, UK), running under

Matlab 7.1 and the VBM5 toolbox developed by Christian Gaser (Structural Brain Mapping Group, University of Jena, Jena, Germany). Images were first segmented using the default prior probability maps to generate modulated and unmodulated GM, WM and CSF by implementing the unified segmentation approach (Ashburner & Friston, 2005). Unmodulated images were adjusted for non-linear effects and affine transformation parameters to yield modulated images. Noise level was reduced by applying a Hidden Markov Random Field weighting and the partitions were lightly cleaned. Images were then smoothed with a 10 mm full width half maximum isotropic Gaussian kernel.

General analyses

We first examined whether there were any differences between the groups other than those in regional brain volume. We tested for group differences on age, IQ and global grey matter (GGM) using three separate ANOVAs with group (4 levels) as between subjects variable. We used the Pearson Chi-Square Test to test for differences in education level and handedness to account for the non-parametric nature of these measures. Finally, we multiplied the p-values from each of these tests by 5 to account for the fact that 5 variables were compared between groups (Age, IQ, Handedness, Education and GGM).

VBM analyses

First, we tested for differences in voxel-wise grey matter volume between the groups using an ANCOVA design in SPM5 with factor group (4 levels) and global grey matter volume (GGM) as covariate. We restricted this first analysis to voxels included in the Empathy mask and tested the null-hypothesis that none of the groups were different from each other (using the F-test contrast [1,-1,0,0;1,0,-1,0;1,0,0,-1;0,1,-1,0;0,1,0,-1;001-1]) thresholded at $p < 0.001$ uncorrected (p_{unc}) or $p < 0.05$ FDR (p_{FDR}) corrected, whichever was *more* stringent, and a cluster extent of 10 voxels. Given that the null-hypothesis was rejected for some brain regions, we investigate the pattern of group differences by performing post hoc tests on all peak voxels. To this end, we extracted the smoothed grey matter volume within these peak voxels for each participant separately using the Nifti toolbox (<http://www.rotman-baycrest.on.ca/~jimmy/NIfTI/>). We then conducted pair-wise comparisons between the groups for each peak separately (using SPSS 16.0 for Windows), while correcting for global brain size, in line with the ANCOVA analysis in SPM5.

Second, to assess whether the Empathy mask captures a significant proportion of the group differences, we repeated the above mentioned ANCOVA within the grey matter mask. We first identified voxels violating the null-hypothesis (none of the four groups differed from each other) and then performed post hoc tests on these voxels within SPM5 to determine which groups were responsible for the significant results. Results were assessed at the same threshold used for the analysis within the Empathy mask for comparison with the number of voxels found in the previous analysis. We used a chi-square test to determine whether the ratio between the volume of significant differences within the Empathy mask (first analysis) and the volume of significant differences within the grey matter mask (second analysis) could have happened by chance alone, given that the Empathy mask comprises 19 % of the grey matter mask. We conducted this for all groups together (i.e. comparing the proportion of violations of the null hypothesis within and outside of the Empathy mask) and, separately, for each patient group versus the control group.

3.3 RESULTS

3.3.1 PART I: META-ANALYSIS

Of the 11 studies on ASD that fulfilled our inclusion criteria (see Table S1), nine reported group differences at a minimum threshold of $p < 0.001$ uncorrected. The total group comprised 305 ASD subjects (275 male) and 293 healthy control subjects (at least 261 male), with a mean age of 28.4 ± 6.8 for the ASD group and 27.5 ± 6.7 for the control group. All papers together yielded 110 foci. The within group analysis resulted in 16 clusters (see Table S2 and Figure 1, green colors) at $p_{\text{fdr}} < 0.05$ (uncorrected p-value of 0.0017). Differences between ASD and control groups fell consistently in left dorsolateral and ventromedial prefrontal cortex (dlPFC, vmPFC), bilateral postcentral gyrus, bilateral temporal pole (on the right side extending into the amygdala), bilateral putamen,

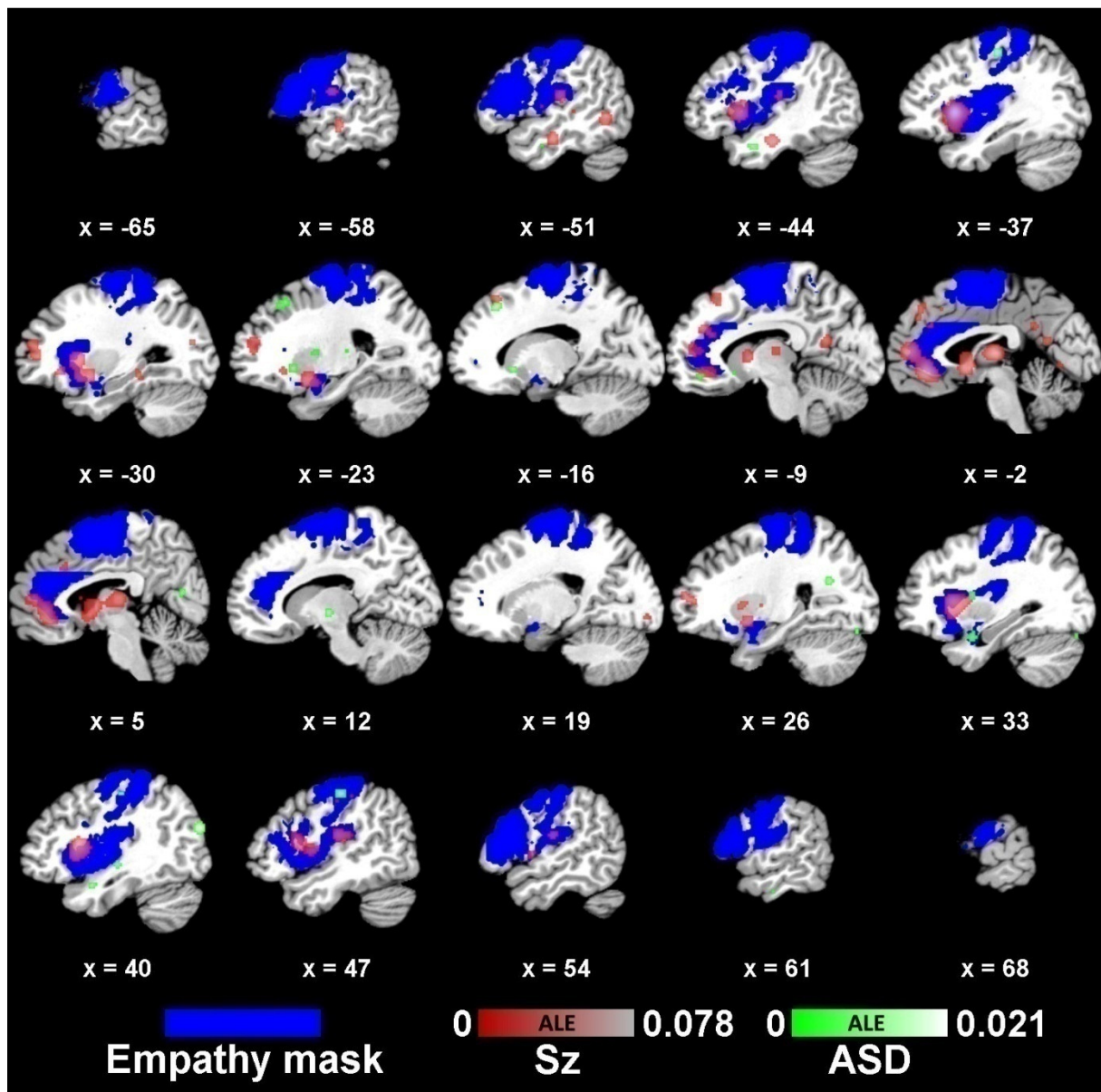


Figure 1: Within group results of meta-analysis overlaid on Empathy mask. Coordinates represent MNI coordinates of the sagittal slice. Sz = Schizophrenia; ASD = Autism Spectrum Disorder. Numbers next to the colored bars indicate ALE-values. The colors for Sz and ASD are made slightly transparent in order to visualize the borders of the underlying Empathy mask.

cerebellum, right thalamus, precuneus, brainstem, right middle insula and regions within the occipital lobe. In total, 13 % of these structural deficits fell inside our Empathy mask (Figure 1, blue colours), which was significantly less than what would have been expected based on chance alone ($p < 0.001$, see Table 1).

	Total	Meta-analysis data		Experimental data			
		Sz vs HC	ASD vs HC	F-test	Sz vs HC	ASD vs HC	Ps vs HC
A) Empathy mask	227752	12384	440	5520	5080	44	75
B) Grey matter mask	1204833	31800	3312	9703	8149	203	261
Percentage (A/B*100%)	19 % ^{***}	39 % ^{***}	13 % ^{***}	58 % ^{***}	62 % ^{***}	22 %	29 % ^{***}

Table 1: Volume of structural group differences within Empathy and Grey matter mask. All volumes are in mm^3 . Sz = Schizophrenia, ASD = Autism Spectrum Disorder, HC = Healthy Control, Ps = Psychopathy. The column labeled 'Total' indicates the total volume of the Empathy mask and the Grey matter mask. The two columns titled Meta-analysis data represent the total volume of structural differences between ASD or Sz and HC based on the ALE analysis. The columns titled Experimental data report the same for the current study: F-test indicates the volume for which at least two of the four groups differed from each other at $p < 0.001$ uncorrected, minimum cluster size of 10 voxels (see eTable 6). The next three columns represent the total volumetric differences between one of the patient groups and the HC group (based on post hoc tests within grey matter and Empathy mask at the same uncorrected threshold). *** refers to a significant difference at $p < 0.001$ using a chi-square test against the distribution of voxels in A and B (i.e. 19%).

For schizophrenia, we identified 60 relevant studies with a total of 2878 schizophrenia subjects (1907 male) and 3073 control subjects (at least 1841 male). Mean age of the schizophrenia group was 33.2 ± 7.7 and 32.4 ± 7.6 for the control group. All papers together yielded 747 foci. The within group ALE resulted in 32 clusters (see Table S4 and Figure 1, red colours) at $p_{\text{fdr}} < 0.05$ (uncorrected p-value of 0.0033). Significant convergence between studies was found in regions implicated in vicarious responses such as bilateral insula / inferior frontal gyrus, anterior cingulate cortex, secondary somatosensory cortex. Other regions included prefrontal, temporal and occipital regions, but also midbrain structures such as caudate, putamen and thalamus. For a complete overview, see Table S4). In total, 39 % of these structural deficits fell inside our Empathy mask, which was significantly *more* than expected based on chance alone ($p < 0.001$, see Table 1).

For psychopathy, only three studies could be identified that met inclusion criteria (see Table S5). Therefore, we were unable to perform ALE analyses with this group.

Cluster size (mm^3)	MNI			Hemi-sphere	Location peak voxel
x	y	z			
ASD larger than Schizophrenia					
120	35	-2	-24	R	Amygdala
Schizophrenia larger than ASD					
384	-48	8	12	L	Frontal operculum - Inferior frontal gyrus (p. Oper. / BA44)

Table 2: Between group ALE analysis of Sz and ASD (whole-brain). Results are thresholded at $p_{\text{fdr}} < 0.05$ with a minimum cluster size of 10 mm^3 . See also Figure 1.

We compared the within group ALE results for ASD and schizophrenia in a subsequent between group analysis. At $p_{\text{fdr}} < 0.05$ we found that the ASD group showed consistently more structural deficits in the right amygdala, whereas the schizophrenia displayed more deficiencies in the left frontal operculum / inferior frontal gyrus (Table 2). Because a conjunction analysis is not possible in GingerALE 2.1, we examined the overlap between the two groups using a logical AND between the two within group images using the `lncalc` function of SPM5. There was only a small overlap of 16 mm^3 between results from the two groups in the right putamen.

3.3.2 PART II: EXPERIMENTAL DATA

General analyses

Regarding general group characteristics (Table 3), there was only a significant group difference in education level due to unusually low scores in the psychopathy group. This is probably related to the way incarceration and their criminal lifestyle interfered with formal education.

M (SD)	C (n = 26)	A (n = 21)	S (n = 20)	P (n = 17)	Total (n = 84)	p-value
Age	36,96 (8,28)	30,57 (10,08)	37,25 (10,24)	38,24 (8,71)	35,96 (9,63)	0.20
IQ	98,77 (14,2)	102,52 (14,81)	90,95 (17,25)	93,76 (17,42)	96,83 (16,12)	0.48
Handedness	R = 88.8% L = 0% NP = 19.2%	R = 71.4% L = 23.8% NP = 4.8%	R = 90.0% L = 10.0% NP = 0%	R = 88.2% L = 11.8% NP = 0%	R = 82.1% L = 10.7% NP = 7.1%	0.11
Education level	4.65 (0.69) Median = 5	5.43 (0.98) Median = 6	4.95 (0.76) Median = 5	2.94 (1.09) Median = 2	4.57 (1.23) Median = 5	< 0.005 ^a
GGM	657,66 (61,43)	677,77 (87,7)	656,12 (67,72)	619,71 (56,85)	661,97 (75,17)	0.46

Table 3: Group characteristics. Values represent the mean and standard deviation (between brackets). IQ is measured using the abbreviated Groninger Intelligentie Test -2 (Luteijn & Barelids, 2004). GGM stands for global grey matter as calculated by VBM5. All p-values were Bonferroni corrected for 5 tests. a = p-value calculated by Pearson Chi-Square Test.

VBM analyses

Differences in regional brain volume were first assessed using a voxel-wise ANCOVA within the Empathy mask. 18 clusters with 25 peaks were significantly different between at least two of the four groups (Table 4 and Figure 2). Differences were most striking in dorsal and ventral premotor regions, the insula and somatosensory cortices. No group differences were found within anterior cingulate gyrus or the amygdalae. Post hoc tests on the peak voxels (Table 5) indicate that grey matter volume was in general largest in the control group for all peaks (except peak 19 in BA45, which was larger for the psychopathy group) and smallest for the schizophrenia group. The schizophrenia group showed significantly smaller volumes even compared to the other two diagnostic groups in most peaks, but there were also peaks in which all diagnostic groups differed from the control group. These were located in dorsal premotor areas (Peak 4, 5 and 12), left ventral premotor (Peak 14) and in primary somatosensory areas (Peak 17). The psychopathy and ASD group differed from the control group mainly in (pre)motor regions (Peak 5, 6, 12-15, 19 and 20), and (primary) somatosensory regions (peak 17). Neither the ASD nor the psychopathy group was different from controls in regions implicated in emotion processing such as the insula and the anterior cingulate cortex. In contrast, the schizophrenia group showed smaller volumes in the insula and adjacent opercula compared to the control group (Peak 7-9, 10, 22 and 23). Directly comparing the psychopathy group against the ASD group reveals that these groups only differ in 8 out of 25 peaks with especially right and medial (pre)motor regions showing larger grey matter volumes for Psychopathy (Peak 1, 3, 6, 16, 19, but not 13) while one left premotor region showed larger volumes in ASD (peak 13). In somatosensory regions, subjects with psychopathy had larger volume in mesial right S1 (peak 21), while the ASD group had larger volumes in SII (Peak 7).

Secondly, we examined how much of the group differences fell within the Empathy mask by conducting the same F-test within the entire grey matter mask (Figure 3 and eTable 6). Regions

within the Empathy mask appear to be disproportionately affected as 58% of the voxels that are significantly different between groups in the gray matter mask also fall inside our Empathy mask (see Table 1, column F-Test). This is striking since the Empathy mask covered only 19% of the gray matter mask. A chi-square test indicates that the proportion is indeed significantly larger than what would be expected based on the size of the Empathy mask (Table 1). Similar analyses per group suggest that this is true for the schizophrenia and the psychopathy group, but not the ASD group (see Table 1). Clusters that fell entirely outside the Empathy mask are indicated by a gray color in eTable 6 and include the posterior part of right superior and medial temporal gyrus, thalamus, primary motor cortex, cerebellum, posterior superior parietal lobe and prefrontal areas.

	Cluster size	F	MNI coordinates			Hemi-sphere	Cluster description
			x	y	z		
P1	1870	11,94	60	-2	6	R	SII (OP4)
P2		9,84	57	12	8	R	vPM (BA44)
P3		9,09	57	19	12	R	BA45
P4	516	9,99	26	-16	60	R	dPM (BA6)
P5		7,27	25	-7	61	R	dPM (BA6)
P6		6,37	23	-15	69	R	dPM (BA6)
P7	1588	9,76	36	-16	6	R	Posterior-Insula and SII (OP1, OP2)
P8		7,49	45	-21	11	R	SII (OP4)
P9		7,31	37	3	13	R	Mid-Insula and SII (OP1)
P10	398	8,37	33	23	-5	R	Anterior Insula
P11	135	8,24	9	-26	48	R	Middle Cingulate Gyrus (BA6)
P12	324	8,14	35	-26	66	R	dPM (BA6)
P13	124	7,97	-37	-17	58	L	dPM (BA6)
P14	44	7,80	-43	6	28	L	vPM (BA44)
P15	13	7,73	57	2	25	R	vPM (BA44)
P16	20	7,72	-8	-51	55	L	Precuneus
P17	70	6,96	50	-15	40	R	SI (BA3b)
P18	13	6,90	5	20	49	R	SMA (BA6, BA1)
P19	80	6,78	54	29	-6	R	BA45
P20	118	6,76	39	-13	52	R	dPM (BA6, BA4a)
P21	18	6,65	12	-43	55	R	Mesial SPL (5M)
P22	152	6,51	-39	-18	19	L	SII (OP1, OP2, OP3)
P23		6,39	-40	-27	13	L	SII
P24	13	6,47	67	-7	29	R	SI (BA1)
P25	24	6,31	4	4	44	R	SMA (BA6)

Table 4: Differences in brain volume between any of the groups (Empathy mask). Thresholded at $p < 0.001$ uncorrected, cluster extend threshold of ten voxels, all clusters survive FDR correction at $p = 0.05$. The location of the peak voxel is given based on the Anatomy Toolbox and inspection of the average anatomy of all participants. Because clusters can extend into regions different from the peaks, we also included these regions in the description. Labels between brackets are taken from the Anatomy toolbox. within the Empathy mask appear to be disproportionately affected as 58% of the voxels that are significantly different between groups in the grey matter mask also fall inside our Empathy mask (see Table 1, column F-Test). This is striking since the Empathy mask covered only 19% of the grey matter mask. A chi-square test indicates that the proportion is indeed significantly larger than what would be expected based on the size of the Empathy mask (Table 1). Similar analyses per group suggest that this is true for the schizophrenia and the psychopathy group, but not the ASD group (see Table 1). Clusters that fell entirely outside the Empathy mask are indicated by a gray color in eTable 6 and include the posterior part of right superior and medial temporal gyrus, thalamus, primary motor cortex, cerebellum, posterior superior parietal lobe and prefrontal areas.

3.4 DISCUSSION

Even though the clinical picture of ASD, schizophrenia (negative symptoms) and psychopathy clearly differ in many respects, they all share a certain dysfunctionality in social cognition and empathy. In this paper we investigate whether these disorders share structural brain abnormalities in a set of brain regions that have been associated with social cognition: shared circuits. Shared Circuits, are brain regions activated when performing actions, experiencing sensations or feeling emotions that

are also activated when witnessing (or imagining) others performing similar actions or experiencing similar sensations or emotions, respectively. We conduct a meta-analysis on previously published grey-matter voxel-based morphometry data and compare these results with our own experimental data. Our data shows that a large proportion of the morphometric differences related to schizophrenia and psychopathy but not ASD fall inside shared circuits. Schizophrenia and psychopathy therefore indeed seem to share a concentration of structural deficits in shared circuits, but this was less the case for ASD.

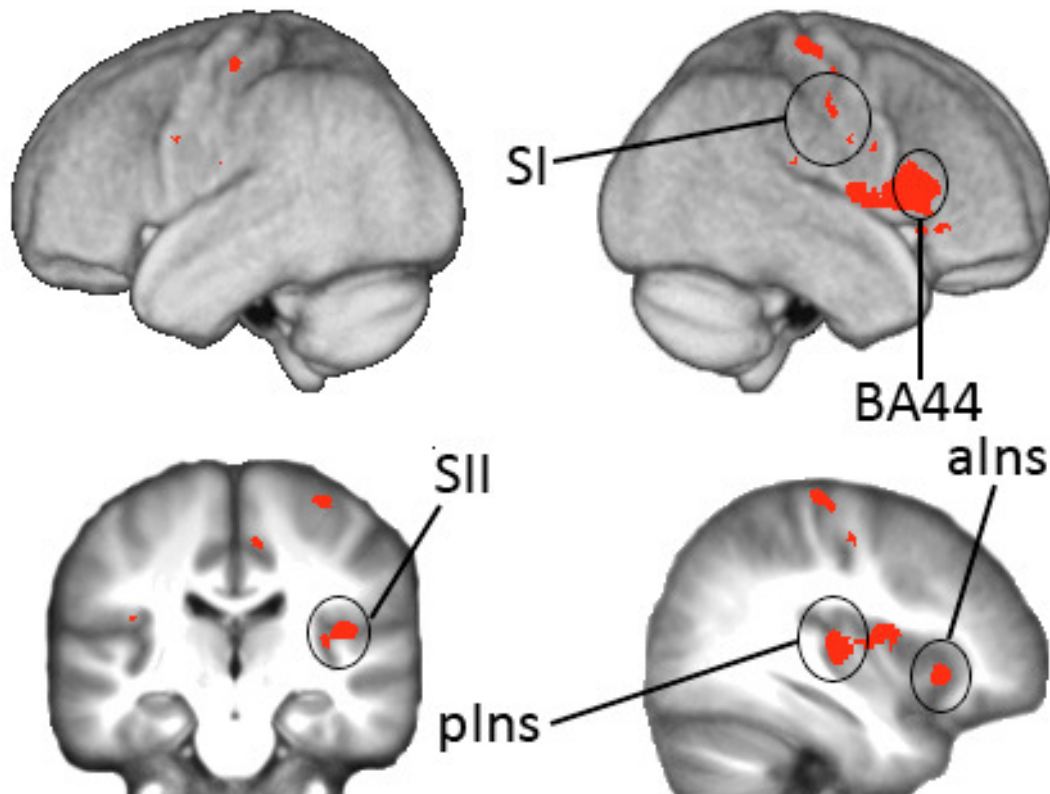


Figure 2: Differences in brain volume between any of the groups (within Empathy mask). Thresholded at $p < 0.001$ uncorrected (all voxels also survive FDR correction at $p = 0.05$) and cluster extend threshold of ten voxels. Results are superimposed on a render of the mean grey matter segment of all included subjects with a depth of 15 voxels on a coronal slice ($y = -22$) and a sagittal slice ($x = 37$).

Although the groups were not equally strongly affected in shared circuits, the ventral premotor cortex (BA6) and the adjacent inferior frontal gyrus (BA44), dorsal parts of the premotor cortex (BA6) and primary somatosensory cortex were implicated in all three disorders. Transcranial magnetic stimulation (Candidi, Urgesi, Ionta, & Aglioti, 2008; Pobric & de Hamilton, 2006) and lesions of ventral premotor cortex and inferior frontal gyrus are known to impair the capacity to perceive the goal directed actions of others (Fazio et al., 2009; Kalenine, Buxbaum, & Coslett, 2010; Pazzaglia, Pizzamiglio, Pes, & Aglioti, 2008; Pazzaglia, Smania, Corato, & Aglioti, 2008) as well as emotion recognition and empathy (Shamay-Tsoory, Aharon-Peretz, & Perry, 2008). In the normal population, differences in brain activity or volume in this region correlate with empathy (Keysers & Gazzola, 2006) (Cheng et al., 2009) and in individuals with ASD, BOLD response in the inferior frontal gyrus correlated with a measure of social functioning (Bastiaansen, et al., 2011). Dorsal premotor cortex (BA6) has also been associated with vicarious responses to action observation

(Cisek & Kalaska, 2004; Gazzola & Keysers, 2009; Keysers & Gazzola, 2009). Finally, primary somatosensory cortex responds during the observation and execution of actions, and during the observation and experience of pain (Keysers, et al., 2010). People experiencing mirror-touch synaesthesia have both increased empathy (Banissy & Ward, 2007) and heightened vicarious primary somatosensory cortex activation in response to tactile experiences of others (Blakemore, Bristow, Bird, Frith, & Ward, 2005b). In addition, lesions in this region can impair the capacity to judge the emotions of others (Adolphs, Damasio, Tranel, Cooper, & Damasio, 2000). These results indicate therefore that reduced grey matter in these regions could contribute to a reduction of someone's tendency and/or capacity to share the sensations and emotions of others and the ability to perceive the inner states motivating the actions of others.

		C paired with			P paired with			A paired with			S paired with		
		P	A	S	C	A	S	C	P	S	C	P	A
P1	SII (OP4)	-0,01	0,80	1,51	0,01	0,80	1,51	-0,80	-0,80	0,74	-1,51	-1,51	-0,74
P2	vPM (BA44)	-0,32	0,19	1,22	0,32	0,50	1,54	-0,19	-0,50	1,04	-1,22	-1,54	-1,04
P3	vPM (BA45)	-0,26	0,44	1,23	0,26	0,70	1,50	-0,44	-0,70	0,79	-1,23	-1,50	-0,79
P4	dPM (BA6)	0,74	0,63	1,57	-0,74	-0,14	0,83	-0,63	0,14	0,97	-1,57	-0,83	-0,97
P5	dPM (BA6)	0,85	0,88	1,34	-0,85	0,04	0,50	-0,88	-0,04	0,46	-1,34	-0,50	-0,46
P6	dPM (BA6)	0,01	0,73	1,08	-0,01	0,73	1,08	-0,73	-0,73	0,34	-1,08	-1,08	-0,34
P7	Posterior-Insula	0,44	-0,18	1,30	-0,44	-0,62	0,86	0,18	0,62	1,50	-1,30	-0,86	-1,50
P8	SII (OP4)	0,40	0,31	1,34	-0,40	-0,09	0,92	-0,31	0,09	1,02	-1,34	-0,92	-1,02
P9	Mid-Insula	0,11	-0,31	1,03	-0,11	-0,42	0,92	0,31	0,42	1,33	-1,03	-0,92	-1,33
P10	Anterior insula	0,13	-0,07	1,22	-0,13	-0,19	1,08	0,07	0,19	1,26	-1,22	-1,08	-1,26
P11	MCG	-0,07	0,38	1,24	0,07	0,45	1,32	-0,38	-0,45	0,88	-1,24	-1,32	-0,88
P12	dPM (BA6)	0,80	0,69	1,46	-0,80	-0,11	0,63	-0,69	0,11	0,73	-1,46	-0,63	-0,73
P13	dPM (BA6)	0,71	-0,15	1,13	-0,71	-0,84	0,43	0,15	0,84	1,30	-1,13	-0,43	-1,30
P14	vPM (BA44)	1,06	1,27	1,14	-1,06	0,19	0,08	-1,27	-0,19	-0,12	-1,14	-0,08	0,12
P15	vPM (BA44)	0,81	0,32	1,31	-0,81	-0,50	0,48	-0,32	0,50	0,99	-1,31	-0,48	-0,99
P16	Precuneus	-0,43	0,78	0,87	0,43	1,22	1,30	-0,78	-1,22	0,07	-0,87	-1,30	-0,07
P17	SI (BA3b)	0,77	0,63	1,33	-0,77	-0,17	0,54	-0,63	0,17	0,70	-1,33	-0,54	-0,70
P18	SMA (BA6)	0,02	0,39	1,17	-0,02	0,37	1,14	-0,39	-0,37	0,77	-1,17	-1,14	-0,77
P19	BA45	-0,86	-0,23	0,51	0,86	0,64	1,38	0,23	-0,64	0,76	-0,51	-1,38	-0,76
P20	dPM (BA6)	0,76	0,44	1,26	-0,76	-0,31	0,50	-0,44	0,31	0,82	-1,26	-0,50	-0,82
P21	Mesial SPL (5M)	-0,29	0,67	0,94	0,29	0,97	1,23	-0,67	-0,97	0,29	-0,94	-1,23	-0,29
P22	SII(OP1)	0,26	0,38	1,22	-0,26	0,13	0,98	-0,38	-0,13	0,84	-1,22	-0,98	-0,84
P23	SII	0,48	0,34	1,25	-0,48	-0,13	0,78	-0,34	0,13	0,91	-1,25	-0,78	-0,91
P24	SI	0,40	0,38	1,25	-0,40	-0,02	0,86	-0,38	0,02	0,86	-1,25	-0,86	-0,86
P25	SMA (BA6)	0,49	0,86	1,22	-0,49	0,38	0,73	-0,86	-0,38	0,35	-1,22	-0,73	-0,35

Table 5: Z-values of post hoc tests between any of the groups (Empathy mask). Same peaks as Table 4 (see numbers in first column). Numbers represent z-values which are calculated by subtracting the mean peak value of the group on the second row from the mean peak value of the group of the first row. This mean difference is divided by the standard deviation of the control group. Yellow indicates a significant positive difference between the two groups ($p < 0.05$) and blue a significant negative difference. Not corrected for multiple comparisons. P = Peak.

The strongest reduction in grey matter volume in shared circuits was found in the schizophrenia group and this was most pronounced in the right anterior insula and posterior BA45 in both our own data and the meta-analysis. These regions are highly interconnected (Cerliani et al., 2011; Jabbi, 2008b) and have been strongly associated with emotional empathy due to their response to the experience and observation of emotions (Bastiaansen, et al., 2009; Jabbi, et al., 2007; Singer, et al., 2004) and the execution and observation of emotional facial expressions (Bastiaansen, et al., 2009; Jabbi, 2008a), respectively. Indeed, facial affect recognition impairments have often been reported in schizophrenia (Hempel, Dekker, van Beveren, Tulen, & Hengeveld, 2010) and have also been linked to increased social dysfunction (Couture, Penn, & Roberts, 2006; Hooker & Park, 2002; Meyer-Lindenberg, 2010) and negative symptoms (Edwards, Jackson, & Pattison, 2002; Kohler et al., 2003; Schneider, Gur, Gur, & Shtasel, 1995; Van't Wout et al., 2007). The anterior insula has also been associated with the sense of self and hallucinations (Craig, 2009) and can therefore be related to negative as well as positive symptoms. Interestingly, correlating structural deficits in schizophrenia with medication (CPZ-equivalents) revealed no significant correlation, challenging the notion that they reflect pharmacological side-effects.

Results of our own data and of the meta-analysis also point to deficits outside shared circuits. For example, we found deficits in the dorsolateral prefrontal cortex, a region important for cognitive flexibility (Shamay-Tsoory, Tomer, Berger, & Aharon-Peretz, 2003) and emotion reappraisal (Ochsner, et al., 2004), the right posterior superior temporal sulcus, which is implicated in gaze following and joint attention (Frith & Frith, 2003) and the perception of biological motion (Grosbras, Beaton, & Eickhoff, 2011) and the medial prefrontal cortex often associated with mentalizing (Amodio & Frith, 2006; Frith & Frith, 2003; C. I. Hooker, Bruce, Lincoln, Fisher, & Vinogradov, 2011). The temporal poles were specifically implicated in ASD, which have been associated with the memory component of social situations (Frith & Frith, 2003).

In summary, having all three diagnostic groups in a single VBM study generated an unexpected finding. Although ASD is the disorder in which shared circuits received most attention in the functional literature, of the three groups with social deficits, individuals in the schizophrenia spectrum actually present with the most pronounced grey-matter abnormalities in empathy related regions. We were able to confirm this with data from previously published studies on ASD and schizophrenia, but not psychopathy due to the lack of available data. The relative salience of grey-matter abnormalities in empathy related regions in schizophrenia suggests that the association between schizophrenia and empathy may merit more attention (Achim, Ouellet, Roy, & Jackson, 2010; Brunet-Gouet et al., 2010).

3.5 CONCLUSION

By including three groups of subjects with social deficits in a single VBM study, we can show for the first time that all three groups share regions of reduced grey matter in premotor and somatosensory brain regions associated with empathy. In addition, by directly comparing the three groups, we were able to show that individuals with schizophrenia show the strongest morphometric changes in grey matter in these regions, and also show reduced grey matter in BA45, the anterior insula and secondary somatosensory cortex, associated with empathy for emotions and tactile experiences. Clearly, social cognition depends on more than empathy, and regions involved in empathy interact with other brain regions that could potentially compensate deficits in empathy in these patients (Keysers & Gazzola, 2007). However, the capacity to vicariously share the actions, emotions and sensations of others is an essential component of our experience of the social world (Decety & Moriguchi, 2007), and the fact that so many of the structural abnormalities in schizophrenia and psychopathy fall within regions associated with empathy suggests that deficits in empathy might be a core feature of these disorders that will deeply challenge their social functioning.

3.6 SUPPLEMENTAL METHODS: ANATOMICAL LIKELIHOOD ESTIMATION (ALE)

IDENTIFYING RELEVANT PAPERS

We performed a structured meta-analysis using the free software from BrainMap GingerALE 2.1 (<http://www.brainmap.org>, (Eickhoff, et al., 2009; Laird et al., 2005; Turkeltaub, Eden, Jones, & Zeffiro, 2002)). To match the review as closely as possible to our own study we only selected papers comparing a male adult group of subjects diagnosed with schizophrenia, autism spectrum disorder (ASD) and/or psychopathy against a healthy control group. In general, papers were considered for our meta-analysis when they were published in article format between 1999 and June 2011, written in English, and when the authors had applied an automated voxel-wise, whole brain comparison of the groups. Furthermore, we only included papers of which the included groups had a mean age of at least 18 years and T1 images were used for the brain comparisons. We also adapted a minimal p-value threshold of at least 0.001 uncorrected and excluded individual peak voxels from a study when they only survived a more lenient threshold. Similar to Nickl-Jockschat and colleagues (Nickl-Jockschat et al., 2011) we chose to include all studies that were published in peer-reviewed journals when they reported including subjects diagnosed with autism spectrum disorder, schizophrenia or psychopathy, regardless of the actual mode of diagnosis.

Some of the manuscripts that fulfilled all these criteria were reports of null-findings. Since null-findings cannot be taken into account using this technique, we had to leave them out of the analysis. However, we did report them in the list of included papers with a special annotation. A considerable amount of work has already been done in an attempt at identifying the structural deficits for autism spectrum disorders and schizophrenia. We therefore decided to use previous reviews to identify the relevant older literature and then extend this list with a literature search of the more recent literature in Pubmed (www.pubmed.org) and Scopus (www.scopus.com).

ALE ANALYSIS

All foci were entered into our ALE analysis. Coordinates reported in the stereotactic space of Talairach and Tournoux were converted into MNI using the Lancaster transform (Lancaster et al., 2007). Then, for each group separately we ran an ALE using the less conservative mask provided within GingerALE 2.1. We applied the revised ALE algorithm of Eickhoff and colleagues (Eickhoff, et al., 2009) to model the probability distributions of the reported foci from our review. This analysis results in “ALE”-maps which represent a voxel wise convergence of results. Using permutation testing with 5000 permutations, we then tested the null-hypothesis that none of the voxels showed a significant convergence of findings across the included studies. We thresholded these “ALE”-maps at a false discovery rate of $p < 0.05$, with a minimal cluster size of 10 mm^3 . Using a Chi-square test we then determined for each group separately whether the observed ratio between voxels falling within the Empathy mask and voxels falling outside the Empathy mask could have happened due to chance given that the ratio between total volume in Empathy mask and total volume in the grey matter mask was 0.19.

The second analysis was conducted to test the null-hypothesis that both groups had the same amount of convergence of results across studies in each voxel. This between groups analysis was again thresholded at a false discovery rate of $p < 0.05$, with a minimal cluster size of 10 mm^3 . We

also wanted to test the conjunction between the groups. Because a conjunction analysis is not possible in GingerALE 2.1, we examined the overlap between two groups using a logical AND between the two within group images.

3.7 SUPPLEMENTAL RESULTS: LITERATURE SEARCH

We used five meta-analyses of grey matter volume or density differences (Cauda et al., 2011; Chen, Jiao, & Herskovits, 2011; Cheung et al., 2010; Nickl-Jockschat, et al., 2011; Via, Radua, Cardoner, Happé, & Mataix-Cols, 2011) to identify older papers published on ASD. The years 2010 and 2011 had not been fully captured by these reviews and we therefore performed additional literature searches restricted to these years to identify the latest work on this topic. We used combinations of the terms “autism”, “asperger”, “HFA”, “autistic” with “VBM”, “voxel based morphometry”, “morphometry” in Pubmed and in Scopus. We then used our inclusion criteria to select relevant papers from this list. This yielded a total of 11 relevant papers of which two were unable to report differences at a minimum threshold of $p < 0.001$ uncorrected, see eTable 1.

We also selected five quantitative meta-analyses on structural deficits in schizophrenia (Bora et al., 2011; Cheung, et al., 2010; Fornito, Yücel, Patti, Wood, & Pantelis, 2009; Honea, Crow, Passingham, & Mackay, 2005; Levitt, Bobrow, Lucia, & Srinivasan, 2010; Williams, 2008). With these reviews we identified relevant papers until 2008 and extended this list of papers with literature searches of the years 2008 until June 2011 in Pubmed and Scopus using combinations of the terms “schizophrenia” with “VBM”, “voxel based morphometry” and “morphometry”. We selected 60 papers that met our inclusion criteria. The included papers are listed in eTable 3. Two studies reported no differences at a minimum threshold of $p < 0.001$ uncorrected.

We were not able to find reviews presenting a meta-analysis of previously published VBM studies on psychopathy and therefore conducted a literature search stretching from 1999-June 2011 using combinations of the terms “psychopathy” with “VBM”, “voxel based morphometry” and “morphometry”. We found two papers that met all our inclusion criterions (see eTable 5).

3.8 SUPPLEMENTAL TABLES

First author	Year	n ASD/ n male	n HC/ n male	Age ASD	Age Hc	S	M/ U	Covariates	T	Stats
(Abell et al., 1999)	1999	15/12	15/12	29	25	12	U	GGM	2.0	p<.001
(Craig et al., 2007)	2007	14/0	19/0	40	35	5	M	GGM or GWM	1.5	p<.01 cluster level
(Ecker et al.)	2011	89/89	89/89	26	28	4	U	Site GBM	3.0	P=0.0041
(Freitag et al., 2008)	2008	15/13	15/13	18	19	12	M	GBM	1.5	p<.001; k=20
(Hyde, Samson, Evans, & Mottron, 2010)	2009	15/15	13/13	23	19	12	U	A	3.0	p<.05 fdr
(Kosaka et al., 2010)	2010	32/32	40/40	24	23	8	M	GGM, A	3.0	p<.05 fdr
(McAlonan et al., 2002)	2002	17/17	24/22	32	33	/	M	n/r	1.5	p<.002 cluster level
(Rojas et al., 2006)	2006	24/24	23/23	21	21	8	M	GGM, A	1.5	p<.01 ^a
(Schmitz, Daly, & Murphy, 2007)	2006	9/9	12/12	38	39	10	U	GBM	1.5	p<.001
(Toal et al., 2010)	2010	65/56	33/30	31	32	8	M	GGM or GWM	1.5	p<.003 cluster level for grey matter; p<0.01 cluster level for white matter
(Wilson, Tregellas, Hagerman, Rogers, & Rojas, 2009)	2009	10/8	10/7	30	29	12	M	GM volume	1.5	p<.05 fdr

Table S1: Whole brain VBM studies contrasting adult subjects diagnosed with ASD against healthy controls. Superscripts: a= thresholded at p=0.001. Abbreviations: GGM = Global Grey Matter; GWM = Global White Matter; GBM = Global Brain Matter (=GGM+GWM); A=Age; G=Gender, k=cluster size, ASD = autism spectrum disorder, HC = healthy control, S = smoothing, M = modulated, U = unmodulated, T = Tesla. Grey colored rows indicate studies with null-findings.

Cluster size (mm ³)	MNI coordinates			Hemi- sphere	Cluster description
	x	y	z		
496	-18	30	44	L	Superior Frontal Gyrus
352	44	-22	50	R	Postcentral Gyrus (BA3b)
344	40	-85	22	R	Middle occipital Gyrus
344	36	2	-24	R	Superior Temporal Gyrus
304	-20	18	-6	L	Putamen
200	-42	0	-28	L	Temporal pole
192	28	-84	-20	R	Cerebellum
184	14	-12	-4	R	Thalamus
184	-36	-20	50	L	Postcentral Gyrus
144	4	-70	12	R	Calcarine Gyrus (BA17/18)
128	30	0	10	R	Putamen
128	28	-62	22	R	Precuneus
120	42	-18	-8	R	Middle insula
112	-12	44	-12	L	Rectal Gyrus
64	-24	0	6	L	Putamen
16	-4	-18	-20	L	Brainstem

Table S2: Significant convergence of VBM studies comparing grey and white matter between ASD subjects and healthy controls. Results are thresholded at $p < 0.05$ corrected for the false discovery rate with a minimum cluster size of 10 mm³. The location of the peak voxel is given based on the Anatomy Toolbox and inspection of the colin MNI brain. Because clusters can extend into regions different from the peaks, we also included these regions in the description. Labels between brackets are taken from the Anatomy toolbox.

First author	n Sz/ n male	n HC/ n male	Age Sz	Age Hc	Illness duratio n	S	M/ U	Covariates	T	Stats
(Antonova et al., 2005)	45/27	43/25	40	34	16.8	12	M	A, G ^d	1.5	p<.05 corr ^c
(Bassitt, Neto, De Castro, & Busatto, 2007)	50/38	30/21	32	31	11.4	12	M	GGM or GWM	1.5	p<.001
(Bergé et al., 2011)	21/12	20/8	25	25	0	8	U	A, G, GGM	n/r	p<.0001; k=100
(Bonilha et al., 2008)	14/11	13/11	40	35	n/r	10	M	---	3.0	p<.05 fdr
(Borgwardt et al., 2010)	28/22	34/24	38	39	16.8	8	M	A, G, GGM	1.5	p<.05 corr
(Bose et al., 2009)	34/34	33/33	40	40	12	12	M	--- ^d	1.0	p<.05 corr
(Cascella et al., 2010)	50/37	90/43	41	46	16.7	8	M	A, G, TIV	1.5	p<.05 fwe
(Chan et al., 2010)	39/30	64/38	29	32	0.9	0	M	A, G, TIV	3.0	p<.05 cluster level
(Cocchi et al., 2009)	21/16	41/32	22	23	0.1	12	M	---	1.5	p<.003 (gray) n/a for white
(Cooke et al., 2008)	52/40	30/24	38	32	13.9	12	M	A, G	1.5	p<.05 fwe
(Cui et al., 2011)	23/16	36/21	25	27	4.04	6	M	G, A	3.0	p<.001 u
(Donohoe et al., 2011)	70/48	38/20	42	33	17.6	8	M	A, G, GGM or GWM	1.5	p<.05 fdr
(Ebdrup et al., 2010)	38/26	43/30	26	27	3.42	8	M	n/r	3.0	n/r
(Euler, Thoma, Gangestad, Cañive, & Yeo, 2009)	20/18	23/16	43	43	n/r	12	M	A, G	1.5	p<.001; k=100
(García-Martí et al., 2008)	17/17	19/19	36	33	n/r	12	U	A, TIV	1.5	p<.05 fwe; k=135
(Ha et al., 2004)	35/21	35/21	28	27	4.9	12	U	--- ^d	1.5	p<.001; k=50
(Herold et al., 2009)	18/11	21/11	29	27	3.4	8	M	IQ, TIV, A, G	1.0	p<.005 ^b ; k=25
(Hirao et al., 2008)	20/10	20/10	37	35	10.6	10	U/ M	TIV	3.0	p<.05 fdr; k=300
(Honea et al., 2008)	169/131	212/103	36	33	n/r	10	M	A, G, IQ, GGM + ^d	1.5	p<.05 fwe; k=5
(Horn et al., 2010)	20/13	20/13	30	30	n/r	10	M	---	1.5	p<.05 fdr
(Hulshoff Pol et al., 2001)	159/112	158/106	36	38	12.3	8	U	A, G, H	1.5	p<.05 corr
(Hulshoff Pol et al., 2004)	159/112	158/106	36	38	12.3	4	U	G, Ha, A	1.5	p<.05 corr
(Jayakumar, Venkatasubramanian, Gangadhar, Janakiramaiah, & Keshavan, 2005)	18/9	18/9	25	26	0.86	12	M	TIV, A, G	1.5	p<.05 fdr
(Job et al., 2002)	34/23	36/17	21	21	n/a	12	U	GBM, G, Ha, He, A, PSC	1.0	p<.05 corr
(Kašpárek et al., 2009)	32/32	18/18	24	24	0.61	12	M	A, GGM	1.5	p<.05 fwe
(Kawada et al., 2009)	26/11	26/11	37	36	9.9	12	M	A, G, TIV	3.0	p<.05 fdr; k=500
(Kawasaki et al., 2007)	30/30	30/30	25	25	4	12	U	--- ^d	1.5	p<.05 fdr
(Kawasaki et al., 2008)	60/30	60/30	25	25	5.1	12	M	---	1.5	p<.05 fwe
(Koutsouleris et al., 2008)	175/130	177/123	32	32	4.3	12	U	A, G	1.5	p<.05 fwe
(Kubicki et al., 2002)	16/14	18/16	26	24	n/a	12	U	GGMI	1.5	p<.05 corr
(Lui et al., 2009)	68/30	68/31	24	25	0.7	8	M	n/r	3.0	p<.05 corr

First author	n Sz/ n male	n HC/ n male	Age Sz	Age Hc	Illness duratio n	S	M/ U	Covariates	T	Stats
(McDonald et al., 2005)	25/18	52/24	37	39	17	4	M	A, G, GBM	1.5	p<.01 cluster level
(McIntosh et al., 2004)	26/13	49/23	37	35	15	12	U	He, G, A, H	1.5	p<.05 corr ^c
(Meda et al., 2008)	200/101	200/112	40	40	n/r	8	U	A, G, S, TIV	1.5	p<.05 fwe
(Molina et al., 2010)	38/12	24/16	34	35	9.8	8	M	A, G, TIV	1.5	p<.001; k=20
(Molina, Martín, Ballesteros, de Herrera, & Hernández-Tamames, 2010)	30/16	31/18	34	37	13.4	n/r	n/r	A, G, E, TIV	1.5	p<.001; k=200
(Moorhead et al., 2004)	25/14	29/13	51	43	n/r	12	M	TIV,A	1.0	p<.05 corr
(Neckelmann et al., 2006)	12/7	12/6	32	32	7.6	12	U	GGM	1.5	p<.001; k=50
(Paillère-Martinot et al., 2001)	20/20	20/20	29	26	10	10	U	A	1.5	p<.01; k=800
(Pomarol-Clotet et al., 2010)	31/21	31/21	42	41	21.8	4	M ^a	---	1.5	p<.01 corr
(Salgado-Pineda et al., 2003)	13/13	13/13	24	23	n/a	8	U	---	1.5	p<.001; k=20
(Salgado-Pineda et al., 2004)	14/7	14/n/r	25	24	1.9	8	M	---	1.5	p<.05 fdr; k=10
(Salgado-Pineda et al., 2011)	14/9	14/9	37	35	14	12	M	---	3.0	p<.05 fdr
(Schaufelberger et al., 2007)	62/44	94/53	28	30	0.48	12	M	GGM	1.5	p<.001
(Schiffer et al., 2010)	12/12	14/14	38	37	16.8	14	M ^a	A	1.5	p<.05 fdr
(Schuster et al., 2011)	27/14	40/17	60	62	29.2	8	M	A, S, G, E	1.5	p<.05 fdr; k=1000
(Segall et al., 2009)	237/173	266/167	35	34	n/r	10	U	S, G, A, TIV		
(Spalletta et al., 2003)	28/14	28/14	35	34	11.0	10	U	---	1.5	p<.05 corr
(Španiel et al., 2011)	40/18	36/17	32	25	3.4	10	M	A, GBM	1.5	p<.05 fdr; k=30
(Suzuki et al., 2002)	45/23	42/22	26	26	5.2	12	U	Age	1.5	p<.05 corr
(Tomelleri et al., 2009)	70/45	79/41	40	40	14.13	12	M	G, TIV	1.5	p<.05 fwe
(Tregellas et al., 2007)	32/21	32/14	40	35	12	12	M	Smoking, GGM	1.5	p<.05 fdr
(Venkatasubramanian, 2010)	30/21	27/19	30	27	3.5	12	M	TIV	1.5	p<.05 fdr
(Walther et al., 2011)	11/8	14/8	35	32	8.93	8	M	---	3.0	p<.01 fdr
(Wilke et al., 2001)	48/27	48/27	33	33	8.6	12	U	A, G, GBM	1.5	p<.001; k=25
(Wright et al., 1999)	15	15/15	32	30	9	12	U	GGM, A, G, H	1.0	p<.01 corr
(Whitford et al., 2005)	31/20	30/20	19	19	0.5	12	M	GGM	1.5	p<.05 corr; k=400
(Whitford et al., 2006)	41/26	47/33	20	19	0.69	12	M	A, G, Ha, GGM	1.5	p<.05 corr; k=100
(Xu, Groth, Pearlson, Schretlen, & Calhoun, 2009)	120/69	120/55	42	43	n/r	12	U	n/r	1.5	p<0.001
(Yamada et al., 2007)	20/10	20/10	39	39	11.6	12	U	GGM	3.0	p<.05 fdr

Table S3: Whole brain VBM studies contrasting adult subjects diagnosed with schizophrenia against healthy controls. Superscripts: a= modulated for non-linear effects only; b=thresholded at p=0.001; c=global normalization, d=2nd-order polynomial age expansion. Abbreviations: GGM = Global Grey Matter; GWM = Global White Matter; GBM = Global Brain Matter (=GGM+GWM); TIV=Total Intracranial Volume; GGMI=Global Grey Matter Intensity; A=Age; G=Gender; corr=corrected for multiple comparisons, method not specified;

Ha=Handedness; He=Height; PSC=Paternal Social Class; E=Education; n/r = not reported, k=cluster size, Sz=schizophrenia, HC = healthy control, S = smoothing, M = modulated, U = unmodulated, T = Tesla. Grey colored rows indicate studies with null-findings.

Cluster size (mm ³)	MNI coordinates			Hemi- sphere	Location peak voxel
	x	y	z		
7280	-36	16	2	L	anterior Insula - Inferior Frontal Gyrus (p. Orb.)
5824	-2	38	-10	L	Anterior Cingulate Gyrus - Mid Orbital Gyrus
5472	36	16	4	R	anterior Insula - Inferior Frontal Gyrus (p. Orb.)
4976	0	-18	6	R	Thalamus (bil.)
1112	-26	50	14	L	Middle Frontal Gyrus
1040	48	-20	16	R	Rolandic Operculum (OP1, OP4)
888	-46	-16	-22	L	Middle Temporal Sulcus
632	-48	-22	16	L	Rolandic Operculum (OP1)
576	-12	30	50	L	Superior Frontal Gyrus
552	-50	-58	-4	L	Middle Temporal Sulcus
504	-6	-60	16	L	Precuneus
496	26	4	-10	R	Putamen
456	-8	40	26	L	Anterior Cingulate Gyrus - Superior Medial Gyrus
328	26	56	10	R	Middle Frontal Gyrus
304	-58	-14	18	L	Postcentral Gyrus (OP1, OP4)
240	-4	42	44	L	Superior Medial Gyrus
208	-58	-20	-10	L	Middle Temporal Gyrus
144	2	24	34	R	Superior Medial Gyrus
128	-28	-78	14	L	Middle Occipital Gyrus
120	-2	-50	28	L	Posterior Cingulate Gyrus
104	-30	-34	-10	L	Hippocampus
88	-48	-32	2	L	posterior Superior Temporal Sulcus
48	20	-92	-8	R	Lingual Gyrus
48	-48	-8	8	L	Rolandic Operculum (OP4)
48	8	12	8	R	Caudate
40	-4	26	44	L	Superior Medial Gyrus
32	-2	-70	-4	L	Lingual Gyrus
32	-46	8	34	L	Precentral Gyrus
24	28	-6	2	R	Putamen
24	50	8	24	R	Inferior Frontal Gyrus (p. Oper.)
16	28	-62	-26	R	Cerebellum
16	48	-18	44	R	Precentral Gyrus

Table S4: Significant convergence of VBM studies comparing grey and white matter between schizophrenia subjects and healthy controls. Results are thresholded at $p < 0.05$ corrected for the false discovery rate with a minimum cluster size of 10 mm³. The location of the peak voxel is given based on the Anatomy Toolbox and inspection of the Colin MNI brain. Because clusters can extend into regions different from the peaks, we also included these regions in the description. Labels between brackets are taken from the Anatomy toolbox.

Publication	n Ps/ n male	n HC/ n male	Age Ps	Age Hc	S	M/U	Covariates	T	Stats
(Müller, et al., 2008)	17/17	17/17	33	31	10	U	---	1.5	p<.05 fdr
(de Oliveira-Souza, et al., 2008)	15/8	15/8	32	32	12	U	TIV	1.5	p<.005; k=5
(Tiihonen, et al., 2008)	26/26	25/25	33	35	12	M	A, TIV	1.0	p<.05 fdr

Table S5: Whole brain VBM studies contrasting adult subjects diagnosed with psychopathy against healthy controls. Abbreviations: TIV=Total Intracranial Volume; A=Age, k=cluster size, Ps=psychopathy, HC = healthy control, S = smoothing, M = modulated, U = unmodulated, T = Tesla.

Cluster size	F	MNI x y z	Hemi- sphere	Location peak voxel / cluster
2002	11,75	60 -2 6	R	SII (OP4)
	9,69	57 12 8	R	vPM (BA44)
	8,97	57 19 12	R	BA45
414	9,84	26 -16 60	R	dPM (BA6)
	6,29	23 -15 69	R	dPM (BA6)
2798	9,68	36 -16 6	R	Posterior-Insula (Iq2) and Mid-insula
	8,11	49 -21 4	R	Ventral bank of lateral sulcus (TE 1.0) and SII (OP1, OP2)
	7,63	42 -21 9	R	Ventral bank of lateral sulcus (TE 1.0)
514	9,53	5 26 45	R	SMA (BA6)
560	8,93	-41 -27 9	L	Ventral bank of lateral sulcus (TE 1.0) and Posterior-Insula
	6,41	-39 -18 19	L	SII (OP2 and OP3)
	6,32	-40 -27 18	L	SII (OP1)
667	8,81	32 24 -6	R	Anterior Insula
176	8,38	-43 6 30	L	vPM (BA44)
468	8,11	9 -26 48	R	MCC
	6,75	11 -43 54	R	Mesial SPL (5Ci)
	6,36	12 -36 49	R	Mesial SPL (5Ci)
305	8,07	35 -26 66	R	dPM (BA6)
150	8,05	57 3 25	R	vPM (BA44)
298	8,02	51 -46 15	R	Superior Temporal Gyrus
79	7,91	-37 -17 58	L	dPM (BA6)
247	7,90	-8 -50 54	L	Mesial SPL (5M)
157	7,47	-2 24 43	L	vPM (BA44)
295	7,27	49 -14 39	R	SI (BA3b, BA4a, BA4p)
	6,24	51 -16 47	R	SI (BA1)
114	6,93	23 30 52	R	Superior Frontal Gyrus (BA8)
43	6,88	-48 -9 39	L	M1 (BA4a, 4p)
42	6,82	-10 -23 12	L	Thalamus
65	6,80	69 -37 1	R	posterior Middle Temporal Gyrus (BA22)
102	6,79	37 -12 48	R	dPM (BA6)
	6,53	40 -15 55	R	dPM (BA6)
39	6,76	53 29 -6	R	vIPFC (BA45)
30	6,58	5 -59 62	R	Mesial SPL (5L)
18	6,45	-8 38 40	L	Superior Medial Gyrus (BA32)
30	6,40	-7 -38 55	L	Mesial SPL (5M)
37	6,40	27 3 62	R	Superior Frontal Gyrus
38	6,32	21 -85 -47	R	Cerebellum
15	6,24	4 4 44	R	MCC (BA6)

Table S6: Differences in brain volume between any of the groups (whole-brain). Thresholded at $p < 0.001$ uncorrected, cluster extend threshold of ten voxels, all clusters survive FDR correction at $p = 0.05$, within the grey matter mask. The location of the peak voxel is given based on the Anatomy Toolbox and inspection of the average anatomy of all participants. Because clusters can extend into regions different from the peaks, we also included these regions in the description. Labels between brackets are taken from the Anatomy toolbox. Grey colored rows correspond to clusters without overlap with clusters within the Empathy mask.

Cluster size	T	MNI coordinates			Hemi-sphere	Cluster location
		x	y	z		
Control larger ASD						
173	4,39	-43	6	30	L	vPM (BA44)
13	3,49	29	3	64	R	Superior Frontal Gyrus
17	3,28	22	30	51	R	Superior Frontal Gyrus
Control larger Psychopathy						
113	4,00	-42	4	30	L	vPM (BA44)
80	3,53	46	-48	18	R	posterior Superior Temporal Sulcus
17	3,49	37	-11	48	R	dPM (BA6)
40	3,48	21	-15	61	R	dPM (BA6)
11	3,29	38	-26	67	R	dPM (BA6)
Control larger Schizophrenia						
414	5,40	26	-16	60	R	dPM (BA6)
1857	5,19	60	-3	6	R	vPM / SII (BA44, BA45, OP4, TE 1.2)
305	4,91	34	-26	66	R	dPM (BA6)
298	4,84	51	-46	15	R	posterior Superior Temporal Sulcus
558	4,82	-41	-27	9	L	Superior Temporal Sulcus, SII (TE 1.1 TE 1.0, OP1, OP3)
514	4,68	5	26	45	R	Superior Medial Gyrus, SMA
295	4,64	49	-14	39	R	Postcentral Gyrus (BA4a, BA4p, BA3b)
2141	4,60	43	-22	15	R	Insula, SII, Heschl's Gyrus (Ig2, OP1, OP2, TE 1.0 TE 1.1)
150	4,59	58	3	25	R	vPM (BA6, BA4a)
157	4,46	-2	24	43	L	Superior Medial Gyrus, SMA
102	4,35	39	-13	52	R	dPM (BA6, BA4a)
43	4,32	-50	-9	38	L	Precentral Gyrus (BA4a, BA4p)
366	4,29	10	-27	48	R	MCC, Paracentral Lobe (BA6, BA4a, SPL 5Ci, SPL 5M)
596	4,17	32	24	-6	R	anterior Insula
15	4,15	4	4	44	R	Superior Medial Gyrus
18	4,09	-8	37	41	L	Medial Frontal Gyrus (BA6)
143	3,99	-44	7	28	L	vPM (BA44)
73	3,94	-37	-17	60	L	dPM (BA6, BA4a)
104	3,58	24	29	51	R	Superior Frontal Gyrus
ASD larger Psychopathy						
37	4,28	43	-1	18	R	SII (OP3)
Psychopathy larger ASD						
30	4,36	5	-59	61	R	mesial SPL (SPL (5A, 5L))
38	4,12	21	-86	-46	R	Cerebellum
65	4,06	69	-36	1	R	Middle Temporal Gyrus
169	3,92	-6	-50	56	L	mesial SPL (SPL(5M, 7A, 5L), BA3a)
21	3,84	28	5	64	R	Superior Frontal Gyrus
30	3,76	-4	-39	52	L	mesial SPL (SPL(5M))
ASD larger Schizophrenia						
2266	4,87	35	-15	6	R	Insula, Heschl's Gyrus, STS (IG1, Ig2, TE 1.0, TE 1.1, OP2, OP3)
537	4,75	30	26	-7	R	vPM
402	4,35	-46	-24	5	L	Superior Temporal Gyrus (TE 1.0, TE 1.1)
42	4,25	-10	-22	13	L	Thalamus
79	4,20	-37	-17	58	L	dPM (BA 6, BA 4a)
96	3,74	13	-26	50	R	mesial SPL (BA4a, BA6, SPL (5Ci))
12	3,73	-8	39	38	L	Superior Medial Gyrus
217	3,72	53	13	6	R	vIPFC (BA45)
41	3,61	34	-20	64	R	dPM (BA6)
38	3,49	56	4	24	R	vPM
53	3,48	7	30	45	R	Superior Medial Gyrus
11	3,35	-48	-9	39	L	Postcentral Gyrus (BA4a)
Schizophrenia larger ASD						
31	3,55	20	-82	-50	R	Cerebellum (Lobule VIIa (Hem))
Psychopathy larger Schizophrenia						
1987	4,96	60	-3	7	R	vPM / SII (BA44, BA45, OP4, TE 1.2)
506	4,47	4	25	46	R	SMA, Superior Medial Gyrus
39	4,44	53	29	-6	R	vIPFC (BA45)
466	4,20	9	-26	48	R	mesial SPL, Precuneus (SPL (5M, 5Ci), BA6, BA4a,

Cluster size	T	MNI coordinates			Hemi-sphere	Cluster location
		x	y	z		
						BA3a)
247	4,18	-8	-50	54	L	mesial SPL, Precuneus (SPL (5M, 7a), BA3a)
268	4,05	37	22	-5	R	anterior Insula
30	3,83	-7	-38	55	L	mesial SPL (5M)
53	3,74	69	-39	1	R	Inferior Temporal Gyrus
121	3,57	-2	25	45	L	SMA, Superior Medial Gyrus
43	3,48	38	1	7	R	mid Insula

Table S7: Post hoc tests inclusively masked by results F-Tests (whole brain). This table represents the results of the post hoc tests belonging to the F-Test within the grey matter mask assessing the null-hypothesis that none of the groups differed from each other. The post hoc tests were conducted only on voxels for which this null-hypothesis had been rejected in order to test the direction of these differences and thresholded at $p=0.001$ uncorrected. The location of the peak voxel is given based on the Anatomy Toolbox and inspection of the average anatomy of all participants. Because clusters can extend into regions different from the peaks, we also included these regions in the description. Labels between brackets are taken from the Anatomy toolbox.

Acknowledgements

We thank A.J. Sibeijn-Kuiper for scanning the subjects and her help in setting up the specific safety protocol for this study and Dr. R. Renken for his help with the data-analysis. We also want to thank all the participants for their cooperation and Prof. Dr. S. Eickhoff and Dr. T. Nickl-Jockschat for sharing data from their review on Autism. We would like to thank Forensic Psychiatric Clinic Veldzicht and their research department (Dr. I. Timmermans) for their help in recruiting the last subjects. C.K. and the research were supported by a VIDI from the Dutch Science Foundation (NWO) and Marie Curie Excellence Grant from the European, and interpretation of the data nor the preparation, review, or approval of the manuscript. None of the authors have conflicts of interest regarding this work. H.M. takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors had access to all the data in the study.

4

BEHAVIOURAL EXAMINATION OF AUTISM, PSYCHOPATHY AND SCHIZOPHRENIA

A version of this manuscript is published as:

Diagnosing Autism Spectrum Disorders in adults: the use of ADOS module 4 (2011)

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Journal of Autism and Developmental Disorders

ABSTRACT

Autism Diagnostic Observation Schedule (ADOS) module 4 was investigated in an independent sample of high-functioning adult males with an autism spectrum disorder (ASD) compared to three specific diagnostic groups: schizophrenia, psychopathy, and typical development. ADOS module 4 proves to be a reliable instrument with good predictive value. It can adequately discriminate ASD from psychopathy and typical development, but is less specific with respect to schizophrenia due to behavioural overlap between autistic and negative symptoms. However, these groups differ on some core items and explorative analyses indicate that a revision of the algorithm in line with Gotham et al. (2007) could be beneficial for discriminating ASD from schizophrenia.

4.1 INTRODUCTION

Although for a diagnosis of an autism spectrum disorder (ASD) symptoms should be present from infancy or early childhood, the disorder may not be detected until later because of several reasons: a well-structured support system, compensation for limitations through high intelligence, the presence of more subtle autistic symptoms, and confusion with or overshadowing by another psychiatric disorder (Kan, Buitelaar, & van der Gaag, 2008; Wing & Potter, 2002, see also www.dsm5.org). Partly due to increasing knowledge of milder forms of autism and more awareness that autistic conditions can be found in individuals of high ability, ASDs are starting to become more widely recognized in adults (Brugha et al., 2009; Fombonne, 2005; Kan, et al., 2008; Wing & Potter, 2002). In clinical practice, we notice a growing demand for diagnostic procedures concerning ASD in adults. However, there is no established diagnostic tradition for ASD in older individuals. It is very challenging to disentangle social and communicative problems associated with ASD from the often complicated clinical picture in adulthood, especially when developmental information is unavailable. Standardized instruments are needed that can facilitate the diagnostic process. Poor self-referential cognition present in many individuals with ASD may hamper self-report measures of autistic symptoms (Johnson, Filliter, & Murphy, 2009; Lombardo, Barnes, Wheelwright, & Baron-Cohen, 2007). Therefore, observation of the individual during social interaction is important in addition to information about difficulties experienced in daily life.

The Autism Diagnostic Observation Schedule (ADOS, Lord, et al., 2000) is a standardized instrument that assesses social interaction, communication, and imagination during a semi-structured interaction with an examiner. The ADOS includes four modules suited for individuals with different developmental and language levels, ranging from children with no expressive language to older and verbally more capable individuals. The psychometric properties of modules 1-3 are well-studied and present the ADOS as a reliable and valid instrument to assess the presence of ASD in children (de Bildt et al., 2004; Gray, Tonge, & Sweeney, 2008; Lord, et al., 2000; Noterdaeme, Sitter, Mildenerger, & Amorosa, 2000; Papanikolaou et al., 2009). Module 4 was developed for adolescents and adults with fluent speech. In the original paper on the ADOS, Lord and colleagues (2000) included module 4 administrations for adolescents and young adults with autism (AD, $n = 16$), PDD-NOS ($n = 16$) and with various other diagnoses ($n = 15$). Their results indicate that, after training as described in the manual (Lord, et al., 1999), ADOS module 4 can be used effectively to distinguish between autism spectrum and non-spectrum, and to a lesser degree between AD and PDD-NOS. Thus far, no further specific studies into the value of module 4 have been reported. When establishing a diagnosis, clinicians need to rule out specific conditions that can cause similar symptoms. Because the control group in Lord's study (2000) was relatively small and very diverse with respect to diagnosis, it is still unclear to what extent ADOS module 4 can support such differential diagnostics.

One disorder that shares symptoms with autism is schizophrenia. Kanner (1943) even borrowed the term autism from Eugen Bleuler, who used it to describe withdrawal from contact with the outside world in adults with schizophrenia (1911). Although autism and schizophrenia have different developmental trajectories, cross-sectionally their clinical presentations overlap (Frith, 2003; Goldstein, Minshew, Allen, & Seaton, 2002; Volkmar & Cohen, 1991). Especially individuals with schizophrenia and negative symptoms show many of the same social deficits as adults with autism

(Frith, 2003; Sheitman, et al., 2004). Autism also shares features with psychopathy, a personality disorder which partly overlaps with antisocial personality disorder (APD). Besides poor behavioural control and a disregard for the rights of other people, individuals with psychopathy have deficits in the emotional and interpersonal domain, such as insensitivity or lack of empathy towards other people. Impairments in empathy are also central to ASD, characterized by a cognitive impairment to take the perspective of other people (Baron-Cohen & Wheelwright, 2004; Gillberg, 1992). Rogers and colleagues (2006) indicate that there could be a subgroup of people with ASD that have additional callous-unemotional traits reminiscent of psychopathy. Others report that some individuals with ASD may *seem* cold and heartless, because they are unaware of how their behaviour affects other people, which could lead to a diagnosis of APD or psychopathy by mistake (Bartels & Bruinsma, 2008; Howlin, 2000; Kohn, Fahum, Ratzoni, & Apter, 1998). Especially in forensic settings, it is important to differentiate ASD from psychopathy, because they require different approaches. It should be noted, however, that unlike in psychopathy there is little evidence of any excess of crimes among people with autism (Howlin, 2000).

The current study will examine the psychometric properties of ADOS module 4 by including relatively homogeneous non-autistic groups: a group of adult males with schizophrenia and marked negative symptoms, males with psychopathy, and typically developing males. Analyses will center on the original ADOS algorithm (Lord, et al., 2000), based on the operationalization of the DSM-IV and ICD-10 criteria for autistic disorder (American Psychiatric Association, 1994; World Health Organization, WHO, 1993), but will also include some preliminary analyses based on revised algorithms for the ADOS. In line with proposals for the revision of the DSM (www.dsm5.org), the revised algorithms of the ADOS for modules 1-3 synthesize the items from the original social interaction and communication domains into the new domain Social Affect (SA, Gotham, et al., 2007). This new notion of communicative and social behaviours as a single set of symptoms is supported by recent studies showing that non-verbal communication and social items load onto the same factor (Constantino et al., 2004; Lord, et al., 1999; Robertson, Tanguay, L'Ecuyer, Sims, & Waltrip, 1999; van Lang et al., 2006). In addition, the revised algorithms include restricted and repetitive behaviours (RRB) as opposed to the original algorithm. Although the narrow time frame of the ADOS might not provide adequate opportunity to measure these behaviours (Lord, et al., 2000), they seem to make an independent contribution to diagnostic stability (de Bildt et al., 2009; Lord et al., 2006). While adults with ASD may have a slightly different behavioural phenotype compared to children (Gotham, et al., 2007), the core difficulties persist in adulthood (Seltzer, Shattuck, Abbeduto, & Greenberg, 2004; Shattuck et al., 2007). Therefore, it is of interest to explore the utility of this promising new metric in our adult population.

4.2 METHODS

4.2.1 PARTICIPANTS

Thirty-two adult males with an ASD were recruited via local mental health organizations (mainly through the specialized Autism Team North Netherlands of Lentis, Groningen, the Netherlands), and through mailing lists for high-functioning individuals with ASD. Six individuals with ASD were recruited from a local forensic clinic (FPC Dr. S. van Mesdag, Groningen, the Netherlands). The participants were considered to be high-functioning by their clinicians and none had an IQ score

below 70. All participants were diagnosed with an ASD by a clinical psychologist or psychiatrist according to DSM-IV-TR criteria (n = 8 AD, n = 17 AS, n = 13 PDD-NOS), based on review of developmental history, current daily functioning, and observation. For this study, the ASD group will be investigated as one diagnostic entity along a continuous dimension of severity for two reasons. First, it is proposed for the near future that distinctions will no longer be made among different types of autism in clinical practice, because they have proven to be “inconsistent over time and place, and to be associated more with severity, language level, and intelligence than specific features” (www.dsm5.org). Individuals with autism and PDD-NOS have also shown qualitatively similar behavioural patterns on the ADOS with varying degrees of severity (Lord, et al., 2000). Second, investigating the subtypes would lead to overly small subgroups.

Eighteen adult males with schizophrenia and predominantly negative symptomatology, mainly outpatients, were selected by a specialized local mental health organization (Psychosencluster, GGZ Drenthe, Assen, the Netherlands). Diagnosis was confirmed by a structured clinical interview, the Dutch version of the Schedules of Clinical Assessment in Neuropsychiatry developed by the WHO (SCAN 2.1, Giel & Nienhuis, 1996). Current symptomatology was assessed by the Positive and Negative Syndrome Scale (PANNS, Kay, et al., 1987).

The psychopathy group consisted of 16 males recruited from two forensic psychiatric clinics (FPC Dr. S. van Mesdag and FPC Veldzicht). As part of the standard clinical procedure, these individuals were assessed with the Psychopathy Checklist Revised (PCL-R), an instrument widely used for the diagnosis of psychopathy (e.g. Hare, 1991). Two diagnosticians obtained consensus on this instrument after separately scoring the items using file information extended with, if necessary, a semi-structured interview.

		N	Mean	Stdev	Range
ASD	Age	38	31.82	11.24	18-66
	IQ	29	101.14	14.67	73-133
Schizophrenia	Age	18	37.00	10.73	19-61
	IQ	18	89.17	13.89	68-112
Psychopathy	Age	16	39.00	10.67	23-60
	IQ	15	92.73	16.10	63-117
Controls	Age	21	34.24	9.14	21-53
	IQ	21	97.19	16.37	73-128

Table 1: Group Characteristics. IQ scores were based on the Groninger Intelligence Test 2 (GIT 2, Luteijn & Barelids, 2004), except for four individuals with ASD who were administered the Wechsler Adult Intelligence Scale (WAIS, Wechsler, 1997) and nine individuals with ASD for whom IQ scores were not obtained (they only took part in the ADOS part of the research project). For these cases, IQ was estimated to be in the normal range based on former IQ tests and clinical impression / daily functioning. GIT 2 scores for one individual with psychopathy were deemed unreliable and discarded.

The typically developing group consisted of 21 typically developing males, who were interviewed to verify that first-degree relatives did not have an ASD or a history of psychosis. Age and IQ was matched with the participants with ASD who also took part in the neuroimaging part of the study (n = 21). There are no significant differences between the groups in terms of age and IQ. For an overview of the group characteristics see Table 1.

4.2.2 MEASURES AND PROCEDURE

Administration of the ADOS was part of the standard procedure of two large neuroimaging studies into the neural basis of empathy conducted in the Social Brain Laboratory (www.bcn-nic.nl/socialbrain.html). All participants gave written informed consent. The studies were approved by the Institutional Review Board of the University Medical Center Groningen (METc). The administration of ADOS module 4 included all standard activities and the optional daily living items to obtain relevant background information. The interviews were administered and scored by trained and certified psychologists. In total, five raters participated in the project including two certified ADOS trainers (AdB, SH). To ensure that agreement between raters remained at the high level requested by the ADOS, we discussed (fragments of) videotapes in two-monthly group meetings. The interviews were scored for consensus from videotape in changing pairs of raters, but included the examiner in the far majority of cases. In contrast to the second rater, the examiner was not blind to clinical diagnosis. The consensus scores were determined on the basis of the video-recording through a discussion in which the judgment of each rater was weighted equally. We only made an exception to this procedure when there was major disagreement (0 vs. 2) for the items B1 (Eye Contact) and B2 (Facial Expressions). Then, we gave priority to the examiner's opinion, because we anticipated that these items might be difficult to judge from videotape alone. Fortunately, due to the high quality of the video-recordings, there was major disagreement in only two out of 93 administrations for eye contact, while for facial expressions such disagreement never occurred. Therefore, it is unlikely that the examiner's previous knowledge influenced the consensus scores.

4.2.3 DESIGN AND ANALYSIS

Algorithms

In this paper, we will use the terms "original algorithm" when referring to the standard algorithm (Lord, et al., 2000) and "revised algorithm" when referring to the application of the revised algorithm based on Gotham et al. (2007). To reach a classification of AD or ASD on the original algorithm of the ADOS, an individual needs to meet thresholds for the communication domain (COM), the social interaction domain (SOC), and for the summation of these two domains (COMSOC), but not for the restricted and repetitive behaviours domain (RRB, Lord, et al., 1999). For the revised algorithm, classification is based on solely thresholding the SARRB domain, which combines social, communication, and restricted behaviour items. Since algorithm items across modules 3 and 4 are comparable and our sample size does not permit independent factor analyses in order to establish specific algorithm items, we applied the revised algorithm for module 3 to our group of high-functioning adults to calculate domain scores and a total score. In line with the explanation on the original algorithm, scores of 3 were converted to 2, and all scores other than 0-3 were treated as 0.

Interrater agreement

Interrater agreement was assessed on the original algorithm at the level of ADOS classification, domains, and items. Agreement between raters at the level of diagnostic classification (AD, ASD, nonspectrum) was calculated through Cohen's weighted kappa in addition to the percentage of agreement. Cohen's kappa takes into account the agreement that can occur by chance between two raters and is therefore more stringent than the mere calculation of the percentage of times the raters' scores lead to the same ADOS classification. Interrater agreement on the domains and the

total score was calculated by means of intraclass correlations (ICC). ICC scores represent correlations across pairs of raters and are higher the more consistent the scores across two different raters are. ICC scores, internal consistency and correlations could not be reliably calculated for the RRB domain, because variance was too limited: for four out of the five items less than five subjects scored different from zero. To assess interrater agreement for separate items, we used mean linearly weighted Cohen's kappa's in line with Lord et al. (2000). Cohen's linearly weighted kappa takes into account the agreement between two raters occurring by chance and considers the difference between a score of zero and one to be smaller than a difference between zero and two. Item B3 was ignored because its score depends on items A9, B1 and B2. In addition, only items were included for which more than five subjects scored different from zero (excluding nine items: A1, A3, A5, D1, D2, D3, D5, E1, E2).

Internal consistency

To measure the internal consistency of the original and the revised domains, we applied Cronbach's alpha. This statistic increases as the intercorrelations among test items within a domain increase.

Comparison of domain means

We used an ANOVA for each scale of both algorithms with fixed factor group, followed up by Tukey's HSD post hoc comparisons. We performed one-tailed Mann-Whitney tests to examine whether the forensic ASD group scored higher than the psychopathy group. To compare group differences at item level, we performed a MANOVA with fixed factor group on all items except the previously mentioned nine items that had limited variance and item B3. Post hoc tests were performed for those items that showed a significant group effect.

Criterion-related validity

Here, criterion-related validity refers to the degree to which the outcome on the ADOS instrument is in agreement with the clinical diagnosis of having ASD or not. We used logistic regression to measure the success of both algorithms in predicting whether a participant received a diagnosis of ASD in clinical practice. Because ADOS classification is based on COM and SOC for the original algorithm and on the combined SARRB domain for the revised algorithm, we used these domains as predictors in two separate analyses. Logistic regression provides information on the sensitivity and specificity for the fixed cut-off point used in clinical practice. Receiver Operating Characteristic (ROC) curves provide information on the sensitivity and specificity of all other possible scores. In addition, it provides an Area under the Curve statistic (AuC), which represents the overall level of agreement between criterion (i.e. clinical diagnosis of ASD) and instrument (i.e. ADOS). The higher the AuC, the higher the probability that a randomly chosen participant with ASD will have a higher score on the instrument than a randomly chosen participant without ASD.

Correlations with participant characteristics

To investigate the relationship of domain scores with participant characteristics, we calculated bivariate correlations for the patient groups between domain scores, and age, IQ, and scores on the negative scale of the PANNS (schizophrenia only).

4.3 RESULTS

4.3.1 INTERRATER AGREEMENT

Interrater agreement at the level of ADOS classification was 81.7% with Cohen's adjusted weighted kappa 0.66, which corresponds to good or substantial agreement (Landis & Koch, 1977). When merging the ADOS-classifications AD and ASD (based on the proposed criteria for DSM V) the agreement increased to 89.2% with kappa 0.73. Intraclass correlations (ICC, Table 2) show high interrater agreement on SOC and COMSOC, and good agreement on COM. Mean agreement across the items was 81.7% with mean weighted kappa 0.66. Weighted kappa's exceeded 0.60 for 14 out of the 21 items with the remainder exceeding 0.50.

N	Social interaction	Communication	Social-Communication
93	0.92 (Lord: 0.88-0.97)	0.79 (Lord: 0.74-0.90)	0.92 (Lord: 0.84-0.98)

Table 2 Intraclass Correlations for Interrater Agreement. Interrater agreement as mentioned for Lord et al. (2000) represents the range for all four modules.

4.3.2 INTERNAL CONSISTENCY

For the original algorithm, the internal consistency is high for SOC (Cronbach's $\alpha = 0.84$), but rather low for COM ($\alpha = 0.52$). This indicates that the items of that domain do not intercorrelate well in our population. Item A4 (Stereotyped Language) performed the worst and its deletion from COM increased alpha to an acceptable level ($\alpha = 0.60$). The reorganization of communication and social interaction items in the SA domain of the revised algorithm creates a consistent domain ($\alpha = 0.87$).

4.3.3 COMPARISON OF DOMAIN MEANS

Original algorithm

All three domains and the total score showed a significant difference between the groups (Table 3). Tukey post hoc comparisons show that for COM, SOC, and COMSOC, the ASD group scores significantly higher compared to the psychopathy group and the control group, but not compared to the schizophrenia group. The schizophrenia group scored significantly higher than the control group on COM, and higher than both the psychopathy and the control group on SOC and COMSOC. For RRB, the ASD group scored significantly higher than the control group, while there was a trend compared to the psychopathy group ($p = .06$). The forensic subgroup with ASD ($n = 6$) scored higher than the group with psychopathy on all domains (data not shown).

Revised algorithm

Both domains and the total score showed a significant difference between the groups (Table 3). Tukey post hoc comparisons indicated that the ASD group scored significantly higher compared to the psychopathy group and the control group on SA, and there was a trend in comparison to the schizophrenia group ($p = .06$). The schizophrenia group scored significantly higher than the control group. For RRB, the ASD group again scored significantly higher than the psychopathy and control groups, but there was no significant difference with the schizophrenia group. For the total SARRB score, the ASD group scored significantly higher than the psychopathy, the control group, and the schizophrenia group, making it the only score for which the ASD group significantly differs from the

schizophrenia group. The forensic subgroup with ASD (n = 6) scored higher than the group with psychopathy on all domains (data not shown).

	ASD (n = 38)	Schizophrenia (n = 18)	Psychopathy (n = 16)	Control (n = 21)	F(3,89) ^a	Post hoc Tests ^b
Original algorithm						
Communication domain (COM)						
Mean	2.55	1.94	1.00	0.71	8.82***	ASD > P **
SE	0.27	0.40	0.26	0.22		ASD > TD ***
Range	0-7	0-7	0-3	0-3		S > TD *
Social interaction domain (SOC)						
Mean	6.13	4.28	1.50	0.95	18.69***	ASD > P ***
SE	5.97	7.62	0.38	0.25		ASD > TD ***
Range	0-13	0-13	0-5	0-4		S > P * / TD **
Social-communication total (COMSOC)						
Mean	8.68	6.22	2.50	1.67	19.69***	ASD > P ***
SE	0.80	0.90	0.52	0.43		ASD > TD ***
Range	0-17	2-17	0-8	0-7		S > P * / TD **
Restricted and repetitive behaviours domain (RRB)						
Mean	0.37	0.33	0.00	0.00	4.07**	ASD > TD *
SE	0.11	0.11	0.00	0.00		
Range	0-2	0-1	0-0	0-0		
Revised algorithm						
Social affect domain (SA)						
Mean	7.39	4.67	1.94	1.48	14.97***	ASD > P ***
SE	0.78	0.95	0.36	0.38		ASD > TD ***
Range	0-17	0-17	0-5	0-5		S > TD *
Restricted and repetitive behaviours domain (RRB)						
Mean	0.97	0.56	0.25	0.10	7.73***	ASD > P **
SE	0.16	0.15	0.11	0.07		ASD > TD ***
Range	0-4	0-2	0-1	0-1		
SARRB total						
Mean	8.37	5.22	2.19	1.57	17.50***	ASD > S *
SE	0.84	0.95	0.40	1.81		ASD > P ***
Range	0-17	0-17	0-6	0-5		ASD > TD ***

Table 3 Summary Statistics Based on the Original and Revised Algorithms. ^a For the univariate comparisons (main effects of group), F scores and their respective significance levels are reported: * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$. ^b Using the same symbols, Tukey's HSD post hoc comparisons are reported in the outer right column to indicate what diagnostic groups are significantly different from each other. ASD refers to autism spectrum disorder, P to psychopathy, TD to typically development, and S to schizophrenia.

4.3.4 GROUP COMPARISON AT ITEM LEVEL

The multivariate test showed that there was a significant main effect of group, $F(66,210) = 1.688$, $p < .005$. Results for the univariate tests are visually presented in Figure 1.

Only four out of 22 items did not differ significantly between the groups. The majority of the remaining items showed a (almost) significant difference between the ASD group compared to the psychopathy and control groups, but not compared to the schizophrenia group. On some of these items the schizophrenia group also scored significantly higher than the psychopathy and/or control group: B2 (Facial Expressions), B6 (Empathy/ Comments on Others' Emotions), and B7 (Insight). Only three items distinguished the ASD from the schizophrenia group: A4 (Stereotyped Language), B10 (Quality of Social Response), and B12 (Overall Quality of Rapport). In addition, there was a trend for the ASD group to score higher than the schizophrenia group on item B11 (Amount of Reciprocal

Social Communication, $p = .07$). Individuals with psychopathy scored comparable to the control group.

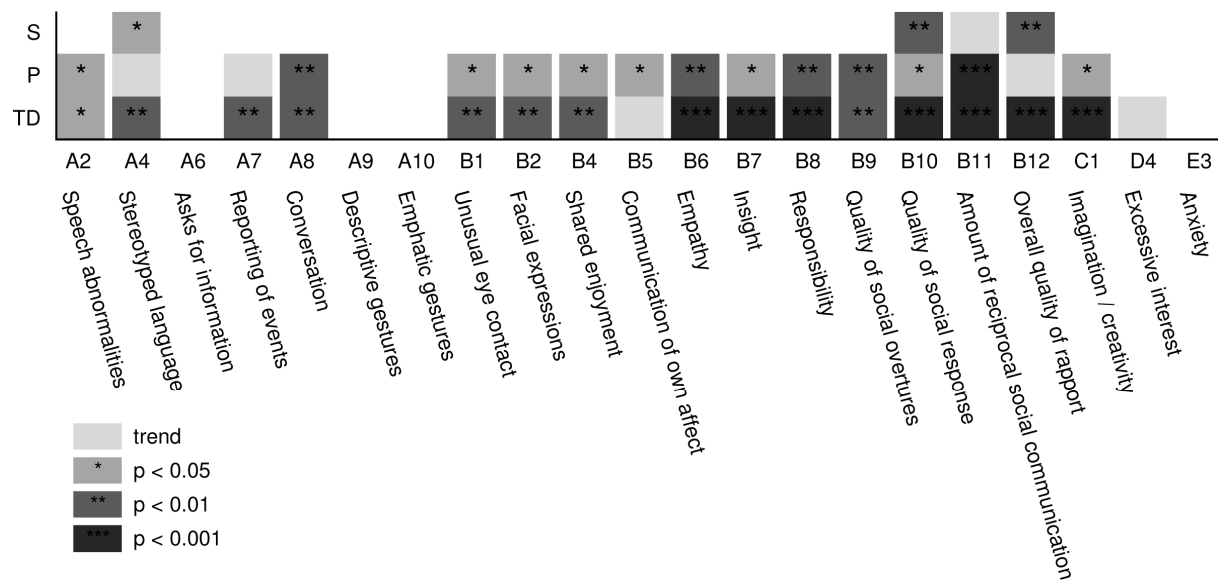


Figure 1. Between-group Comparisons at Item Level. Post hoc comparisons of the ASD group versus the other three groups at item level (S = schizophrenia, P = psychopathy, TD = typical development). Dark grey boxes filled with *** represent a statistically significant difference at $p < .001$. Middle grey boxes filled with ** represent a statistically significant difference at $p < .01$. Light grey boxes filled with * represent a statistically significant difference at $p < .05$. Unfilled light grey boxes represent a statistical trend ($p < .1$). In all these cases, the mean of the ASD group was higher compared to the respective group.

4.3.5 CRITERION-RELATED VALIDITY

The ADOS was able to correctly classify 74.2% of the cases in our sample as having ASD or not (based on the clinical diagnosis assigned). Logistic regression analysis showed that SOC ($p < .005$) but not COM ($p = .27$) made a significant contribution in predicting whether a participant in our sample had a clinical diagnosis in the autism spectrum or not (Table 4). The SARRB domain significantly contributed to prediction (Table 4, $p < .005$). The odds ratios presented in table 4 indicate that augmenting scores of one point on SOC or SARRB, increase the probability that the individual has received a clinical diagnosis of ASD by 38% and 33%, respectively.

ADOS Algorithm	Domain	Clinical classification						
		B	S.E.	Wald	df	Sig.	Odds ratio	95% C.I.
Original	Communication	0.21	0.20	1.21	1	0.271	1.23	0.85 - 1.79
	Social Interaction	0.32	0.09	11.77	1	0.001	1.38	1.15 - 1.66
Revised	SARRB	-0.29	0.07	18.52	1	0.000	1.33	1.17 - 1.52

Table 4. Logistic Regression Analyses for Criterion-related Validity. Odds ratios express how much the probability that an individual has received a clinical diagnosis of ASD increases with augmenting scores on the ADOS.

ROC curves for the original and revised algorithms resulted in AuC values of .812 and .796, respectively (1 = perfect agreement). This indicates that in general the ADOS scores quite adequately predicted whether someone had a clinical diagnosis of ASD or not. Application of the standard cut-off for autism spectrum on the original algorithm (i.e. 7) gives only moderate sensitivity (0.61) but good specificity (0.82) in our sample. Lowering the threshold to 6 increases the sensitivity (0.68) and keeps the specificity at the same level (0.82). Lowering the threshold to 5

increases the sensitivity further (0.79), but it decreases the specificity (0.73). For the revised algorithm, a cut-off of 5 seems optimal in the current population with adequate sensitivity (0.71) and specificity (0.82).

4.3.6 CORRELATIONS WITH PARTICIPANT CHARACTERISTICS

There were no significant correlations between the domain scores, and IQ or age for the groups with ASD, schizophrenia, nor psychopathy (data not shown). In the group with schizophrenia, the presence of negative symptoms as measured by the PANNS correlated positively with SOC ($r = 0.59$, $p < .05$) but not COM ($r = 0.12$). The PANNS also correlated positively with SA ($r = 0.66$, $p < .005$). Thus, the more negative symptomatology an individual with schizophrenia had, the higher his scores on the ADOS. PANNS scores correlated in particular with items that are similar to negative symptoms, such as (flat) facial expressions (B2, $r = 0.59$, $p < .05$), (lack of) shared enjoyment (B4, $r = 0.81$, $p < .01$), (lack of) asking the examiner for information (A6, $r = 0.66$, $p < .01$), and (difficulty with) communication of own emotions (B5, $r = 0.53$, $p < .05$).

4.4 DISCUSSION

Systematic instruments are needed that can facilitate the complicated diagnostic process concerning ASD in adults. The current study is the first that examined the psychometric properties of ADOS module 4 in an independent sample of high-functioning adult males with an established clinical ASD diagnosis compared to meaningful and relatively homogeneous clinical and non-clinical groups. Our findings show that ADOS module 4 is a reliable instrument. At all levels (i.e. classification, domains and items) raters obtained substantial agreement. In addition, ADOS module 4 has good general criterion-related validity. It is able to correctly classify the majority of individuals and higher scores on the ADOS predict a higher probability of having a clinical ASD diagnosis. The high Areas under the Curve are further indications that ADOS scores can predict whether an individual actually has an ASD. Furthermore, group comparisons between the ASD and other groups show that the ADOS is valuable in differentiating between ASD, and psychopathy and typical development. The distinction between psychopathy and ASD even holds when only taking into account forensic individuals with ASD (although the group size was rather small to perform such an analysis). The finding that ASD and psychopathy are so well-discriminated by means of ADOS scores is promising for forensic psychiatric settings.

Another finding is the similarity between ASD and schizophrenia with respect to ADOS scores. Clearly, individuals with schizophrenia and marked negative symptoms show behaviour that is very similar to ASD (Frith, 2003). Some patients with schizophrenia even have autistic-like symptoms that covary with negative symptoms (Sheitman, et al., 2004). In line with these data, we show that the degree of negative symptomatology correlates significantly with ADOS scores, in particular with items resembling negative symptoms, such as (lack of) directed facial expressions and shared enjoyment. This resemblance makes it difficult for an observational instrument such as the ADOS to differentiate these groups on that behaviour (see Reaven, Hepburn, & Ross, 2008 for a similar finding in children with childhood-onset schizophrenia). The findings underscore previous recommendations of using a comprehensive assessment that incorporates information on daily functioning and early development with direct observation to reach a clinical diagnosis (Lord, et al., 1999). Nevertheless, four items did show a difference between these groups: individuals with ASD

use more stereotyped language, less reciprocal social communication, and display qualitatively poorer social responses and overall rapport. This suggests that core social items and stereotyped language discriminate individuals with ASD from those with schizophrenia.

Although findings are preliminary, the revised SARRB domain, which combines social, communication and repetitive behaviour items, seems promising in this and other respects. It not only discriminates ASD from all other groups including schizophrenia, but also has high internal consistency, and does well in identifying ASDs: a higher score on this domain predicts a higher probability of a clinical ASD diagnosis with 33% per additional point. Another positive indication for the revised algorithm is the confirmation that stereotyped language fits better with the RRB factor than with the original communication domain. Notwithstanding the caution of interpreting ASDs in adults in exactly the same way as in children, the revised algorithm as developed for modules 1-3 seems promising for module 4 as well. More research is needed in a larger sample containing individuals with more severe autistic symptoms and lower levels of daily functioning to further investigate the revised algorithm.

A marked finding is the limited role of the original communication domain in the identification of ASDs in this sample. Despite group differences between ASD and psychopathy/typical development, the communication domain does not predict a clinical ASD diagnosis. Combined with its low internal consistency, the communication domain as such does not seem to add to the validity of ADOS module 4 in the current sample. However, when communication items are incorporated in the revised algorithm, a consistent scale (SA) emerges that is valuable in the diagnostic procedure for ASD. Similarly, although restricted and repetitive behaviours were rare in our ASD sample, their contribution to SARRB supports the distinction of ASD from schizophrenia. The relatively short duration of the ADOS interview naturally could have played a role in the paucity of RRBs (Lord, et al., 1999). However, combining these two findings also fits the general clinical picture: in adolescents and adults with ASD there is a greater prevalence of impairment in non-verbal communication and social reciprocity than in verbal communication or repetitive behaviours and stereotyped interests (Shattuck, et al., 2007). In fact, repetitive behaviours decline most strongly with age (Seltzer et al., 2003). Apart from ageing, individuals in our sample might have had relatively more intact verbal skills from the outset as they were all considered to be high-functioning. Stereotyped language, however, does differentiate the ASD group from all other groups in our sample. This may be typical of our high-functioning group, because idiosyncratic language and language complexity are positively associated (Volden & Lord, 1991). Cultural differences in the use of gestures might also have played a role. Typically developing adults in our sample, for instance, used few emotional and only occasional descriptive gestures themselves.

The sensitivity in our sample was rather low (0.61), which means that not every individual with a clinical diagnosis of ASD obtained a concurrent classification on the ADOS. It is probable that the characteristics of our group played a role in this. Our sample consisted of high-functioning individuals that signed up for an extensive research project. They are probably situated at the milder end of the spectrum and some might have been able to (partly) compensate some behaviour due to their high intelligence. Resulting relatively low scores make it difficult for the ADOS to identify these individuals. Our findings resemble the outcomes in ADOS modules 1-3, in which lower

sensitivity (SE) was found for distinctions involving children with milder ASDs (module 3 by de Bildt, et al., 2009, SE = 0.64; ; Gotham et al., 2008, SE = 0.49; Gotham, et al., 2007, SE = 0.68; Lord, et al., 2000, SE = 0.80, versus later studies:). The high specificity (0.82), on the other hand, means that a positive ASD classification on the ADOS is a very strong indication for a clinician to consider diagnosing ASD. Sensitivity and specificity are tightly linked and the aim of the assessment determines which one is most important. High specificity is essential when one needs to be certain that the individuals selected actually have an ASD, for instance in autism research. High specificity can, however, lead to underinclusiveness. When the aim of the assessment is to screen for ASD, high sensitivity is crucial in order not to miss any potential case. For this purpose, lower thresholds could be considered at the expense of specificity. To prevent overinclusiveness, developmental history and current daily functioning should then be carefully reviewed. As this study included only a specific ASD group and specific control groups, further research is needed to establish the optimal cut-off points on the ADOS module 4.

This study has a number of limitations that should be taken into account when interpreting the results. First, compared to studies on the psychometric properties of modules 1-3 (de Bildt, et al., 2009; Gotham, et al., 2008; Gotham, et al., 2007; Oosterling et al., 2010), our study has a small sample size ($n = 93$). However, it is the first study examining module 4 in an adult population with ASD compared to specific and meaningful groups. Second, we are focused on high-functioning adult males with ASD, which means results cannot be generalized to the entire ASD population. Future studies on module 4 should comprise a larger sample, including individuals with lower levels of daily functioning, since the high-functioning character of our sample may have influenced the results. On the other hand, exactly these individuals are not always recognized during childhood. Therefore, increasing knowledge on module 4 seems most important for individuals showing milder autistic symptoms. In this light, it will also be important to include a group of high-functioning adult females, who run the risk of being undiagnosed because they might be especially good at compensating their behaviour (Attwood, 1999; In 't Velt-Simon Thomas & Mol, 2008). Third, no standardized measures were available for the clinical diagnosis of ASD, which characterizes current practice in adult psychiatry. However, the normal clinical procedure included review of developmental history and current functioning and observation. In addition, most participants with ASD were recruited through a specialized centre. Fourth, we did use standardized measures to diagnose schizophrenia, but not to review early developmental history in this group. Therefore, we cannot eliminate the possibility that ASD was present before the onset of schizophrenia. However, this possibility is minimized by the fact that these individuals were extensively tested in a specialized psychosis centre and selected for this study by experienced clinicians. The control groups in the current sample were comparatively homogeneous and aimed to challenge the ADOS by comparing ASDs with other psychiatric groups with social deficits. For the investigation of ADOS' value in differential diagnostics, examining different subtypes of schizophrenia and other diagnostic groups will be of great relevance as well (e.g. anxiety disorder, depression, ADHD, and OCD).

In summary, the ADOS module 4 is a reliable instrument that has good predictive value for ASD. It can adequately discriminate ASD from psychopathy and typical development in an adult population. With respect to schizophrenia, discrimination is more difficult due to behavioural overlap. These groups are, however, different on some core items. Although ADOS module 4 fails to classify ASD in

a significant proportion of our higher functioning and more mildly affected ASD group, its ASD classification is a strong lead for a clinician to at least consider an ASD diagnosis. Explorative analyses of the revised algorithm indicate that a revision -in line with modules 1-3 and developments in criteria for ASD- could be beneficial for discriminating ASD from schizophrenia.

Acknowledgements

Thanks to all the participants for their time and effort. For assistance in recruitment and/or IQ testing: J. Ferwerda, M. Meijer, and V. Baas. Audiovisual service of GGZ Drenthe for video-recordings. E. Haitel for manual support. The work was supported by a Nederlandse Organisatie voor Wetenschappelijk Onderzoek (NWO) VIDI grant and a Marie Curie Excellence Grant of the European Commission to CK.

5

THE ROLE OF VICARIOUS BRAIN RESPONSES IN PSYCHOPATHY

ABSTRACT

Psychopathy is a personality disorder with serious deficits in the interpersonal and affective domain combined with an antisocial lifestyle. One of the core symptoms of individuals with psychopathy is a profound lack of emotional empathy (Blair, 2005) and this has been related to their ability to use or hurt other people without significant feelings of remorse or sorrow. One explanatory model of the development of psychopathy relates their early insensitivity to the sadness and fear of others to their inadequate moral development (Blair, 2007). When children perceive distress cues, such as fear and sadness in the context of moral transgressions, they learn to combine the negative experience of these distress cues with the moral transgression. These negative associations discourage the child from future transgressions. The early insensitivity to the sadness and fear of others impedes this process in children with psychopathic tendencies. However, this model does not explain why the sadness and fear of others should be distressing for normal children in the first place. A framework that has received much attention over the past years within the neuroscientific literature suggests that understanding other people relies (partly) on vicariously triggering states in the self similar to those in others (e.g. Bastiaansen, et al., 2009; Gallese, et al., 2004; Iacoboni & Dapretto, 2006; Keysers, et al., 2010; Pineda, 2008; Preston & de Waal, 2003; Rizzolatti & Craighero, 2004). In this review we examine whether this latter mechanism might be functioning abnormally in subjects with psychopathy. We do this by first providing a more detailed description of the deficits attributed to psychopathy and its relation to various types of aggression and empathy. We then briefly discuss a current neurobiological model for empathic responses and expand this model in order to incorporate data from the psychopathy literature and propose a mechanism that might integrate reduced vicarious responding into existing models of psychopathy.

5.1 PSYCHOPATHY AS A DISORDER OF EMPATHY

Psychopathy is not listed in the current edition of the Diagnostic and Statistical Manual for Mental Disorders (American Psychiatric Association, 2000), but does show considerable diagnostic overlap with one of its categories: antisocial personality disorder (APD). Both disorders are characterized by poor behavioural control and a disregard for the rights of other people but more emphasis is placed on deficits in the emotional and interpersonal domain when assessing for psychopathy (Coid, et al., 2009; Hare & Neumann, 2009). However, although individuals with psychopathy often fulfil the criteria for APD, the reverse is not true (Hare & Neumann, 2009). Several methods exist for assessing psychopathic traits; the one most commonly used for forensic populations is the Psychopathy Checklist - Revised (PCL-R, Hare, 2003; Hare, et al., 2001). Because of the focus on the criminal lifestyle, the PCL-R is not meant for research in the healthy population. In addition, a substantial amount of collateral information is needed in order to complete the instrument, which is usually not available for healthy volunteers. The Psychopathy Personality Inventory (PPI) is an extensive self-report questionnaire which can be used for research in healthy control groups (Lilienfeld & Andrews, 1996).

One of the core problems of psychopathy is a profound lack of empathy (Blair, 2005). It is a criterion in both the PCL-R and the PPI. The description of this item in the PCL-R manual gives the impression of someone who understands, but does not feel or care. It describes a person who has the ability to put himself in the shoes of others in a cognitive sense, but shows no affective response to this. The empathy deficit is captured in the PPI through the subscale Coldheartedness, which measures a propensity toward callousness, guiltlessness and unsentimentality (Lilienfeld & Andrews, 1996). In both instruments the lack of empathy seems therefore to apply mostly to what has often been called an emotional component of empathy.

Apart from a deficit in affective empathy, psychopathy is also characterized by an elevated risk for both instrumental and reactive aggression (Blair, 2006; Cornell, et al., 1996). Reactive or emotional aggression is triggered in response to a perceived threat or provocation. Instrumental aggression, on the other hand, describes the use of violence with the intent to achieve a goal (Cornell, et al., 1996) (see Table 1 for a description). Increased risk for violence was also found in community samples scoring high on psychopathic traits (Coid, et al., 2009; Neumann & Hare, 2008).

Aggression type	Classification	Characteristics
Instrumental	Goal-directed	Almost always a plan and a goal present before offence Victim more often stranger Premeditated, time for reflection Can turn into reactive aggression
Reactive	In response to provocation or threat	Victim is often close friend or relative More often fatal injury Anger during offence Presence of provocation No plan Frustration based, explosion of aggression

Table 1: Types of aggression from (Cornell, et al., 1996).

A link between empathy and aggression has been described in earlier studies (e.g. Feshbach & Feshbach, 1982; Miller & Eisenberg, 1988). Miller and Eisenberg claimed for example that

'individuals who vicariously experience the negative reactions of others that occur because of their own aggressive behaviour may be less inclined to continue their aggression or to aggress in future interactions' (Miller & Eisenberg, 1988, page 324). Several reviews have confirmed this negative, albeit small, relationship between occurrences of aggression and measures of empathy in children (but see Lovett & Sheffield, 2007; Miller & Eisenberg, 1988), adolescents (Jolliffe & Farrington, 2004; Lovett & Sheffield, 2007) and adults (Jolliffe & Farrington, 2004).

The increased level of instrumental aggression has been associated with a lack of moral socialization (Blair, 2007). An interesting model in that respect is the Violence Inhibition Mechanism (VIM, Blair, 1995), in which the importance of empathy for moral socialization is stressed. The VIM represents an emotional learning system, thought to establish the basics of morality, utilizing the fact that humans usually find distress in others aversive. Essentially, the model states that observers become negatively aroused when someone else in the vicinity displays distressing emotions, like fear or sadness. If actions on the part of the observer were responsible for the distress of the other, the two (negative affect and action leading to the distress) are paired. Eventually this pairing becomes internalized so that even the imagination of these acts activates the VIM and decrease the likelihood of behaviour that triggers distress in others. Behaviours that do cross this line are now recognized as moral transgressions. The VIM is activated more strongly when distress cues are more intense, but may be overruled by other cognitive processes. The model served as an explanatory model for the development of guilt, feelings of sympathy, empathy and remorse as well as the ability to inhibit violent actions and the development of the distinction between moral and conventional transgressions (Blair, 1995). The model has since then been expanded into the Integrated Emotion Systems (IES, Blair, 2006; Blair, Mitchell, & Blair, 2005) to incorporate data associated with the response set modulation (Patterson & Newman, 1993) and fear hypotheses (e.g. Lykken, 1995; Patrick, 1994) as well as data generated on the interaction between temperament and socialization by Kochanska (1993; 1997). With relation to psychopathy, the core hypothesis has however not changed: it is the insensitivity of psychopathic individuals to the distress cues of other people that makes them fail to associate negative affect to violence, and hence prevents them from developing normal morality and inhibiting violence appropriately.

An implication of this model is that individuals that would be unable to properly perceive the emotions of others would be unable to trigger negative affect in response to the negative emotions of others, and may thus fail to develop morality and inhibit violence. In accord with that logic, subjects with psychopathy have been found to perceive emotions of others less accurately. Psychopathic individuals are less able to recognize emotions from spoken words (Bagley, Abramowitz, & Kosson, 2009; Blair et al., 2002) and recognize emotions from facial expressions (Blair et al., 2004; Hastings, Tangney, & Stuewig, 2008; Kosson, Suchy, Mayer, & Libby, 2002), although the emotion that is most affected seems to differ from study to study (fear in Blair, et al., 2004; disgust in Kosson, et al., 2002). It is at present still not completely clear whether psychopathy is related to a deficit for specific emotions (Blair, 2006), or whether the emotion deficit is of a more general nature (Herpertz et al., 2001). In addition, problems with facial affect recognition are not limited to subjects diagnosed with psychopathy. For example, Dolan and Fullam (Mairead Dolan & Fullam, 2006) also found subjects diagnosed with antisocial personality disorder (APD) to be impaired in recognizing facial expressions, most notably sadness. Moreover, a recent meta-analysis

examining facial affect recognition in antisocial populations also reported deficits most strongly related to fear and sadness, this was however not directly correlated with measures of psychopathy.

Other research indicates that psychopathic individuals are not only less accurate in emotion recognition, but also experience less affect in response to the negative emotions of others. Male adults with psychopathy show diminished autonomic responses to slides depicting distress cues (Blair, et al., 1997). Aniskiewitz and colleagues showed a reduced autonomic response in psychopathic subjects when they observed others receiving electrical shocks (1979). In addition, the startle reflex of psychopathic individuals is less potentiated when they watch pictures containing negative or thrilling content (Levenston, et al., 2000; Patrick, et al., 1993).

In summary: Diagnostic definitions of psychopathy (PCL-R and the PPI) include a disorder of empathy and individuals satisfying these definitions display increased levels of reactive and instrumental aggression. Blair (1995; 2006) relates inadequate morality and violence control to an early deficit in responding to the distress of others. As shown above, there is indeed evidence that psychopathic individuals are less accurate at classifying the emotions of others and respond less to these emotions, although the problems are not always limited to distress emotions. An important question is not only *how* these problems lead to inadequate socialization, but *why* individuals with psychopathy respond less to emotions of others. In other words, why are distress cues not distressing for them?

5.2 A MODEL OF VICARIOUS RESPONSES

A framework that has received much attention over the past years within the neuroscientific literature states that understanding others relies (partly) on triggering states in the self similar to those in others (e.g. Bastiaansen, et al., 2009; Gallese, et al., 2004; Iacoboni & Dapretto, 2006; Keysers, et al., 2010; Pineda, 2008; Preston & de Waal, 2003; Rizzolatti & Craighero, 2004). This is not a new idea, as a similar mechanism was proposed already over a hundred years ago by Theodore Lipps (for a nice overview see the work of Preston and de Waal (2003)) and this mechanism has been associated with the development of morality as early as the seventeen-hundreds (Chapter I, Section I, Paragraph 2, Adam Smith, 1759). However, this theoretical framework received additional impetus from the discovery of mirror neurons, almost two decades ago (di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992). These neurons were found in the macaque monkey in frontal area F5 and respond not only when a monkey performed goal-directed actions but also when the monkey saw or heard goal-directed actions (di Pellegrino, et al., 1992; Gallese, Fadiga, Fogassi, & Rizzolatti, 1996; Kohler et al., 2002). The investigators suggested that this system enriches our perception of the actions of others by providing the observer with an embodied feeling of intentionality, conveyed by the resonance of its own goal directed motor programs (Gallese, et al., 1996; Keysers & Gazzola, 2006). Obviously, it is hard to perform similar single cell recording studies in humans (but not impossible, see Mukamel, Ekstrom, Kaplan, Iacoboni, & Fried, 2010) and the research in this area continued using different techniques, mostly functional Magnetic Resonance Imaging (fMRI). This research has made it plausible that a similar mechanism exists in humans for action recognition in premotor as well as parietal regions, as several studies have now demonstrated the involvement of these regions not only during action execution, but also when seeing (Dinstein, Hasson, Rubin, & Heeger, 2007; Filimon, Nelson, Hagler, & Sereno, 2007; Gazzola & Keysers, 2009;

Grèzes, Armony, Rowe, & Passingham, 2003; Iacoboni et al., 1999; Ricciardi et al., 2009; Turella, Erb, Grodd, & Castiello, 2009) or hearing (Gazzola, et al., 2006; Ricciardi, et al., 2009) others performing actions. Most recently, single cell recordings in humans have demonstrated the existence of mirror neurons in at least some brain regions (Mukamel, et al., 2010).

From here researchers started to examine whether this phenomenon also includes the processing of emotions of others. The first evidence came from a seminal study conducted by Wicker and collaborators (2003). In this study, subjects were first asked to observe short movie clips of pleased, disgusted or neutral looking actors smelling the content of a cup. The second part of the experiment required the subjects to smell pleasant, disgusting or neutral odours. The researchers demonstrated that smelling a disgusting odour activates a part of the anterior Insula (aIns) which was also recruited while subjects observed an actor smell a disgusting odour. The recruitment of the aIns during both observation and experience was later confirmed in a study requiring subjects to taste unpleasant liquids and observe others tasting unpleasant liquids (Jabbi, et al., 2007) and also while reading disgusting vignettes (Jabbi, Bastiaansen, & Keysers, 2008). Later studies have demonstrated that a similar mechanism exists for the observation of pain (Costantini, Galati, Romani, & Aglioti, 2008; Jackson, Meltzoff, & Decety, 2005; Lamm, Nausbaum, Meltzoff, & Decety, 2007; Morrison, Lloyd, Di Pellegrino, & Roberts, 2004; Singer, et al., 2004). Results from studies like these led Gallese, Keysers and Rizzolatti (2004) and later Bastiaansen and colleagues (2009) to conclude that a sharing mechanism not only exists for actions but also for the perception of emotions, which relies on regions implicated in emotional processing, but also includes motor and somatosensory components.

The role of the somatosensory cortex in sharing states of others was first investigated by Keysers and colleagues (2004), who observed that part of the secondary somatosensory cortex was activated not only while subjects observed movies of someone touch the leg of another, but also while subjects were touched on the leg in a similar way. The involvement of the somatosensory cortex during the observation of other people's tactile experiences has subsequently been demonstrated by others (Blakemore, Bristow, Bird, Frith, & Ward, 2005a; Ebisch et al., 2008). Later, it became evident that viewing the actions of others and executing similar actions both activate the primary somatosensory cortex for most subjects at the individual level (Gazzola & Keysers, 2009). Because the primary somatosensory cortex is activated by the tactile and proprioceptive sensations, while performing an action, this has led to the idea that viewing the actions of others not only triggers vicarious motor activations in premotor and posterior parietal regions, but also vicarious tactile/proprioceptive activations in somatosensory cortices (Keysers, Kaas, Gazzola, 2010). Jointly, these studies led investigators to postulate a role for somatosensation in vicarious social perception (Keysers, et al., 2010; Pineda, 2008).

The commonality of all these studies seems to be a mechanism by which neural representations involved in executing the observer's own actions or in feeling the observer's emotions and sensations are re-activated when observing, listening or imagining someone else performing these actions (or experiencing these sensations and emotions). This sharing mechanism or vicarious activation appears to provide observers with an embodied feeling (i.e. depending on cortical representation of the body in somatosensory, motor or interoceptive cortices) of the experiences of

others. Indeed, in typical individuals, inter-individual differences in self-report measures of trait empathy correlate with the strength of these vicarious activations (Gazzola, et al., 2006; Jabbi, et al., 2007; Singer, et al., 2004). According to de Vignemont and Singer (de Vignemont & Singer, 2006), empathy occurs when the imagination or perception of the affective state of another triggers an affective state in the self which resembles the state of the other, without confusion about the source. This definition dovetails with the above reviewed neuroscientific observation that observing emotions triggers vicarious neural activations in brain regions normally associated with feeling similar emotions (Bastiaansen, et al., 2009). In contrast to the affective focus of de Vignemont and Singer, the studies reviewed above indicate that observers also recruit their own somatosensory and motor cortices when witnessing what others do and feel (Caspers, et al., 2010; Keysers & Gazzola, 2009; Keysers, et al., 2010; Pineda, 2008). We will therefore extend this definition of de Vignemont and Singer to include sensations and actions, leading to a definition of embodied empathy that is larger than the concept of affective empathy. Furthermore, it should be noted that although the neuroscience data fits the first part of the definition (sharing), it does not shed light on whether there is confusion about the source. Because it is difficult to address this question of self-other distinction using neuroscience, we will further simplify our working definition to: ***embodied empathy occurs when the imagination or perception of the affective state, sensation or action of another triggers a representation of this affective state, sensation or action in the self which resembles that of the other.*** We will refer to these spontaneous neural responses as vicarious responses⁴ and the brain circuits that are re-activated as shared circuits (as they are shared between the first and second person perspective), and consider them the neural basis of embodied empathy.

A recent review provided a detailed analysis of the available data on shared circuits in humans (Keysers, et al., 2010), with a special focus on regions with somatosensory properties. Figure 1 is adapted from Figure 1c in this review. Rostral anterior cingulate cortex (ACC), parts of the primary somatosensory cortex (mainly Brodmann areas 1 and 2), secondary somatosensory cortex (SII), the anterior insula (alns), the premotor cortex (PM) and parts of the supramarginal gyrus (PF and PFG) and adjacent ventral intraparietal cortex (VIP) all display vicarious properties (Keysers, et al., 2010) and are given a red colour in Figure 1. An addition to the original model is the supplementary motor area (SMA), which has also been reported to activate under both observation and execution conditions (Caspers, et al., 2010; Gazzola & Keysers, 2009; Mukamel, et al., 2010). Another area added to the model is the primary motor cortex, because of its importance in the implementation of behavioural responses (as are PM and SMA). To underline the importance of these areas in programming of motor responses, these regions have been given thick striped borders around the ovals. The superior temporal sulcus (STS), extended into the posterior middle temporal gyrus has also been reported in studies on vicarious responses (Caspers, et al., 2010; Gazzola & Keysers, 2009). This region contains multisensory neurons and seems to provide important input into the vicarious system (Keysers & Perrett, 2004; Nelissen et al., 2011). However, neurons in this region in monkeys have not yet been found to augment their firing during blind action execution, suggesting

⁴ 'experienced in the imagination through the feelings or actions of another person' (<http://oxforddictionaries.com/>)

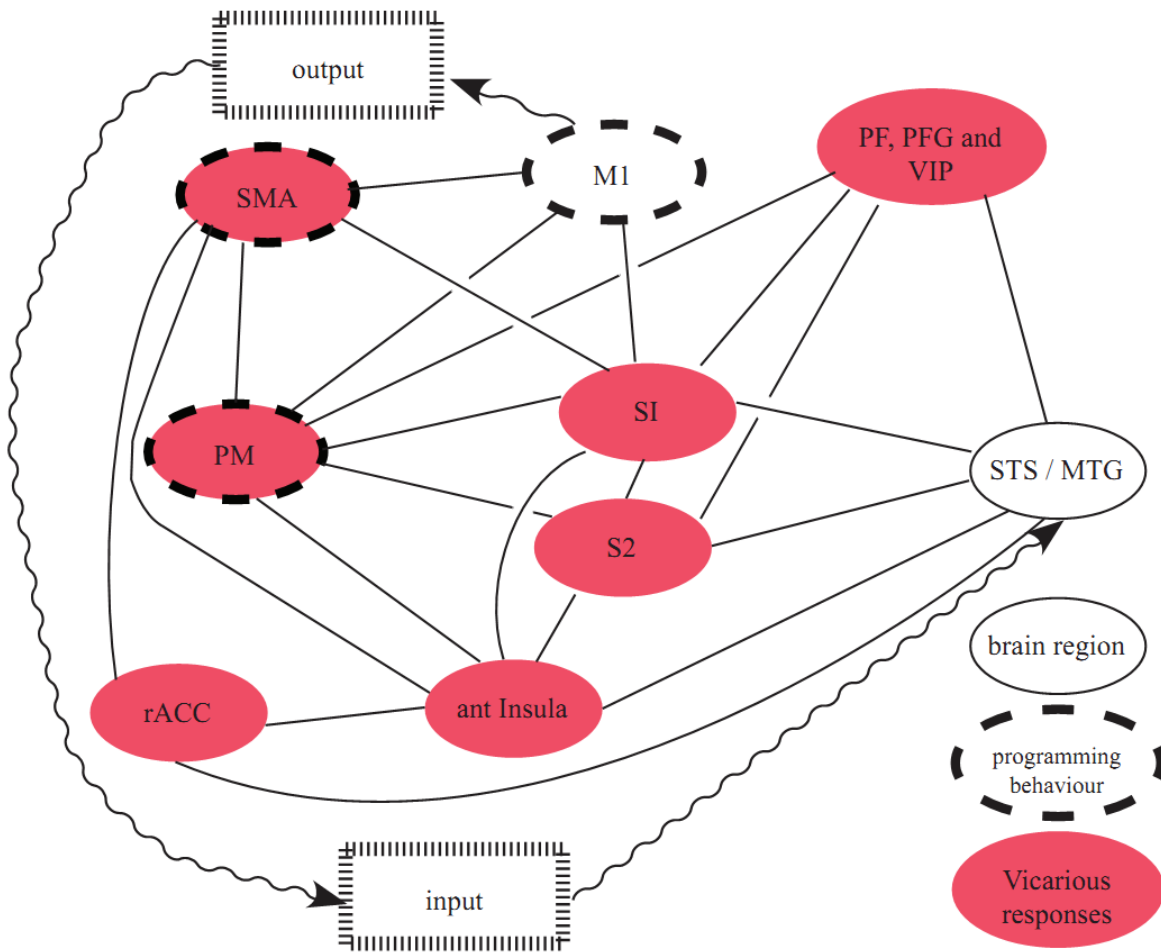


Figure 1: Schematic overview of brain regions involved in vicarious responses. Lines represent reciprocal connections unless specified by an arrow. For the description, see text.

that STS activation during action execution in human fMRI studies might not reflect mirror neurons (Keysers & Perrett, 2004). Connections between the regions in the present model are taken from the original model (Keysers, et al., 2010) where possible. The next section will describe the connections that were not specified in the previous model.

The following represents a combination of primate and human data. The anterior part of the insula appears to be reciprocally connected with S2 (Augustine, 1996), but only receives input from SI (Augustine, 1996). This is in agreement with data from Cerliani and collaborators who report connections between SI and the insula, but most strongly to its posterior parts (Cerliani, et al., 2011). SMA also receives input from the alns (Augustine, 1996). In addition, alns is reciprocally connected with PM and the ACC (Augustine, 1996). Cerliani and colleagues (Cerliani, et al., 2011) also observed connections between alns and the vPM and adjacent inferior frontal gyrus (IFG). Previous studies have also revealed connections between the SMA and M1 (Luppino, Matelli, Camarda, & Rizzolatti, 1993; Picard & Strick, 1996), SI (Luppino & Rizzolatti, 2000) and PM (Luppino, et al., 1993). S2 is also connected with PM (Luppino & Rizzolatti, 2000).

In summary, the framework for shared circuits has been linked to embodied empathy and includes regions that are related to action performance, somatosensory information processing and emotional responses. Because in healthy individual, vicarious activations in shared circuits have been linked to embodied empathy, and psychopathy has been associated with reduced affective empathy, we will now examine whether there are indications within the neuroimaging literature that psychopathy is associated with abnormal vicarious activations in shared circuits.

5.3 VICARIOUS RESPONSES IN PSYCHOPATHY

In general the neuroscientific literature on psychopathy is still relatively small. Although the estimated point prevalence of psychopathy (0.006, Coid, et al., 2009; 0.012 Neumann & Hare, 2008) compared to for example autism (0.0013, Fombonne, 2005) or schizophrenia (0.0046, Bhugra, 2005), only a relatively small number of studies have used neuroimaging to identify structural (Table 2) or functional (Table 3) abnormalities in participants with psychopathy. The most robust evidence for abnormalities in shared circuits stems from structural studies. This is because structural scanning does not depend on a particular task, and results from different labs can therefore be more easily integrated. Unfortunately, many investigations focus on a priori selected brain regions, and can therefore not be integrated in a meta-analysis. Only six papers are published so far that report whole-brain analyses (see Table 2, grey coloured rows), too little for an ALE-meta-analysis (see also Chapter 3, this volume). Except for Müller and colleagues (2008), the five remaining manuscripts report differences in regions known to exhibit vicarious responses (de Oliveira-Souza, et al., 2008; Meffert, Bastiaansen, & Keysers; Schiffer, et al., 2011; Tiihonen, et al., 2008; Yang, et al., 2009a), as indicated in Figure 1. De Oliveira-Souza and colleagues (2008) compared a community sample of 15 subjects (8 females) with chronic and recurrent misbehaviours against a control group and observed structural deficits in bilateral supramarginal and angular gyrus and bilateral insula. Another study showed structural brain deficits in SI and the right insula (Tiihonen, et al., 2008). Yang et al. (2009a) observed cortical thinning in several regions including the right lateral prefrontal cortex and the temporal cortex. Although specific coordinates were not provided in this paper, these abnormalities seem to incorporate right ventral premotor regions, extending into the temporal cortex. The authors also observed that cortical thinning in these regions was more pronounced in subjects scoring high on the affective domain captured by the PCL-R. Schiffer and colleagues (2010) used the Psychopathy Checklist Screening Version (PCL:SV), but

	Analysis	Subjects	Results
(Raine, Lencz, Bihrlé, LaCasse, & Colletti, 2000)	Volumetric analysis of PFC (volume of grey and white separately)	34 control subjects; 26 subjects with SUD; 21 APD subjects. Mean PCL-R = 14.2(5.5); 20.1 (6.0); 28.5 (5.7). From temporary employment agencies.	11% reduction of PFC grey matter in APD group compared to control group and 14% compared to the group with SUD.
(Laakso et al., 2001)	Volumetric analysis of hippocampus after manual tracing	34 control subjects; 18 PP. Mean PCL-R = n/a; 31.2 (5.4). PP where derived from pre-trial forensic psychiatric evaluation, charged with violent offence. Not all PP scored above the cut-off. Comorbid with alcoholism, Cloniger Type 2.	Factor 1 of the PCL-R correlated negatively with mid hippocampal volume on the right, within the offender group.
(Laakso et al., 2002)	Volumetric analysis of PFC subregions	33 control subjects; 24 PP. Mean PCL-R = n/a; 27.6 (9.0). PP where derived from pre-trial forensic psychiatric evaluation, charged with violent	No significant correlations between prefrontal grey of white matter volumes and PCL-R.

	Analysis	Subjects	Results
		offence. Not all PP scored above a reasonable cut-off. Comorbid with alcoholism, Cloniger Type 2.	
(Raine et al., 2003)	Volumetric analysis of corpus callosum	25 control subjects; 15 PP. Mean PCL-R = 10.8(3.0); 30.3(5.3). From temporary employment agencies.	Volume and length increased in PP group, thickness decreased in PP group.
(Raine et al., 2004)	Volumetric analysis of bilateral hippocampus	16 unsuccessful PP, 12 successful PP, 23 control subjects. From unemployment agencies. Mean PCL-R = 31.5(23-40); 27.7(23-31); 10.9(2-14).	Greater asymmetry in anterior portion of the hippocampus in unsuccessful PP group
(Yang et al., 2005b)	Volumetric analysis of PFC (volume of grey and white separately)	16 unsuccessful PP, 13 successful PP, 23 control subjects. From unemployment agencies. Mean PCL-R = 30.1(5.3); 26.3(2.6); 10.9(2.8).	Reduction of grey matter volume in PFC only in unsuccessful group. PFC grey matter volume correlates negatively with PCL-R score.
(de Oliveira-Souza, et al., 2008)	Whole-brain voxel-based comparison of T1 anatomical scans	15 control subjects; 15 PP. PCL:SV = 0.4(1); 17.8(3.8). Community sample with chronic and recurrent misbehaviours, but no prosecution. Both groups 7 females.	The whole-brain analysis shows some evidence for the involvement of shared circuits (supramarginal gyrus, and insula).
(Müller, et al., 2008)	Whole-brain voxel-based comparison of T1 anatomical scans	17 PP; 17 control subjects. Mean PCL-R = 33.3(4.06); n/a. Forensic inpatients.	Decreased grey matter volume in the right temporal pole.
(Tiihonen, et al., 2008)	Whole-brain voxel-based comparison of T1 anatomical scans	12 PP, 14 APD, 25 control subjects. PP and APD from university forensic psychiatric hospital for pre-trial assessment. Mean PCL-R = 34.6(3.1); 25.9(2.8); n/a	Whole-brain comparison revealed differences in (amongst others) bilateral SI and right insula.
(Craig et al., 2009)	Diffusion tensor imaging using fractional anisotropy.	9 control subjects; 9 PP. Mean PCL-R = n/a; 28.4(25-34).	Fractional anisotropy of the right uncinate fasciculus lower in the PP group. This correlates negatively with F2.
(Yang, et al., 2009a)	Whole-brain analysis of cortical thinning	27 PP; 32 control subjects. Community sample. Further information not available	PP displayed cortical thinning in right sided ventral PM / temporal cortex, more pronounced in subjects scoring high on the affective domain. Coordinates not provided.
(Yang, Raine, Narr, Colletti, & Toga, 2009b)	Analysis of manually traced amygdala volumes.	32 control subjects; 27 PP. Mean PCL-R = 10.6(2.8); 28(4.9). From temporary employment agencies.	PP group displayed bilateral amygdala reductions, which correlated negatively with psychopathy F1.
(Boccardi et al., 2010)	Volumetric analysis of hippocampus after manual tracing	12 PP, 14 APD, 25 control subjects. PP and APD from university forensic psychiatric hospital for pre-trial assessment. Mean PCL-R = 34.6(3.1); 25.9(2.8); n/a	No significant correlations between volume and PCL-R scores in the offender group. Size and asymmetry not different from control, but more subtle differences were observed.
(Glenn, Raine, Yaralian, & Yang, 2010)	Volumetric analyses of the striatum (separately for caudate body and head and lenticular nucleus)	22 control subjects; 22 PP. Mean PCL-R = 12.9(3.5); 27.2(4.1). From temporary employment agencies.	Group differences were found for striatum, post hocs indicated larger bilateral lenticular nuclei.

	Analysis	Subjects	Results
(Schiffer, et al., 2011)	Whole-brain voxel-based comparison of T1 anatomical scans	14 non-offenders without SUD, 13 non-offenders with SUD, 12 violent offenders without SUD, 12 violent offenders with SUD. Forensic inpatients. PCL:SV = 4.4(2.6); 6.5(2.6); 9.3(2.9); 12.8(2.8). NB all offender groups score below the cut-off of 18.	The volume of regions that were larger in the violent group correlated positively with PCL:SV (bilateral amygdala, left nucleus accumbens, right caudate). The insula was smaller in the violent group and its volume correlated negatively with PCL:SV.
Chapter 3, this volume	Whole-brain voxel-based comparison of T1 anatomical scans	17 PP, 21 ASD, 20 Sz, 20 control subjects. PCL-R = 32.3(3.4); n/a; n/a; n/a. PP recruited from forensic psychiatric hospitals.	Relative large proportion of brain deficits in the whole-brain analysis fell inside regions belonging known to exhibit vicarious responses (primary somatosensory cortex and dorsal and ventral premotor cortex)

Table 2: Structural MRI studies of criminal psychopathy. Successful is defined as getting away with crime. PP = Psychopathy group. Not in all studies do all individuals score above widely accepted cut-offs on the psychopathy measure used. Such studies were still included in this list if they reported correlational analyses with the relevant instrument suggesting more abnormalities in more severely psychopathic individuals. SUD = individual diagnosed with substance abuse disorder. APD = Antisocial Personality Disorder, a DSM category that overlaps with, but is not identical to psychopathy, as defined using the PCL-R. ASD = Autism Spectrum Disorder. Sz = Schizophrenia. n/a = not available. Community samples were included in the table if they were related to serious behavioural problems. Mean scores of PCL-R or PCL:SV are supplied with standard deviation or range if available.

did not use a high inclusion threshold. Instead they contrasted violent offenders against non-offenders in a whole-brain analysis and correlated brain volume in the resulting areas against the - relatively moderate - PCL:SV scores. They observed a positive correlation between PCL:SV score and volume in regions that were larger in the violent group (bilateral amygdala, left nucleus accumbens, right caudate) and a negative correlation between PCL:SV and brain volume in the insula, which was smaller in the violent group. In addition, we recently contrasted a healthy control group against a psychopathy group and showed that the psychopathy group was related to reduced grey matter volume in shared circuits. These deficits were restricted to premotor and somatosensory regions (Chapter 3, this volume) and did not include regions related to emotional processing such as the ACC and the insula.

Other investigations of morphological differences have focused on a priori selected brain regions such as the amygdala (Tiihonen et al., 2000; Yang, et al., 2009b), the hippocampus (Boccardi, et al., 2010; Laakso, et al., 2001; Raine, et al., 2004), the corpus callosum (Raine, et al., 2003), the striatum (Glenn, et al., 2010) or the prefrontal cortex (Laakso, et al., 2002; Raine, et al., 2000; Yang, et al., 2005b). Studies that focused on the prefrontal cortex might have included regions known to respond vicariously during the observation of others, such as the premotor cortex. But as these investigations generally used large regions of interest, it is difficult to ascertain whether the premotor cortices indeed showed abnormalities.

An overview of the available functional neuroimaging studies on criminal psychopathy is presented in Table 3. The challenge with that literature, as recently reviewed by Koenigs and colleagues (2010) is that these studies vary widely in terms of task, making it impossible to identify regions

consistently impaired in a particular function, vicarious activations in particular. In addition, many of the studies use sample sizes smaller than what is often considered the bare minimum for fMRI to lead to reliable results ($n > 15$, Thirion, et al., 2007). With these caveats in mind, to our knowledge the only study directly assessing the integrity of vicarious responses using fMRI in criminal psychopathy was conducted within our own lab (Chapter 2, this volume). We recently compared 18 subjects diagnosed with criminal psychopathy with 26 healthy control subjects while they observed emotional hand interactions (see Figure 2 for example frames) and whilst experiencing similar hand interactions themselves. We showed a large hypoactivated network of brain regions (including regions that were activated during the experience of similar interactions, i.e. shared circuits) in the psychopathy group compared to the control group while they were passively observing hand movies but not when they were experiencing these hand interactions themselves (Chapter 2, this volume). Moreover, when we specifically asked our subjects to feel with one of the hands in the screen, the BOLD response in many regions that had previously been hypoactive was now significantly normalized compared to the control group, as indicated by a significant interaction between task (passive observation vs. instructions to empathize) and group. These results suggest that individuals with psychopathy can vicariously share the experiences and actions of others but do not do so as strongly compared to the control subjects under passive observation conditions, and that shared circuits (bilateral dorsal and ventral premotor cortex, bilateral primary and secondary somatosensory cortex, bilateral insula, mid cingulate gyrus and pre-supplementary motor cortex) indeed show abnormal vicarious activations in autism when participants are not instructed to empathize with others.



Figure 2: Three still frames from an example of each movie type used in Chapter 2: A neutral touch, a loving caress, a painful attempt to bend the finger of another and an excluding slap by one of the hands in the screen.

However, a number of experiments that did not directly attempt to assess vicarious activations also, albeit less directly, at the presence of abnormal vicarious activations in shared circuits. Studies using pictures from the International Affective Picture System (IAPS Lang, Bradley, & Cuthbert, 2008) often do so to induce mood, and to study the neural basis of differential mood manipulation across groups. Research indicates that subjects diagnosed with psychopathy show differential brain responses while viewing positive and negative IAPS pictures in shared circuits such as premotor cortex for both positive and negative pictures and anterior / mid cingulate cortex and the insula for

negative pictures, although in this particular study many of these regions were actually more activated by the psychopathy group (Müller, et al., 2003). This finding is particularly relevant for vicarious activations given that many of the IAPS pictures contain social stimuli that are known to trigger vicarious activations. For example, many positively valenced stimuli include actions that would trigger premotor activation (e.g. sensual caresses, image 4607, or holding a baby, 2057) and many of the negative stimuli also contain the kind of pain that is known to trigger vicarious activations in the ACC and insula (e.g. facial expressions of crying hungry children, 2800, bodily mutilations, 3053, a needle entering the skin, 9594). Harenski and colleagues (2010) also used pictures from the IAPS database, supplemented with pictures from media sources and grouped these into pictures displaying moral violations, negative but non-moral pictures and neutral pictures. However, their results give no indication of group differences within shared circuits, in contrast with the results from Müller et al. (2003). However, there is an important difference between these two studies. Where Müller and colleagues (2003) contrasted their emotional categories against a resting condition, the moral condition in Harenski et al. (2010) was contrasted against the non-moral or the neutral condition. This is important in terms of vicarious activations. Although IAPS pictures are able to trigger vicarious responses in the observer, the content of these pictures is usually much more diverse, compared to stimuli designed to trigger vicarious responses in specific neural systems, such as movies of stroking a leg (Keysers, et al., 2004) or pictures of painful needle pricks into the hand or foot (Jackson, et al., 2005). This will necessarily lead to a less consistent and more diffuse vicarious response in response to IAPS pictures (see also Bastiaansen, et al., 2009). As the stimulus categories of Harenski et al. (2010) were well balanced in terms of social content, contrasting the emotional conditions against the neutral condition has probably cancelled out all vicarious responses to these pictures. In agreement with this line of reasoning is the observation that the overall contrast of moral or non-moral against neutral did not reveal BOLD responses within shared circuits. It is therefore difficult to related this dataset to vicarious responses in psychopathy.

Two other neuroimaging paradigms studying criminal psychopathy have done so using facial expressions (Deeley, et al., 2006; Dolan & Fullam, 2009). These studies can provide information about the integrity of the shared circuit in psychopathy given that facial expressions have previously been reported to trigger vicarious responses in healthy subjects (e.g. Botvinick et al., 2005; Carr, Iacoboni, Dubeaut, Mazziotta, & Lenzi, 2003; Saarela et al., 2007; van der Gaag, Minderaa, & Keysers, 2007). Indeed, one of these two studies showed hypoactivation in premotor and primary somatosensory cortex in a psychopathy group compared to a control group, while subjects were observing faces in a gender discrimination task (Deeley, et al., 2006). On the other hand, Dolan and colleagues (2009) did not report any significant group differences outside the amygdala (Dolan & Fullam, 2009). This might be explained by the fact that their facial stimuli were also unable to activate parts of the shared circuit, whereas Deeley and colleagues (2006) did report such responses. Perhaps the comorbidity with schizophrenia plays a role in the absences of vicarious responses in the study by Dolan and colleagues (2009), as this disorder has previously been related to deficits in shared circuits as well (Gallese, 2003; Salvatore, et al., 2007; Chapter 3, this volume).

Finally, tasks using more abstract stimuli can be of importance. Sommer and colleagues (2010) presented their subjects with stimuli optimized to probe Theory of Mind functions. Participants had to judge the emotion of a character based on little vignettes accompanied by line drawings.

Previous research has indicated that short stories can also trigger responses in shared circuits (e.g. Jabbi, et al., 2008) and indeed the study by Sommer and colleagues (Sommer, et al., 2010) observed within group activations in the inferior parietal lobule, which has been indicated to be part of the vicarious system (see Figure 1). However, a direct group contrast did not reveal any significant differences in this region. Because participants were instructed to deliberately reflect about the mental states of others in Sommer et al. (2010), it may resemble the deliberate empathy condition of our study (Chapter 2, this volume), and contribute to a vision in which psychopathy shows abnormal vicarious activations in shared circuits only, or most strongly, when participants are not instructed to empathize or reflect about the inner states of others. Other studies listed in Table 2 seem less informative with regard to the functionality of shared circuits because they did not use stimuli known to trigger vicarious activations in shared circuits.

We know of one other group that examined the association of the integrity of shared circuits with psychopathic traits, using techniques other than fMRI/PET. Fecteau and colleagues (2008) observed a negative correlation between motor evoked potentials (MEPs) and the Coldheartedness subscale of the PPI during the observation of needles penetrating human hands. The polarity of this effect is surprising, because MEPs are normally reduced when viewing the pain of others, so that a negative correlation means that participants ranking higher on the PPI-cold-heartedness scale (i.e. more psychopathic individuals) display more of the phenomenon that is thought to be a marker of vicarious activations. However, their sample did not include truly psychopathic individuals; rather, they related psychopathic variation in the general (non-criminal) population to the variation in MEPs. The fact that their finding is contrary to what we expect might therefore also reflect a more general problem with relating research within healthy populations with the research done within forensic populations, as it is unclear whether neurobiological variations within the healthy population reflect those in the forensic psychopathic population: the study of depression has shown that people within the general population with more pronounced depressive traits can show neural activations that are very different from those characterizing ‘true’ clinical depression (Koenigs, et al., 2010).

	Paradigm	PCL-R / PCL:SV	n	Remarks
(Intrator et al., 1997)	Lexical decision task. Subjects had to decide whether the presented word was a word or a non-word. Words were emotional or neutral.	PP:29.9(2.9) NP:9.1(4.4)	9 9	SPECT
(Kiehl, et al., 2001)	Affective memory task using short word lists.	PP:32.8(2.9) NP:16.6(6.0)	8 8	
(Veit, et al., 2002)	Classical aversive delay conditioning. Neutral faces used as conditioned stimuli and painful pressure as unconditioned stimulus.	PP:25.3 (7.0) SP:n/a CG:n/a	4 4 7	
(Müller, et al., 2003)	Passive emotion observation. Pictures from the IAPS picture database were used to induce positive, neutral en negative mood.	PP:36.8(2.6) CG:n/a	6 6	
(Kiehl, et al., 2004)	Lexical decision task. Subjects were presented with blocks of words mixed with pseudo words and had to decide whether the presented string was a word. Words could be abstract or concrete.	PP:32.8(2.9) CG:n/a	8 8	
(Birbaumer, et al., 2005)	Classical aversive delay conditioning, similar to (Veit, et al., 2002)	PP:24.9(5.2) CG:n/a	10 10	group selected on high F1 scores (cut-off = 10.5)

	Paradigm	PCL-R / PCL:SV	n	Remarks
(Deeley, et al., 2006)	Gender discrimination task of faces with emotional expressions.	PP:29.3(24-34) CG:n/a	6 9	
(Müller, et al., 2008)	Influence of emotion induction on cognitive task. Emotion induction through blocks of IAPS pictures, cognitive task was Simon task.	PP:30.5(28-35) CG:9(0-4)	10 12	emotion induction did not influence task performance
(Dolan & Fullam, 2009)	Gender discrimination task of faces with negative emotions (anger, disgust, fear and sad) expressions.	PCL:SV PP:17.4(2.3) NP:8.4(3.3)	12 12	comorbidity with schizophrenia
(Hoff, et al., 2009)	n-back task (0, 1 and 2) using line drawings of facial expressions or scrambled line drawings facial expressions.	PP:36.8 CG:n/a	1 12	no direct comparison between patient and control group. control group 6 male.
(Harenski, et al., 2010)	Moral decision making. Subjects had to rate the severity of moral violations depicted in these pictures.	PP:31.8(2.5) NP:13.3(3.1)	16 16	selected out of a very large group of prisoners (72). authors also provide additional correlational analyses on this total group
(Sommer, et al., 2010)	Emotional theory of mind task. Subjects watched line drawing of three interacting individuals with a sentence describing the scene. After the third picture, the subject had to determine how the protagonist was feeling. This depended on the outcome of the interaction.	PP:28.6(1.2) NP:9.6(2.2)	14 14	
(Veit, et al., 2009)	Competitive reaction time: Ss played a game against a confederate and could punish the confederate if they won, but could also be punished. Manipulation meant to trigger reactive aggression.	PCL:SV PP: 16.11(3.6) Range: 9-21	10	no control group. not all participants scored above a reasonable cut-off. PCL scores were used for correlation analyses.
Chapter 2, this thesis	Shared circuits of emotional hand interactions. Subjects observed hand interactions passively and while actively empathizing with the hands in the screen. To localize brain regions normally recruited for these hand interactions, all subjects also experiences these hand interactions.	PP:32.3(3.6) CG:n/a	18 26	

Table 3: Functional neuroimaging studies of criminal psychopathy. PP = psychopathy group, CG = community control group, NP = forensic non-psychopathy group, SP is social phobia group. Not in all studies do all individuals score above a reasonable cut-off on the psychopathy measure used. Such studies were still included in this list if they reported correlational analyses with the relevant instrument suggesting more abnormalities in more severely psychopathic individuals. n/a = not available. Community samples were included in the table if they were related to serious behavioural problems. Mean scores of PCL-R or PCL:SV are supplied with standard deviation or range if available. All studies use fMRI unless otherwise indicated.

In summary, only six studies have provided whole-brain analyses of structural deficits. Five of these, including our own, have evidenced abnormalities in the volume of grey-matter in regions associated with vicarious activations in psychopathy. Deficits have been observed in premotor cortex, the insula and regions related to somatosensation, although not consistently so. In addition, three functional studies evidence abnormalities in how strongly participants with psychopathy recruit shared circuits while viewing hands interacting with each other, IAPS pictures and facial expressions, even though most of these studies were not specifically designed to probe the integrity of vicarious responses. A study designed to probe Theory of Mind functions was unable to show any group differences within shared circuits. Jointly this literature might be taken to suggest that structural abnormalities in shared circuits coexist with abnormal vicarious activation while participants watch the emotions, sensations and actions of others without being explicitly asked to reflect or empathize with the stimuli. In contrast, when asked to empathize or reflect about these states, these functional abnormalities in vicarious activations are greatly reduced.

5.4 MODULATION OF VICARIOUS RESPONSES

A central finding of our fMRI study of psychopathy is the fact that we observed strongly reduced vicarious activations in this group while participants were passively observing the interactions of hands without further instructions, but that this difference was much reduced, if they were asked to empathize with the actors. This suggests that the absence of vicarious responses in subjects with psychopathy has more to do with a reduced propensity to generate vicarious responses compared to an incapacity to produce these responses (Chapter 2, this volume). In line with this observation, a study that investigated neural responses to facial expressions while the primary task of subjects was unrelated to the emotions (gender discrimination) observed a hypoactivation of parts of the shared circuits (Deeley, et al., 2006). In contrast, a study that asked their subjects to ‘allow themselves to feel the emotions the pictures suggest’ (Müller, et al., 2003, page 154) observed increases in these regions, and one that asked to reflect about the emotions of characters in vignettes failed to find differences in shared circuits (Sommer, et al., 2010). The effect of cognitive modulation of vicarious activations in psychopath is reminiscent of the fact that studies of vicarious activations in healthy volunteers has also shown that a number of factors can influence the intensity of vicarious activations (de Vignemont & Singer, 2006). In this paragraph we will investigate the characteristics of the modulation of vicarious responses in healthy controls.

In an elegant study, Singer and colleagues (2006) showed that the perceived fairness of an individual influences the intensity of vicarious activations towards that individual, with this influence larger in males than female participants. In this experiment male and female subjects first played a Prisoners Dilemma game with two confederates (hired actors) who were playing either fairly or unfairly. These two confederates were then seated on either side of the subject during a subsequent fMRI session. On different trials, either confederate or the subject received a painful shock on the hand. The subjects in the scanner were able to see their own hand as well as those of the two confederates. A cue indicated what kind of shock was delivered and to whom. The anterior cingulate cortex (ACC), a brain region known for its processing of the affective dimension of painful experiences and was activated in both groups during painful stimulation to the participant. The ACC was also activated in both groups (male and female) when they observed the fair player

being shocked. But contrary to the women, the men did not recruit this area when they observed the unfair player being shocked. Instead, in the male group an increased BOLD response was observed in the left ventral striatum / nucleus accumbens, which correlated with their expressed desire for revenge. This indicates that both men and female players can share the painful consequences of a shock for the confederates, but whether they do so not only depends on the relationship with the confederate but also on the gender of the empathizer. This is particularly interesting with respect to the research of vicarious responses in psychopathy as it shows that modulatory effects of the context (in this case fairness) can interact with characteristics of the perceiver (gender) - much as the instruction to empathize had a different effect on individuals with and without psychopathy (Chapter 2, this volume).

Other studies have also shown that the social importance of a stimulus can influence the strength by which shared circuits are recruited. Avenanti and colleagues (Avenanti, Sirigu, & Aglioti, 2010) recorded motor evoked potentials (MEP) from white and black participants while they observed black or white hands being administered painful stimuli. The muscle specific MEP was reduced only when subjects observed hands belonging to the same racial group. Hein et al., (2008a) let football fans witness the pain of fans of their own team or of fans of a rivalling team. They found that vicarious pain activations were larger to the pain of fans of the supported team, confirming that vicarious activations are sensitive to the in-group/out-group belonging of the target individual. Two other studies manipulated their stimuli in order to make them more or less socially relevant for the subject. Kilner and colleagues (2006) showed subjects movie clips of an actor performing actions while facing them or facing away from them. They recorded whole-head MEG during the display of these movies and observed a drop of power in the α -band in contralateral parietal regions only when the moving actor was facing the subjects. Jackson and others (2006) also manipulated the context by showing their participants intransitive actions shown from a first-person perspective or from a third-person perspective. The contralateral sensory-motor cortex was more strongly activated during the observation of actions shown from a first-person perspective.

Other studies have manipulated the relevance of certain aspects of their stimuli in more explicit cognitive ways. For example, Lamm and colleagues (2007) instructed their subjects to observe photographs of hands being pricked with needles. The participants were informed that some of the photographs were taken of patients undergoing a biopsy of their anaesthetized hand and that this would be unpleasant but not painful and that the other photographs represented painful injections. They observed less vicarious activations when subjects were attending to the numbed hands compared to the non-numbed hands. Interestingly, in the same study, the authors found that the instructions given to the participants also modulated the intensity of vicarious activations: when asked to assess how intense the pain is for the patient compared to how unpleasant, participants activated their somatosensory cortex more strongly. This is in harmony with a recent review of fMRI studies on empathy for pain (Lamm, et al., 2011) that showed that somatosensory regions are more consistently activated in paradigms where images of body parts in painful situations were displayed compared to designs where pain in someone else was indicated by the appearance of a cue (Lamm, et al., 2011). The role of attention is also illustrated by an experiment conducted by Gu and Han (Gu & Han, 2007). Subjects were again instructed to watch displays of hands in painful situations. The pain network was more engaged when subjects had to rate the pain as opposed to counting the

number of hands in the stimulus. These studies reviewed above indicate that attention is an important component in recruiting shared circuits, either explicitly focussed or implicitly manipulated. Apart from the influence of attentional processes in the here and now, the influence of previous experiences on vicarious responses has also been studied in healthy volunteers.

Cheng and collaborators (Cheng et al., 2007) observed an attenuated vicarious response in the insula and the anterior medial cingulate cortex in professional acupuncturists, compared to a control group, while they were watching photographs of needles pricking hands. The authors suggested that their increased experience with needles made them more skilled in regulating their emotional responses to these painful pictures. Indeed, compared to the control group, the expert group activated other structures that suggested increased top-down regulation of emotional responses in this group.

In summary, the above mentioned studies show that the intensity of vicarious responses is not only determined by characteristics of the observer (e.g. self-related empathy), but represents an interaction between characteristics of the observer (e.g. gender, race), characteristics of the target (e.g. perceived fairness, group, race), task instructions (e.g. what to attend to) and previous experiences. In the next part we will link this research to psychopathy.

5.5 ABNORMAL MODULATION OF VICARIOUS RESPONSES IN PSYCHOPATHY

5.5.1 PINPOINTING A MECHANISM

If psychopathy is indeed related to deficits in vicarious responses, this might be related to two general problems. First of all, a primary deficit in premotor, somatosensory and/or emotional systems, which would be measurable when the participant executes actions or feels his own sensations and emotions can impair vicarious activations in these regions. For instance, research with subjects born without hands (Gazzola et al., 2007) or a subject without arms and legs (Aziz-Zadeh, Sheng, Liew, & Damasio, 2011) illustrates that the ability to mirror the actions of others depends on the possibility of the body to perform these actions in the first place. In addition, individuals unable to experience disgust are also impaired at perceiving disgust in others (Adolphs, Tranel, & Damasio, 2003; Calder, Keane, Manes, Antoun, & Young, 2000).

There are some studies demonstrating structural deficits in premotor and somatosensory regions (de Oliveira-Souza, et al., 2008; Chapter 3, this thesis; Tiihonen, et al., 2008; Yang, et al., 2009a), but there is no functional evidence in the literature supporting a primary deficit in motor execution or somatosensory related processes in psychopathy. A primary deficit in emotional processing is more likely, as it is one of the defining characteristics of psychopathy; a person who seems to be unable to experience a normal range of emotions (item shallow affect, Hare, et al., 2001). There is also evidence for deficits in emotional processing from behavioural and physiological studies (see above). However, as emotion induction is a tricky experimental manipulation, it is still hard to establish from these studies whether these abnormalities stem from a primary deficit in experiencing emotions or a secondary effect in triggering these emotions in response to emotional displays that are, as mentioned above in the context of IAPS pictures, often social in nature.

Secondly, reduced vicarious responses in psychopathy might be related to the inadequate recruitment or inhibition of *vicarious* activations in shared circuits (i.e. not when the participant himself does or feels, but while witnessing others do so). As reviewed above, the implicit manipulation of attention modulates the recruitment of shared circuits in healthy volunteers. More importantly, some studies observed that this effect was dependent on personal/genetic characteristics of the volunteers, such as gender or race (Avenanti, et al., 2010; Singer, et al., 2006). This is particularly relevant with respect to psychopathy. Perhaps attentional processes also play a role in the reduced vicarious responses we observed when psychopathic individuals were passively observing short movie clips of hand interactions. It may well be that what is relevant for control subjects differs considerably from what captures the attention of subjects with psychopathy. Not only have abnormalities in attentional processes in psychopathy already been proposed in the response modulation hypothesis (Patterson & Newman, 1993, page 717). Their criminal lifestyle has also led to an increased exposure to violence compared to control subjects, which might enable them to inhibit emotional responses, similarly to the acupuncturists in the study by Cheng and colleagues (2007). Also, abnormalities in the uncinus fasciculus, connecting the temporal lobe with limbic and premotor regions could mean that visual information in the temporal is conveyed less effectively to limbic and premotor regions under vicarious conditions (Craig et al., 2009).

The neural implementation of the modulation of vicarious responses is at present not well understood. As described above, a diversity of factors can influence the strength of these responses in healthy volunteers and it is therefore very likely that more than one neural mechanism subserves the modulation of shared circuits. Here we will therefore propose a tentative and speculative neuro-cognitive model that proposes that abnormalities in the amygdala may cause the brain of psychopathic individuals to vicariously activate shared circuits less than normal under spontaneous conditions. This effect might be counteracted by the vmPFC of psychopathic individuals when they are instructed to pay attention to the emotions of others. We hope that this notion will connect long held theories about the role of amygdala in the development of psychopathy with the more recent notion of abnormal vicarious activations we propose, and help explain why deficits in psychopathy may depend on whether participants are or are not instructed to pay attention to the states of others.

5.5.2 THE AMYGDALA

A region often associated with abnormalities in psychopathy is the amygdala. In the literature, amygdala deficits have typically been associated with deficits in fear conditioning specifically or more generally with the association of particular social cues with particular (negative) affective states. Here we will argue that the well documented deficits in the amygdala might also influence vicarious activations, thereby bridging previous theories of psychopathy and abnormalities in vicarious activations. This is because of a role of the amygdala in modulating activity in the posterior Superior Temporal Sulcus (pSTS) that in turn drives vicarious activations. In particular, the amygdala might normally ensure that attention is automatically directed towards the emotions of others, and hence facilitate spontaneous vicarious activations. If this automatic process is reduced, voluntary attention may still enable normal levels of vicarious activations.

The amygdala is an almond-shaped mass of grey matter located bilaterally within the anteromedial part of the medial temporal cortex. The amygdala of primates consist of 13 very densely interconnected nuclei (Freese & Amaral, 2009; Sato et al., 2011). Each nucleus has a unique pattern of connectivity with the rest of the cortex. Not much is known about the connectivity of the human amygdala, but the macaque amygdala is considered a useful proxy (Freese & Amaral, 2009). In the macaque monkey, the amygdala is connected with many parts of the neocortex, but seems to be most densely connected with the insula, the medial prefrontal cortex and the temporal cortex (see Figure 3). This puts the amygdala in a position to influence some brain regions implicated in vicarious response directly (e.g. the insula) but also more indirectly, for example through its connections with higher order visual cortex such as the pSTS that serves as an input to the other nodes within the shared circuit (see Figure 3). Functionally, the influence of the amygdala on subsequent cortical processing of visual information was demonstrated in an elegant study performed by Vuilleumier et al. (2004). In this study, a control group was compared to two groups with left-sided medial temporal sclerosis. Damage due to sclerosis was confined to the hippocampus in one group, but extended to the amygdala in the other. Subjects were presented with visual stimuli containing always two faces and two houses. Depending on the task, subjects had to determine whether the faces or the houses were the same or different. Faces could either be fearful or neutral and either task relevant (when they had to judge faces) or irrelevant (when they had to judge houses). Whereas the control and hippocampal-only group showed enhance BOLD response in regions of the visual cortex upon viewing of fearful faces (irrespective of task condition), the amygdala group showed no such modulation. In fact, the extend of left-sided amygdala damage correlated negatively with the parameter estimates of the fearful versus neutral contrast in several brain regions including parts of the left posterior fusiform gyrus, left occipital cortices, right superior temporal sulcus, bilateral ACC and right parietal cortex. This suggests that the amygdala damage does not only influence regions of higher-order visual cortex, but also regions related to emotional processing and vicarious responding, such as the ACC and the parietal cortex.

The amygdala has received relatively much attention within the field of psychopathy considering the paucity of neuroimaging data on this disorder. Whole-brain examinations of anatomical images have typically not reported differences in the amygdala, but this may be due to the amount of smoothing that is often used in these studies (Honea, et al., 2005). Studies applying manual parcellation of the amygdala have been more successful in finding a reduced volume in this structure (Tiihonen, et al., 2000; Yang, et al., 2009b). fMRI studies have also reported aberrant BOLD responses in the amygdala in subjects with psychopathy, despite the problems related with imaging this structure using fMRI (Adolphs, 2010). These studies have observed that the amygdala is hypoactive during fear conditioning (Birbaumer, et al., 2005), while memorizing negatively valenced words (Kiehl, et al., 2001) and when observing negative facial expressions (Dolan & Fullam, 2009). The BOLD response in the amygdala was also more strongly positively correlated with the severity of moral violation ratings in a low scoring compared to a high scoring psychopathy group (Harenski, et al., 2010).

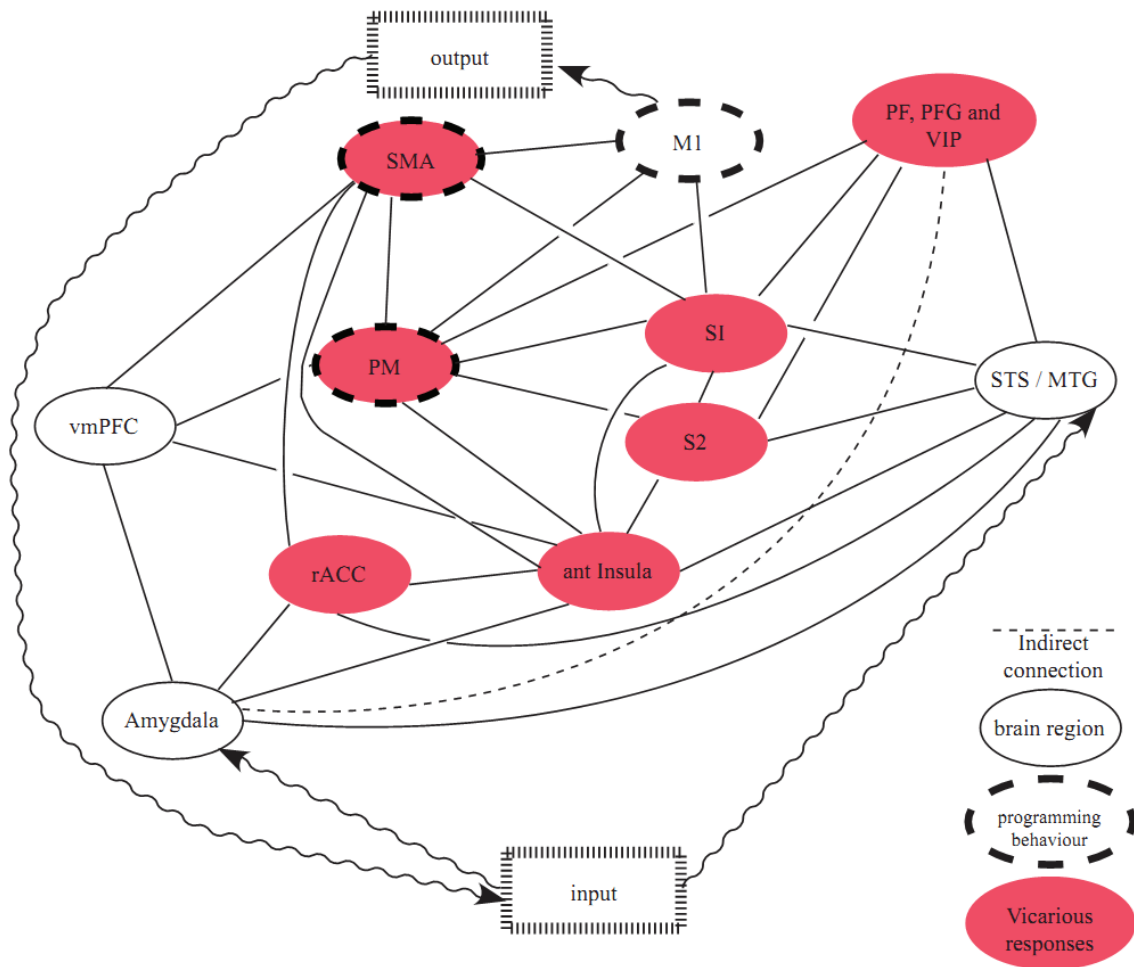


Figure 3: Updated from Figure 1.

Research on the amygdala within the realm of social cognition generally focuses on three domains, namely social behaviour, emotion and reward learning (Adolphs, 2010). According to Adolphs (2010) the results from these different research areas converge to suggest a role of the amygdala in assessing stimulus saliency. Saliency is a complicated construct that describes the characteristics of a certain stimulus in terms such as ‘arousal’, intensity, relevance, unpredictability and ambiguity. The higher a stimulus ‘scores’ on these characteristics, the more salient it is and the more it will attract a powerful orienting response (Adolphs, 2010). Illustrative for the importance of the amygdala in determining the relevant parts of the environment comes from the case report of patient SM, a well documented patient with a selective lesion to bilateral amygdala due to Urbach-Wiethe disease. In one of the first studies that reported on her functional deficits, it was shown that she was unable to recognize fear from static facial expressions (Adolphs, Tranel, Damasio, & Damasio, 1994). However, a subsequent study using an eye tracker revealed that this was related to her failure to make use of the information in the eye region of the face. After an instruction to observe the eyes she was able to recognize fear (Adolphs et al., 2005).

In psychopathy, the amygdala has mainly been associated with deficits in instrumental learning (Blair, 2006) and the reduced ability to recognize and experience fear (Patrick, 1994). The saliency account of the amygdala broadens that perspective. It predicts that subjects with amygdalar

damage may not be spontaneously looking at the normally most ‘salient’ relevant parts of the social environment. There are several indications that a saliency account of psychopathy can explain additional findings of the literature on psychopathy. For example, children with psychopathic tendencies have a diminished ability to recognize fear. This ability was significantly improved after an instruction to observe the eye region (Dadds et al., 2006), which indicates that their problem is not so much an inability to recognize fear but an diminished capability to pick out the most relevant bits. Similarly, in our study we observed a large network of brain regions to be hypoactive during the passive observation of interacting hands, including bilateral amygdala and pSTS. After we instructed our participants to feel with the hands in the movies, many regions, including bilateral amygdala and pSTS, were no longer hypoactive compared to the control subjects (Chapter 2, this volume). Another study that reported hyperactivity in shared circuits in psychopathic individuals while they were observing IAPS pictures also reported an increased amygdala response while they observed these IAPS pictures (Müller, et al., 2003). Intriguingly, these investigators also specifically asked their subjects to ‘allow themselves to feel the emotions the pictures suggest’ (Müller, et al., 2003, page 154), an instruction very similar to the one we used during the second part of our experiment.

The extension of the amygdala as a saliency detector also fits with the response modulation hypothesis of psychopathy put forward by Patterson and Newman (Patterson & Newman, 1993). According to the authors, response modulation involves a ‘temporary suspension of a dominant response set and a brief concurrent shift of attention from the organization and implementation of goal-directed responding to its evaluation’ (Patterson & Newman, 1993, page 717). Within this framework, Newman and colleagues (2010) investigated the effect of attention on fear responses within a group of subjects diagnosed with criminal psychopathy. Subjects were shown green or red letters that were written in uppercase or lowercase. Beforehand they were instructed that painful shocks could be delivered after the appearance of a red letter, but never after a green letter. During the actual experiment, letters were presented one after the other and subjects had to perform a task which required them to focus on the colour (thread focused condition) or on the case (alternative focused condition) of these letters. The psychopathy group demonstrated a fear potentiated startle only during the thread focused condition but not during the alternative focused condition. This result stands in contrast with other studies that have observed abnormalities on indices of fear responding (e.g. Birbaumer, et al., 2005; Lykken, 1957; Patrick, et al., 1993). The authors suggested that this was related to the inability of psychopathic subjects to identify the relevant information in their attentional periphery which predicted a painful shock.

In summary: The amygdala is not only involved in instrumental learning and the processing of emotions such as fear, but seems also important in detecting salient social information and the subsequent boosting of visual processing of these stimuli. Studies indicate that deficits in the amygdala can be compensated by encouraging participants to voluntarily direct attention to social stimuli. Reduced vicarious activations during spontaneous observation of our hand-stimuli could therefore be (partially) explained by reduced amygdala responses. These reduced amygdala responses might then have led to reduced STS responses which in turn reduced vicarious activations. In accord with that interpretation, instructions to attend to stimuli reduces abnormalities in

amygdalar patients and in our paradigm, in psychopathic individuals. This raises the question which mechanism underlies the volitional recruitment of shared circuits.

5.5.3 THE VENTRAL MEDIAL PREFRONTAL CORTEX

In the above we have argued that shared circuits in psychopathy might not be adequately recruited compared to control subjects due to deficits in the amygdala. We have also reviewed studies that show that task instructions and manipulations of attention can alter the initial deficits seen in psychopathy (Chapter 2, this volume; Dadds, et al., 2006; Newman, et al., 2010), which implies some room for top-down control in subjects with psychopathy to compensate a deficit in automatic orientation to salient social stimuli as implemented by the amygdala. A region that could contribute to this function is the vmPFC. This region has previously been linked to emotion reappraisal (Ochsner, et al., 2004) due to its recruitment while subjects were asked to increase or decrease their negative emotions in response to negative or neutral pictures pictures. The vmPFC was also recruited more strongly in a group of acupuncturers while they observed needles pricking hands. This increased activation of the vmPFC was related to their increased experience with regulating emotional responses while viewing pain in others and it might have been related to the attenuated recruitment of shared circuits in this group. In yet another study subjects observed pictures of hand injections or hand biopsies. Subjects were informed that the biopsies, in contrast to the injections, were not painful due to anaesthesia. Subjects showed an increased activation of the vmPFC while observing hand biopsies in comparison to hand injections suggestion that the vmPFC was involved in down-regulating vicarious emotional responses in the situations that subjects knew to be not painful (Lamm, et al., 2007). These studies indicate that the vmPFC is indeed involved in regulating emotional responses in healthy volunteers.

This is interesting regarding the data we acquired in our own study. When our subjects were asked to feel with one of the hands in the screen, this led to a normalization of the BOLD response in the psychopathy group in many areas, including parts of the shared circuit (i.e. the left insula and the ACC). However, we still observed group differences during this task in several regions. During this task the vmPFC was more strongly recruited in the psychopathic individuals. The increased activation of this region during the empathy condition is compatible with the idea that this region was important in up-regulating the response in parts of the vicarious system, such as the insula and the ACC. It may also have been involved in the normalization of the BOLD response in the amygdala, as these regions are highly connected (see also figure 3). However, the vmPFC has also been associated with psychopathy with respect to stimulus reinforcement learning and response reversal (Blair, 2010) and recently also with deficits in emotion regulation (Harenski & Kiehl, 2010). Future research needs to establish whether the vmPFC is crucial for emotion regulation and whether this function is relatively spared in psychopathy.

5.6 CONCLUSION

In this review we have focussed on the embodied empathy deficit in psychopathy. Data from previous studies suggests that individuals with psychopathy respond less to the emotions of others and are also less able to classify these emotions. In this review we suggest that this might be related to reduced vicarious responding in psychopathy. One study has directly tested this hypothesis and has indeed confirmed this prediction; the psychopathic individuals showed an attenuated response during this fMRI paradigm in premotor, somatosensory and insular cortex while passively observing emotional hand interactions (Chapter 2, this volume). Other than that, only two studies could provide indirect evidence for functional abnormalities in shared circuits. Additional evidence from structural imaging also shows that there is some evidence for structural deficits in shared circuits.

It should be noted that the available neuroimaging data on psychopathy is still very limited. Consequently, the model presented in this review is based on a small dataset and is therefore tentative. Further research is necessary to confirm our instruction dependent finding of hypoactivation in shared circuits. With this caveat in mind, we have proposed that the spontaneous recruitment of shared circuits in psychopathy may be less strong compared to control subjects due to deficits in the amygdala, which impairs the detection of salient information (Adolphs, 2010), but can be wilfully compensated to a certain extent by the regulatory influences of the vmPFC (see also Harenski & Kiehl, 2010; Ochsner, et al., 2004). We furthermore suggested that a lack of vicarious activations might also at least partly be related to a more primary deficit in experiencing emotions.

This theory extends two existing models on psychopathy. First of all, the response modulation theory (Patterson & Newman, 1993) predicts that individuals with psychopathy are less able to gather information from their periphery, while engaged with ongoing behaviour. Our model complements this by predicting that psychopathic individuals are in general more impaired in locating salient information. This means that their ability to pick up salient information is not only impaired during task performance, but also when no specific task is at hand to lead their attention away from the salient information. Secondly, the Integrated Emotion Systems (Blair, 2006) states that moral development is promoted through the pairing of distressing emotions, like fear or sadness, with moral transgressions. The lack of moral development in psychopathy is explained through this model by their reduced response to the distressing emotions of others. The saliency account of vicarious modulations we propose can explain why distressing emotions in others are less distressing for individuals with psychopathy. It is fascinating that the amygdala, that plays a role in associating actions to aversive affect during learning, might also have a role in deploying attention to these social stimuli, which will then trigger vicarious activations. This suggests that a deficit in this region could reduce both the vicarious responses that we have to experience for moral development, and the association of these vicarious responses to the actions that caused them.

Acknowledgements

I thank Christian Keysers, Marte Swart, Jojanneke Bastiaansen and Valeria Gazzola for their helpful discussions and reading drafts of the manuscript.

6

GENERAL CONCLUSION

In this thesis, we investigated the neural correlates of empathy in subjects diagnosed with psychopathy. To this purpose, we adopted the following definition of empathy: embodied empathy occurs when the imagination or perception of the affective state, sensation or action of another triggers a representation of this affective state, sensation or action in the self which resembles that of the other (see Chapter 1 and 5, this volume). This definition was inspired by the definition used by de Vignemont and Singer (2006) and fits with the neuroscientific observation that the premotor cortex is recruited both when we perform actions and when we observe others performing similar actions (Caspers, et al., 2010; Keysers & Gazzola, 2009), that the somatosensory cortex is activated both when we see conspecifics getting touched and when we are touched in similar ways ourselves (Keysers, et al., 2010; Pineda, 2008) and that observing emotions of others triggers neural activations in insular and cingulate cortices normally associated with experiencing emotions ourselves (Bastiaansen, et al., 2009). These so-called vicarious responses occur in shared circuits and might provide the observer with an embodied sense of the experiences of others (e.g. Gallese, et al., 2004; Keysers & Gazzola, 2006). With this definition in mind, we investigated the functional and structural neural correlates of empathy in a group of subjects diagnosed with criminal psychopathy. In this final chapter, we will summarize and discuss the results of the different chapters.

6.1 VICARIOUS BRAIN RESPONSES IN PSYCHOPATHY

Previous psychophysiological research has indicated that individuals with psychopathy respond less to emotions of others (e.g. Aniskiewicz, 1979; Blair, et al., 1997; Levenston, et al., 2000; Patrick, et al., 1993) and we hypothesized that this may be related to a reduced recruitment of shared circuits. In **chapter 2**, we therefore directly investigated whether psychopathic individuals show reduced vicarious brain responses compared to a control group recruited from the community. Our paradigm consisted of three separate experimental conditions: Observation, Empathy and Experience. During the Observation experiment, subjects were asked to observe short movie clips of emotional hand interactions without any further instruction. We used a range of interactions with different valences to test whether group differences are specific for particular emotions or whether they also apply to emotionally neutral stimuli. The presented emotions were: love (two hands caressing each other), pain (e.g. one hand hitting the other) and social rejection (one hand pushing away the other friendly hand). A neutral movie always started with one hand touching the other, so as to attract attention, to which the second hand then responded non-emotionally. In the Empathy experiment, the participants subsequently observed the painful and loving movies again, but were now asked to specifically feel with one of the hands in the screen. Finally, during the Experience experiment, we let subjects experience similar hand interactions themselves.

During the Observation experiment, we observed an attenuated blood-oxygenated level-dependent (BOLD) response in the psychopathy group in many regions that belong to the shared circuit, including the premotor cortex, primary and secondary somatosensory cortex and emotional areas such as bilateral insula and mid-cingulate gyrus. In addition, regions outside shared circuits were also hypoactive compared to the control group, including the amygdala and posterior superior temporal sulcus (pSTS). In fact, there were no regions that were more active in the psychopathy group during this experiment. This pattern of group differences was drastically different in the

subsequent Empathy experiment. Whereas the psychopathy group was associated with a general hypoactivation during the Observation experiment, this group now showed many regions that were more strongly recruited compared to the control group. An interaction analysis between experiment (Observation or Empathy) and group indicated that the BOLD response in many regions that had been hypoactive during the Observation experiment, was significantly normalized during the Empathy experiment in the psychopathy group. There were no regions for which the difference in BOLD response between the two groups was significantly increased during the Empathy experiment, compared to the Observation experiment.

Further analyses showed that the group differences during the Observation experiment could not be explained by group differences in looking pattern (as measured using eyetracking), rating of the movies or significant differences in baseline brain activation. In addition, the analysis of the Experience experiment indicated that the groups did not differ from each other on the BOLD response while they performed similar interactions themselves. Together these results suggest that psychopathy is not so much related to a complete inability to produce vicarious responses, when they observe others, or to feel similar emotions themselves, but rather a reduced tendency to produce vicarious responses spontaneously. It also suggests that there is room for improvement, as the psychopathy group was able to adjust their responses after an explicit instruction. However, even after this instruction, the BOLD response in the psychopathy group was not identical to that in the control group. The psychopathy group did, for example, still recruit bilateral primary somatosensory cortex less, while they were empathizing with the hands in the screen. This raises the question as to whether there are structural deficits underlying their reduced recruitment of shared circuits. We investigated this in the next chapter by comparing T1 weighted anatomical images between three groups of psychiatric patients and a control group.

6.2 STRUCTURAL BRAIN DEFICITS IN PSYCHOPATHY

As we had observed in chapter 2 that subjects with psychopathy were able to normalize the recruitment of shared circuits up to a certain point, but not all the way, we wanted to investigate whether structural abnormalities might underlie their deficit to recruit these regions. In addition, we were interested to see whether these potential structural abnormalities were unique to psychopathy, or more common to disorders that have been linked to deficits in shared circuits, such as Autism Spectrum Disorder (ASD, Iacoboni & Dapretto, 2006) and schizophrenia (Gallese, 2003; Salvatore, et al., 2007). In chapter 3, we therefore examined the structural integrity of shared circuits; not only in our psychopathy group, but also in a group diagnosed with ASD and a group diagnosed with schizophrenia (see Box 6.1 for a behavioural comparison of these three groups).

First, we conducted a structured meta-analysis in order to gather knowledge about previously identified structural deficits in these disorders. We searched the literature for publications reporting whole-brain voxel-wise comparisons between any of the aforementioned patient groups and a healthy control group and then performed an activation likelihood estimation (ALE) on this literature. Roughly, an ALE is a coordinate-based meta-analysis approach, that can be used to detect convergence between reported peak coordinates from different studies (Eickhoff, et al., 2009; Turkeltaub, et al., 2011). Based on the available literature, we were unable to make any claims concerning psychopathy, as there were too few published studies meeting the inclusion

criteria for our meta-analysis. We were able to perform an ALE for schizophrenia and ASD and used the outcome of this ALE to compare the spatial extent of grey matter differences in- and outside the shared circuit, for each group separately. The mask we adopted to represent the shared circuit covered 19% of the total grey matter in the brain. The meta-analysis indicated that 39% of the structural abnormalities associated with schizophrenia fell inside the shared circuit, which was more than could have been expected based on chance alone, given that the shared circuit encompasses only 19% of the total grey matter. In contrast, 13% of the structural abnormalities associated with ASD fell inside the shared circuit, which was significantly lower than could have been expected based on chance alone. These results from the literature indicate that structural deficits in schizophrenia are relatively concentrated in the shared circuits, whereas they are more pronounced outside the shared circuit for ASD.

Second, we performed an analysis on our own structural data and observed a similar pattern. Again, we compared the spatial extent of grey matter differences in- and outside the shared circuit, for each group separately. We observed that 62% of the voxels, which differed between the control group and the schizophrenia group, fell inside the shared circuit, which was significantly more than could have been expected based on chance alone. Only 22% percent of the voxels, which differed between the ASD group and the control group, fell inside shared circuits, which means that this group was not specifically related to more deficits in shared circuits. In addition, the psychopathy group was related to an increased amount of structural deficits in shared circuits (29%). Oddly enough, none of these differences fell inside regions associated with emotion processing, such as the insula, the anterior cingulate cortex (ACC), the amygdala or the orbitofrontal cortex (OFC). Instead, differences in this group were restricted to premotor regions and somatosensory cortex.

In summary, we observed that deficits in shared circuits were most pronounced in the schizophrenia group and less so in the ASD group. This is interesting, considering that the functional integrity of vicarious responses has been most extensively investigated in ASD, although findings are inconsistent (for a review see Thioux, Bastiaansen, & Keysers). Apart from our fMRI study (chapter 2, this volume), this has not been tested in criminal psychopathy and has received little attention in schizophrenia (Bastiaansen, et al., 2011; Enticott, et al., 2008; Fahim, et al., 2004; Quintana, et al., 2001). In contrast to this focus on ASD, our results indicate that individuals with schizophrenia actually present with the most pronounced grey matter abnormalities in shared circuits, both within the literature and our own data. The relative salience of grey matter abnormalities in empathy related regions in schizophrenia suggests that the association between schizophrenia and empathy may merit more attention (Achim, et al., 2010; Brunet-Gouet, et al., 2010). In addition, we also observed an increased proportion of volumetric differences in shared circuits in psychopathy. However, the spatial extent of these volumetric abnormalities was much smaller in this group compared to the schizophrenia group. This leads to the following question: Given that subjects with psychopathy are able to produce relatively normal vicarious responses when they actively empathize with others and are associated with only minor structural deficits in shared circuits, why is it that vicarious responses are not spontaneously triggered as much compared to control subjects while they passively view movies of hand interactions. We tried to answer this question in chapter 5.

6.3 MODULATION OF VICARIOUS ACTIVATION IN PSYCHOPATHY

In chapter 5, we have reviewed existing data on criminal psychopathy, that suggests that psychopathic individuals respond less to emotions of others (Aniskiewicz, 1979; Blair, et al., 1997; Levenston, et al., 2000; Patrick, et al., 1993) and are also less able to classify these emotions (Bagley, et al., 2009; Blair, et al., 2004; Blair, et al., 2002; Hastings, et al., 2008; Herpertz, et al., 2001; Kosson, et al., 2002). These studies are compatible with the notion that psychopathy is indeed related to decreased vicarious brain responses, although this cannot be concluded from psychophysiological evidence alone. Deficits in vicarious neural sharing have been specifically related to amoral behaviour, such as instrumental aggression by Decety and Moriguchi (2007), but as mentioned in the previous paragraph, these deficits have until now only been directly investigated once and further research is therefore needed to confirm or falsify the results from chapter 2. Given the premise that deficits in recruiting shared circuits are related to psychopathy, we propose two causes for attenuated vicarious responses in psychopathy in chapter 5.

First, psychopathy could be related to a primary deficit in action execution, somatosensory processing and / or experiencing emotions. In this scenario, individuals with psychopathy are unable to share experiences of others, because they lack the necessary tools to experience something similar themselves. Given that shallow affect is one of the defining features of psychopathy (Hare, 2003; Hare, et al., 2001), this could be a plausible explanation for a lack of emotional sharing. Although a primary deficit in experiencing emotions is therefore conceivable, we found no proof that this extends to action performance and somatosensation in the literature, nor did we find group differences while subjects were performing hand interactions with the experimenter during the Experience experiment (chapter 2, this volume). However, we cannot rule out that small problems in these domains do exist, given the fact that we have observed some structural deficits in premotor and somatosensory cortices in our own data and in the limited data that has already been published (de Oliveira-Souza, et al., 2008; Tiihonen, et al., 2008; Yang, et al., 2009a).

Secondly, reduced vicarious responses in psychopathy might be related to an additional problem with adequately recruiting shared circuits when observing others. Comparing the data from chapter 2 and 3, it becomes evident that the functional deviations in the psychopathy group during the Observation experiment greatly outweigh the structural abnormalities observed in chapter 3. More importantly, many of the functional abnormalities during the Observation experiment disappear when psychopathic individuals are actively engaged in feeling with the actors in the movies. If reduced vicarious responses in psychopathy were entirely due to a primary deficit in shared circuits, this would have been unlikely. Based on our own data, it is therefore likely that if psychopathy is indeed related to reduced vicarious responses, these are at least partly caused by problems with properly recruiting shared circuits when psychopathic individuals observe others. This raises the question of what mechanism could explain why reduced vicarious responses occur in psychopathy under some circumstances, but not all.

In chapter 5, we proposed that the spontaneous recruitment of shared circuits in psychopathy is less strong compared to control subjects due to deficits in the amygdala. An amygdalar deficit could impair their detection of salient information (Adolphs, 2010) and the subsequent visual processing, thereby leading to reduced vicarious responses downstream. In addition, we proposed that

psychopathic individuals may be able to wilfully compensate this reduction of vicarious responses up to a certain extent by recruiting the regulatory influences of the ventral medial prefrontal cortex.

In short, this theory indicates that psychopathic individuals are not as responsive to emotions of others, because they fail to pick up on the relevant cues that are indicative of these emotions in others. An interesting study, performed by Dadds and colleagues (2006) fits with this hypothesis. In their study, they tested emotion recognition in children with psychopathic tendencies and observed a significant impairment in the recognition of fear. When they next instructed these children to observe the eye-region, this impairment was no longer present. The authors therefore suggested that “emotion-recognition problems in psychopathy are owing in part to a failure to direct attention to the emotionally significant aspects of the environment” (Dadds, et al., 2006, page 281).

The theory of reduced vicarious responses also fits with the response modulation theory (Patterson & Newman, 1993), which predicts that individuals with psychopathy are less able to gather information from their periphery while engaged with ongoing behaviour. Our model complements this by predicting that psychopathic individuals are in general more impaired in locating salient information. This means that their ability to pick up salient information is not only impaired during task performance but also when no specific task is at hand to lead their attention away from the salient information. In addition, our theory extends the Integrated Emotion Systems (Blair, 2006), which states that moral development is promoted through the pairing of distress cues with moral transgressions. The lack of moral development in psychopathy is explained by their early reduced responses to distressing emotions of others. The saliency account of vicarious modulations explains why distressing emotions in others are less distressing for them in the first place: when psychopathic individuals fail to pick up on distress cues and thus show attenuated vicarious responses to these emotions, they will also feel these emotions less. This model generates a few predictions that could be tested.

First of all, the model predicts that variations of the BOLD response in the amygdala should modulate (parts) of the shared circuit during free viewing conditions. This prediction can first be tested in healthy control subjects, using the standard paradigms of vicarious responses (see chapter 1, this volume) without specific instructions on where to look and apply functional connectivity analyses such as psychophysiological interactions (PPI, Friston et al., 1997) or granger causality (Goebel, Roebroeck, Kim, & Formisano, 2003) to examine how the BOLD response in these regions is related. Similarly, the involvement of the ventral medial prefrontal cortex should be investigated using a comparable approach under varying task instructions and cognitive manipulations.

Secondly, the theory presented in chapter 5 suggests that task instructions are very important with relation to the emotion deficit in psychopathy. It is therefore very important to investigate this more precisely. This means that paradigms should include free viewing conditions, as well as conditions with an implicit or explicit manipulation of attention, either through task instructions or through the careful manipulation of attention through the content of stimuli. This will provide important information on how malleable the emotion deficit in psychopathy actually is and lead to information that might eventually be used in the development of therapies. It is important to note that free viewing conditions are ecologically most valid: we do not constantly ask ourselves in daily

life to feel with others or to classify their emotions; we just know what they are and act accordingly. It is therefore also under these conditions that we would like an emotional deficit to improve.

Lastly, it will be interesting to investigate subjects with schizophrenia and predominantly negative symptoms alongside psychopathy. The data from chapter 3 on structural differences suggests that schizophrenia is more related to a structural deficit in shared circuits, compared to psychopathy. This means that the schizophrenia group should be less able to wilfully modulate their vicarious responses under similarly salient conditions, compared the psychopathy group, even though they may be associated with similar deficits during free viewing conditions (but see Bastiaansen, et al., 2011' using a similar paradigm with movies of facial expressions).

6.4 IS PSYCHOPATHY REALLY AN EMPATHY DEFICIT?

Psychopathy is associated with an empathy deficit by definition (Hare, 2003; Hare, et al., 2001), but not all data in this thesis points in that direction. In chapter 2, we used three self-report questionnaires as measures of empathy. Oddly enough, the psychopathy group did not differ significantly from the control group on any of these measures. If anything, they even scored a bit more empathic compared to the controls (although not significantly so). This result stands in sharp contrast with the diagnosis they received and our neural data. Of the 18 included patients, 17 received the maximum lack of empathy score on the PCL-R and the remaining subject received an intermediate score on this item. This means that this group was almost maximally related to a lack of empathy in terms of the PCL-R. How can this discrepancy be explained?

A problem with self-report questionnaires, like the empathy questionnaires we have used in this thesis, is the necessity for self-reflection and the ability to understand others. However, psychopathy is a personality disorder, which is by definition characterized by a lack of insight. Cleckley (1982) also described this lack of insight, as noted by Lilienfeld and Fowler (2006, page 109)

In the sense of realistic evaluation, the psychopath lacks insight more consistently than some schizophrenic patients. He has absolutely no capacity to see himself as others see him. It is perhaps more accurate to say that he has no ability to know how others feel when they see him or to experience subjectively anything comparable about the situation (Cleckley, 1982, page 350)

The discrepancy between what we see these psychopathic individuals do (as reported in the PCL-R) and how they report themselves to be doing (as reported in self-report questionnaires) is often attributed to their manipulative nature and boastful disposition. But it is equally likely that these differences could be attributed to their diminished capacity for self-reflection and reduced understanding of people. It would therefore be interesting to use additional measures of self-reflection, when self-report questionnaires are unavoidable. It also raises the question as to whether the correlation between vicarious responses and empathy in healthy volunteers (e.g. Gazzola, et al., 2006; Jabbi, et al., 2007; Singer, et al., 2004) is more pronounced in individuals with relatively more insight into themselves.

In addition, the lack of empathy seen in psychopathy still needs to be more clearly defined. As self-report measures seem unreliable and the way empathy is defined in the PCL-R leaves much room for subjective interpretation, this needs to be approached in a different manner. Preferably a multifaceted method should be developed, with which subjects can be characterized in terms of an empathic profile, including facets like behavioural and physiological responses to emotions of

Box 6.1: Behavioural characteristics of psychopathy

In **chapter 4**, we examined the quality of social interactions in psychopathy, ASD and schizophrenia, compared to a healthy control group using the Autism Diagnostic Observation Schedule (ADOS Lord et al., 2000; Lord, Rutter, DiLavore, & Risi, 1999). The ADOS uses a semi-structured interview setting to judge the quality of social interaction, communication, and imagination with an examiner and was administered to the psychopathy group in order to rule out any overlap with autistic symptoms (Hansman-Wijnands & Hummelen, 2006).

The ADOS consists of four modules, of which the fourth module is used in the adult population. Because of the paucity of data on the validity of the ADOS in this population, especially in forensic settings, we decided to use the data from our three psychiatric groups to gain more knowledge about the selectivity and sensitivity of this instrument in diagnosing ASD. The ADOS is not designed to identify psychopathic features and this is illustrated by the fact that none of the recruited psychopathic individuals had to be excluded from our fMRI study based on the outcomes of this interview. Nevertheless, we were able to gain some knowledge about the psychopathy group by using this instrument.

We show that the psychopathy group behaves relatively normal within the setting of the ADOS, compared to both the schizophrenia and autism group, although the psychopathy group tend to have slightly higher (but non-significant) scores compared to the control group. A similar argument could not be made for the schizophrenia group, as this group was not distinguishable from the ASD group on all items of the ADOS. This overlap with schizophrenia indicates that the behavioural characteristics measured by the ADOS, are not unique to ASD. Nevertheless, they were not characteristic of psychopathy.

This does not mean that the interviews with psychopathic individuals were perfectly normal. During the consensus meetings, we often felt that something was odd about the interaction. However, this was not captured by any of the items of the ADOS that might have indexed this: Quality of social response, Amount of reciprocal social communication and Overall quality of rapport. It might therefore be interesting to adopt a technique recently used by Fowler and colleagues (2009). In this study lay observers watched small excerpts (5s, 10s and 20s) from an interview and had to rate psychopathic features based on short descriptions of these features. It appears that these first impressions were enough to enable a moderately reliable rating of psychopathy features, in particular where it concerned the interpersonal characteristics of their behaviour.

others, emotion recognition tasks (covering a whole range of emotions) and tasks within the domain of theory of mind. Such a test battery would then provide insight into the specific impairments in individuals with psychopathy, instead of merging them all together into one, rather vague, concept of empathy. Further research has to be conducted to determine the relevant measures that should be included into such a test-battery. A similar approach has already been adopted in the domain of schizophrenia by the National Institute of Mental Health initiative titled “Measurements and Treatment Research to Improve Cognition in Schizophrenia” (MATRICS⁵). A goal of MATRICS was to develop a Consensus Cognitive Battery (CCB) in order to standardize the diagnostic process and the evaluation of new treatments. Ideally, such a test battery should then be adopted by researchers of different labs, in addition to their main investigative paradigm if this includes components of empathy, in order to foster the comparability of results across labs.

6.5 SUB TYPING PSYCHOPATHY AND EMOTIONAL RESPONSES

An important goal for future research will be the classification of psychopathy into sub types (see also Patrick, 2006). In this thesis, we studied a highly psychopathic group of individuals; of the 18 that were included into the fMRI study, 15 received a score of 30 or higher and three subjects had a total score of at least 26. In theory, two individuals scoring 30 on the PCL-R can have diagnostic overlap on just 5 items out of 20, and thus present with an entirely different clinical picture. This has been recognized by several research groups and has led to research which focuses on for example high scores on specific factors of the PCL-R (e.g. Birbaumer, et al., 2005; Mitchell et al., 2006; Patrick, et al., 1993; Patrick, Cuthbert, & Lang, 1994). Nevertheless, much of the research on psychopathy focuses on total scores of the PCL-R, the present study included. This might explain some of the inconsistencies reported in the literature. For example, it is still not clear whether psychopathy is related more to a general blunted response to emotions (e.g. Herpertz, et al., 2001), instead of a specific impairment for just a few (e.g. Blair, 2006).

During the Observation experiment, we observed a general neural hypo-responsiveness towards our emotional stimuli in the psychopathy group (Chapter 2, this volume). A first explanation for this effect is that it might be related to a specific psychopathic subtype. Looking more closely at the items of the PCL-R indicates that the psychopathy group included in this thesis scored very high on the affective dimension of the PCL-R. It is possible that specific deficits in emotional sharing arise only when the affective impairment is mild, but that no differences between the quality of diverse emotional responses can be detected when the impairment is very pronounced. In addition, an attenuated BOLD response was not only observed during the presentation of emotional hand interactions, but also during neutral interactions. This might indicate that psychopathy is related to a more blunted social response in general.

An alternative explanation is that the emotional deficit in psychopathy is dependent upon the type of stimulus. Although most paradigms studying emotional responses in psychopathy use facial expressions or IAPS pictures, we presented our subjects with hand interactions, which has never been done before. We used the interactions of hands because they involve goal directed actions, sensations and emotions, and can thereby induce vicarious activations in all three of the systems

⁵ www.matrics.ucla.edu/

associated with empathy at once (Bastiaansen, et al., 2009; Keysers & Gazzola, 2009). Perhaps salient information was equally difficult to extract from all our stimuli, irrespective of the used emotion, which led to the general group differences we observed. In comparison, the ease with which the salient information is found in facial expressions may differ per emotion, which will necessarily lead to more pronounced group differences in the difficult emotion if the impairment does indeed depend on the detection of salient information as we have argued in chapter 5 and has previously been proposed by Adolphs (2010).

6.6 A WORD OF CAUTION

The study presented in chapter 2 is the first to show an attenuated vicarious response in a group of psychopathic individuals for actions, touch and emotions. It is also the first to specifically assess vicarious activations in a group of psychopathic individuals. Although a relatively large sample of patients was included compared to other fMRI studies on psychopathy, 18 patients is not enough to start designing new therapies based on this study alone. Further research is needed in order to replicate or falsify the findings reported in this thesis.

In addition, the model presented in chapter 5 was, unfortunately, based on a relative small dataset, as the available neuroimaging data on psychopathy is still very limited. For that reason, we have focused our discussion of the modulation of vicarious responses in psychopathy on two regions that have often been implicated in psychopathy: the amygdala and the ventral medial prefrontal cortex. It should also be noted that the discussion in chapter 5 is therefore a relatively theoretical account of the possibility of reduced spontaneous vicarious responding in psychopathy and the likely underlying mechanisms. Future research needs to determine whether this account of psychopathy stands firm, or whether it needs to be reviewed.

6.7 CONCLUDING REMARKS

In short, we suggest with our own data that psychopathy is not so much an *incapacity* to vicariously activate representations of actions, sensations and emotions of others, but more a lacking *propensity* to do so spontaneously. Although their reduced recruitment of shared circuits might be partially related to a primary deficit in experiencing emotions, the influence of external task instructions suggests an additional role for attentional processes. We have suggested that this relies on deficits in the amygdala, which impair the detection of salient information in the environment. These reduced amygdala responses can in turn lead to reduced visual processing in regions such as the pSTS, which reduces vicarious activations. We have further proposed that this detection of salient information is not only disrupted during ongoing behaviour, as suggested by the response modulation hypothesis (Patterson & Newman, 1993), but also during passive observation. As our data also suggests that psychopathic individuals are capable of regulating this reduced vicarious response, we have additionally suggested a top-down modulatory influence of the ventral medial prefrontal cortex in response to explicit external requirements.

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NEDERLANDSE SAMENVATTING

Ons dagelijks leven bestaat uit talloze interacties met andere mensen. Om die goed te laten verlopen, is het belangrijk dat we tot op zekere hoogte begrijpen hoe andere mensen zich voelen, wat ze denken en wat hun intenties zijn. Met andere woorden, we hebben empathie nodig. Empathie kun je opvatten als een paraplueterm voor meerdere processen, die allen bijdragen aan dit begrip voor andere mensen. Zo'n brede term is voor gericht wetenschappelijk onderzoek echter niet praktisch en dus hanteren wetenschappers meestal specifiekere definities van empathie, die nauw aansluiten op de onderzoeksvraag. Batson (2009) deelt deze definities grofweg in twee categorieën op, afhankelijk van de vraag die een onderzoeker zich stelt. Zo zijn sommige onderzoekers meer geïnteresseerd in de manier waarop mensen begrijpen wat anderen denken of voelen, terwijl anderen zich juist richten op het gedrag dat uit empathie voortvloeit. Stel, je gaat bij vrienden eten en jullie zitten gezellig aan de grote keukentafel, terwijl de gastheer druk bezig is met het voorbereiden van de maaltijd. Terwijl je zijn kunstige hakmethode bewondert, gaat het ineens mis en snijdt hij zich diep in zijn duim. Je bespeurt meteen een wee gevoel in je maag, staat op met knikkende knieën en voelt je bijna alsof je eigen duim is geamputeerd. Maar waarom voel je dat eigenlijk? Jij hebt toch niet in je duim staan hakken?

Met deze vraag houdt de eerste groep onderzoekers zich bezig. De tweede groep onderzoekers is vooral geïnteresseerd in het gedrag dat daarop volgt. Ga je helpen door de verbanddoos te zoeken, of loop je zenuwachtig in de rondte, onderwijl ach en wee roepend? Volgens Batson (2009) willen onderzoekers die geïnteresseerd zijn in de eerste vraag een bijzondere vorm van kennis verklaren (*hoe* begrijpen we anderen), terwijl onderzoekers die de tweede vraag proberen te beantwoorden, een bijzondere vorm van actie willen verklaren (waarom reageren we op die manier op andere mensen). Hoewel beide vragen van belang zijn, zal in dit proefschrift vooral de eerste vraag centraal staan. We hebben deze vraag bestudeerd door neurale processen in kaart te brengen bij een groep mensen voor wie diepgaande empathie in situaties zoals hierboven beschreven niet zo vanzelfsprekend is, namelijk mensen met een diagnose psychopathie. Om de neurale processen te kunnen onderzoeken hebben we gebruik gemaakt van 'Magnetic Resonance Imaging' (MRI), waarmee we wilden bekijken welke hersengebieden van belang zijn bij het observeren van andere mensen die iets doen en/of voelen. In deze samenvatting zal de opzet van dit onderzoek worden beschreven, gevolgd door de belangrijkste bevindingen, zonder al te veel gebruik te maken van neurowetenschappelijke vaktermen.

WAT IS EMPATHIE?

Om de opzet van het onderzoek in dit proefschrift goed uit te kunnen leggen, is het belangrijk dat de hier gehanteerde definitie van empathie helder is. Ook onder onderzoekers die zich bezighouden met de hoe-vraag zijn er namelijk weer verschillende definities mogelijk. Dit komt omdat er meerdere mechanismen zijn, waarmee we andere mensen kunnen begrijpen. Een voorbeeld kan dit duidelijker maken. Stel, je zit tegenover een vriendin en zij begint ineens te huilen. Voor jou komt dit niet als een verrassing, want ze heeft net te horen gekregen dat haar contract niet wordt

verlengd. Terwijl je op haar zat te wachten, wist je al dat ze waarschijnlijk verdrietig en boos zou zijn, maar ook onzeker, vooral omdat ze kinderen heeft om voor te zorgen. Al beredenerend kun je dus tot op zekere hoogte voorspellen hoe iemand zich zal voelen en waar diegene over na zal denken. Dit wordt cognitieve empathie genoemd. Onderzoek naar cognitieve empathie houdt zich dus vooral bezig met de vraag hoe mensen actief het perspectief van anderen in kunnen nemen en kunnen beredeneren wat andere mensen denken en voelen. Daarnaast wordt er ook een vorm van empathie onderscheiden die affectieve empathie heet. Dit is een meer directe vorm van empathie en heeft te maken met het meevoelen met andere mensen. Zoals in het voorbeeld van het etentje hierboven, het gevoel dat je meteen kreeg toen je vriend zich in zijn duim sneedt. Daar hoefde je niet over na te denken, dat voel je gewoon meteen. Dat proces valt onder affectieve empathie.

Er zijn dus in ieder geval twee stromingen binnen het empathie onderzoek, maar hier houdt het zeker niet op. Er zijn onderzoekers die meer categorieën onderscheiden of een ietwat andere indeling hanteren, maar dat is voor de bespreking van de resultaten in dit proefschrift niet van belang. De hoofdzaak is, dat het begrijpen van andere mensen een ingewikkeld proces is waar veel verschillende mechanismen aan ten grondslag kunnen liggen. Onderzoek naar empathie zal zich dus altijd beperken tot een onderdeel van dit fenomeen en dit proefschrift is daarop geen uitzondering. De definitie van empathie die wij hanteren luidt als volgt: er is sprake van empathie, wanneer het inbeelden of waarnemen van de gevoelens, sensaties of handelingen van een ander, een lichamelijke toestand creëert in de waarnemer, die overeenkomt met de lichamelijke toestand van de ander⁶. Deze definitie sluit dus het beste aan bij affectieve empathie en heeft weinig met beredeneren te maken. Het volgende stuk zal duidelijk maken waar deze definitie vandaan komt en wat we er eigenlijk mee bedoelen.

SPIEGELNEURONEN

De omschrijving van empathie zoals wij die hanteren, is afgeleid van het werk van De Vignemont & Singer (2006) en sluit aan bij eerdere bevindingen gedaan in het neurowetenschappelijk onderzoek naar apen en mensen. In 1992 werden in Parma door wetenschappers per toeval spiegelneuronen ontdekt bij makaken (di Pellegrino, et al., 1992), een apensoort die veel gebruikt wordt voor medisch en neurowetenschappelijk onderzoek. Tijdens dit onderzoek werden de eigenschappen van individuele neuronen in de premotor cortex bestudeerd door middel van micro-electroden in het brein. De premotor cortex is een gebied in het voorste gedeelte van de hersenen, dat onder andere belangrijk is voor het uitvoeren van doelgerichte handelingen. De apen waren getraind om, na het verschijnen van een bepaalde stimulus, objecten van verschillende grootte op te pakken. De onderzoekers ontdekten echter, dat deze neuronen niet alleen meer actief waren tijdens het uitvoeren van een handeling, zoals het pakken van een pinda, maar ook wanneer de onderzoeker een pinda van het plankje pakte.

Deze ontdekking heeft aardig wat aandacht gekregen binnen de neurowetenschappelijke literatuur. Er werd verondersteld dat dit proces de waarnemer mogelijk een soort van belichaamd gevoel van

⁶ Engelse versie: Embodied empathy occurs when the imagination or perception of the affective state, sensation or action of another, triggers a representation of this affective state, sensation or action in the self which resembles that of the other

handelingen van anderen geeft, als het ware doordat de motor cortex van de waarnemer mee resoneert met de acties van een ander (zie bijvoorbeeld Gallese, et al., 1996; Keysers & Gazzola, 2006). Er is inmiddels ook aardig wat onderzoek verricht naar dit mechanisme bij mensen. Uiteraard is het moeilijk om experimenten uit te voeren vergelijkbaar met die bij de makaak, aangezien daarvoor micro-electroden in het brein moeten worden gestopt. Het onderzoek op dit gebied is daarom vooral voortgezet met behulp van andere technieken. Vaak is hiervoor functionele Magnetische Resonantie Imaging (fMRI) ingezet, maar ook Transcraniële Magnetische Stimulatie, Electroencefalografie en Magnetoencefalografie. Omdat we in dit proefschrift gebruik hebben gemaakt van fMRI, zal deze techniek hier kort worden uitgelegd.

FUNCTIONAL MAGNETIC RESONANCE IMAGING (FMRI)

Een MRI scanner maakt gebruik van een krachtig magnetisch veld, in combinatie met radiosignalen. Door de sterke magneet worden deeltjes met een magnetisch veld (bijvoorbeeld watermoleculen) in de richting van het magnetische veld van de scanner gedraaid. Vervolgens krijgen die deeltjes een tikje, doordat de scanner een kort radiosignaal uitzendt en raken ze uit het veld geslagen. Omdat de deeltjes liever weer comfortabel in de richting van het sterke magnetische veld van de scanner willen gaan liggen, zullen ze zich na korte tijd weer naar dat veld voegen. Hierbij komt een signaal vrij, dat gedetecteerd kan worden door de apparatuur. Doordat het magnetische veld niet overal even sterk is, kan worden achterhaald waar deze signalen vandaan komen en zo kan er een beeld worden gereconstrueerd van het brein.

Door verschillende instellingen te gebruiken kunnen compleet andere plaatjes van het brein worden gemaakt. Wanneer de scanner wordt ingesteld op watermoleculen kun je hele mooie plaatjes maken van de structuur van het brein, doordat niet alle plekken even waterrijk zijn. Dit heet een structurele of anatomische scan en vormt de basis van het onderzoek dat in **hoofdstuk 3** wordt beschreven. Daarnaast kun je kijken naar het brein in actie. Er kan namelijk worden bepaald welke gebieden meer zuurstofrijk bloed bevatten in vergelijking met andere regionen. Zuurstofrijk bloed is in tegenstelling tot zuurstofarm bloed ook magnetisch en kan dus door de scanner worden beïnvloed. De hoeveelheid zuurstofrijk bloed is een maat voor de hoeveelheid neurale activiteit in dat gebied. Met deze techniek hebben we het onderzoek in **hoofdstuk 2** verricht.

FMRI EN ‘SHARED CIRCUITS’

Het grote voordeel van een MRI scanner is natuurlijk dat we niets stuk hoeven te maken om naar het brein te kijken. Zelfs de diepst liggende hersenstructuren zijn met deze techniek toegankelijk. Een MRI apparaat heeft hier echter wel even de tijd voor nodig. Om het brein in actie te meten hanteren we in dit proefschrift een ‘repetition time’ van anderhalve seconde. Dat betekent dat we elke anderhalve seconde een volledige scan van het brein maken. Dit is uiteraard een erg grove schaal in vergelijking met de snelheid van breinprocessen. Bovendien bevat een voxel⁷ van een vierkante millimeter ongeveer 10000 tot 100000 neuronen. De resultaten die we met deze techniek verkrijgen zeggen dus noodzakelijkerwijs iets over processen op de grote schaal en niet over de activiteit van individuele neuronen, zoals in het onderzoek met apen dat hierboven werd beschreven. Daarom zullen we de term spiegelneuron niet meer gebruiken. In plaats daarvan

⁷ De kleinste eenheid van MRI metingen, vergelijkbaar met een pixel in een digitaal plaatje.

spreken we bij het onderzoek naar mensen met behulp van MRI over ‘shared circuits’ (Gallese et al., 2004; Keysers & Gazzola, 2006). ‘Shared circuits’ zijn gebieden in de hersenen, die zowel geactiveerd worden wanneer jij een handeling uitvoert, een aanraking voelt of een emotie ervaart, maar ook als je dit waarneemt (of inbeeldt) bij een ander⁸. Deze definitie sluit nauw aan bij de definitie van empathie zoals die in dit proefschrift wordt gehanteerd.

Experimenten waarmee ‘shared circuits’ door middel van fMRI worden onderzocht bevatten doorgaans twee condities: een ervaringsconditie waarin je zelf iets meemaakt of doet en een waarnemingsconditie waarin je datzelfde bij een ander ziet gebeuren. De ervaringsconditie wordt gebruikt om de neurale circuits te lokaliseren die iemand aanspreekt om bepaalde handelingen uit te voeren of gevoelens te ervaren. Een kort voorbeeld van handelingen kan dit duidelijker maken. Stel je voor dat je geïnteresseerd bent in de ‘shared circuits’ voor handelingen met de hand en de voet. Je laat je deelnemers aan het onderzoek daarom kijken naar korte filmpjes van dergelijke handelingen, zoals bijvoorbeeld het openen van een zakje of het indrukken van het gaspedaal. Het kijken naar deze handelingen zal als het goed is de motorische cortex activeren, maar je weet dan nog niet of dat specifiek het gedeelte is voor handen- of voetenacties. Daarom laat je de deelnemer ook handen- en voetenacties uitvoeren. Door nu het patroon van hersenactivatie tijdens de waarneming van handenacties te vergelijken met de hersenactivatie tijdens het uitvoeren van dezelfde acties, weet je welke gebieden specifiek zijn voor handenacties en welke daarvan ook geactiveerd worden als je proefpersoon kijkt naar iemand die deze acties uitvoert.

De eerste fMRI studies bij mensen hebben zich vooral gefocust op het uitvoeren van handelingen. Vergelijkbaar met het onderzoek bij apen, is onderzocht of mensen ook hun eigen motorisch neurale repertoire aanspreken wanneer ze anderen waarnemen die acties uitvoeren. Het blijkt dat we dit inderdaad doen als we andere mensen handelingen zien uitvoeren (Dinstein, et al., 2007; Gazzola & Keysers, 2009; Grèzes, et al., 2003; Iacoboni et al., 1999; Ricciardi et al., 2009; Turella, et al., 2009) maar ook als we horen dat andere mensen handelingen uitvoeren (Gazzola, et al., 2006; Ricciardi, et al., 2009).

Het onderzoek bij mensen beperkte zich echter niet tot handelingen. Men was ook geïnteresseerd in het observeren van emoties bij anderen mensen. Ook hier geldt weer, als je echt wilt weten of een gebied een ‘shared circuit’ is voor een bepaalde emotie, dan heb je een observatie- en een ervaringsconditie nodig. Dit is precies wat Wicker en collegae (2003) deden in een studie die voor het eerst aantoonde dat mensen een gebied in de hersenen activeren (de insula) wanneer ze vieze geurtjes ruiken, maar ook wanneer ze andere mensen dat zagen doen.

Dat de insula inderdaad onderdeel is van een ‘shared circuit’ voor walging, werd later bevestigd in een studie waarin deelnemers vieze smaakjes proefden en anderen dat ook zagen doen (Jabbi, et al., 2007): Een gedeelte van de insula werd geactiveerd tijdens beide condities. Sterker nog, dat gedeelte werd ook actief als de deelnemers aan het onderzoek verhaaltjes met walgelijke inhoud lazen (Jabbi et al., 2008). Verder onderzoek heeft dit soort overlap in andere hersengebieden

⁸ De letterlijke vertaling van ‘shared circuits’ is gedeelde circuits. Wat daarmee bedoeld wordt is dat deze gebieden in ieder geval worden aangesproken tijdens twee omstandigheden: wanneer je zelf iets meemaakt en wanneer een ander iets meemaakt.

aangetoond voor pijn (Costantini et al., 2008; Jackson et al., 2005; Lamm et al., 2007; Morrison et al., 2004; Singer, et al., 2004), maar ook voor gewone aanrakingen (Blakemore et al. 2005a; Ebisch et al., 2008, Keysers, et al. 2004).

Het lijkt er dus op dat dit mechanisme niet alleen bestaat voor acties, maar ook voor emoties en aanrakingen. Verschillende onderzoekers stellen dat dit mechanisme je helpt om anderen te begrijpen (e.g. Bastiaansen, et al., 2009; Gallese, et al., 2004; Iacoboni & Dapretto, 2006; Keysers, et al., 2010; Pineda, 2008; Preston & de Waal, 2003; Rizzolatti & Craighero, 2004). En inderdaad, een aantal onderzoeken laten zien dat ‘shared circuits’ sterker worden aangesproken door mensen die aangeven meer empathisch te zijn (Gazzola, et al., 2006; Jabbi, et al., 2007; Singer et al., 2004). Vandaar dat dit mechanisme ook interesse opwekte bij onderzoekers die zich bezig houden met mentale stoornissen. Er zijn namelijk een aantal mentale stoornissen die samengaan met een verminderd inlevingsvermogen in andere mensen en dit zou verband kunnen houden met allerlei problemen op sociaal gebied, zoals het hebben van vrienden, het behouden van een baan en grensoverschrijdend gedrag. De stoornis die centraal staat in dit proefschrift is psychopathie, maar ook stoornissen als autisme en schizofrenie worden in verband gebracht met problemen met empathie.

‘SHARED CIRCUITS’ BIJ MENSEN MET PSYCHOPATHIE

De hoofdvraag van dit proefschrift is of mensen met psychopathie de ‘shared circuits’ voor handelingen, emoties en aanrakingen minder activeren wanneer ze anderen waarnemen die een handeling uitvoeren, een emotie ervaren of een aanraking voelen. Psychopathie is een mentale stoornis, die valt onder de categorie persoonlijkheidsstoornissen. Persoonlijkheidsstoornissen worden gekenmerkt door een star en duurzaam patroon van gedachten, gevoelens en gedragingen (American Psychiatric Association, 2000). Om mentale stoornissen te classificeren maakt men veelal gebruik van de Diagnostic and Statistical Manual of Mental Disorders IV - Text Revision (DSM-IV-TR, American Psychiatric Association, 2000). Psychopathie staat echter niet vermeld in dit handboek. Er wordt wel vrij veel onderzoek naar de stoornis gedaan en elementen van deze psychische aandoening lijken een grotere rol te gaan spelen in de nieuwe versie van de DSM (zie hiervoor DSM5.org).

De standaard die op dit moment echter wordt gehanteerd met betrekking tot de diagnose psychopathie is niet de DSM-IV-TR, maar de Psychopathy Checklist - Revised (PCL-R, Hare, 2003; Hare, Vertommen, Brink, & Ruiters, 2001). De PCL-R bevat een lijst met 20 symptomen, die door een getrainde beoordelaar worden gescoord op basis van dossiermateriaal en een interview. Elk item krijgt een score van 0, 1 of 2, waarbij een hogere score betekent dat de eigenschap duidelijker aanwezig is. Dit kan leiden tot een maximale score van 40, waarbij momenteel in Nederland een score van 26 wordt gehanteerd voordat men spreekt van psychopathie. De PCL-R is ontwikkeld om mensen met een crimineel verleden te beoordelen (Patrick, 2009) en is ook minder geschikt om buiten deze setting toe te passen. Dit omdat er doorgaans geen uitgebreid dossiermateriaal is over iemand zonder crimineel verleden of langdurige hospitalisatie, maar ook omdat er nogal een focus ligt op de aard van de criminele activiteiten. Iemand zonder crimineel verleden zal daarom per definitie lager scoren op deze lijst, zelfs als de persoonlijkheidskenmerken die bij psychopathie horen in essentie wel aanwezig zijn.

De items van de PCL-R kunnen worden onderverdeeld in een aantal categorieën. De meest gehanteerde onderverdeling deelt de items op in inter-persoonlijke / affectieve items en gedragsitems. Deze laatste items vertonen veel overeenkomst met antisociale persoonlijkheidsstoornis, een categorie die wel in de DSM-IV-TR voorkomt (American Psychiatric Association, 2000). De nadruk bij psychopathie volgens de PCL-R ligt echter veel meer op symptomen die aangeven hoe een individu met anderen omgaat en kwalificaties over zijn of haar gevoelsleven. Een van de items van de PCL-R beschrijft het empathiegebrek bij individuen met psychopathie. Een onderdeel daarvan luidt als volgt: ‘Elk besef van de pijn, angst of het ongemak van anderen is louter abstract en verstandelijk’ (Hare, Vertommen, Brink, & Ruiters, 2001, pagina 73). Psychopathie wordt in deze definitie dus vooral gekoppeld aan de (afwezigheid van) een response op emoties van anderen en dus een deficiëntie in affectieve empathie.

Ook psychofysiologisch onderzoek naar de emotionele responsiviteit van mensen met een psychopathie diagnose wijst in die richting. Daaruit blijkt dat ze minder reageren op de emoties van anderen (e.g. Aniskiewicz, 1979; Blair, et al., 1997; Levenston, et al., 2000; Patrick, et al., 1993). Bovendien blijken mensen met een hoge score op de psychopathie vragenlijst ook minder goed te zijn in het herkennen van emoties bij anderen (e.g. Bagley et al., 2009; Blair et al., 2002; Blair et al., 2004; Hastings et al., 2008; Kosson et al., 2002). Onderzoek naar de meer cognitieve kant van empathie wijst uit dat mensen met psychopathie meestal niet verschillen van anderen op deze vorm van empathie (Blair et al., 1996 ; Dolan & Fullam, 2004; Richell et al., 2003 ; Sommer et al., 2010, maar zie Dolan et al., 2004).

Naast een tekort aan affectieve empathie, wordt psychopathie ook gekenmerkt door een verhoogd risico voor zowel instrumentele als reactieve agressie (Blair, 2006; Cornell, et al., 1996). Reactieve agressie is een reactie op een waargenomen bedreiging of provocatie. Instrumentele agressie is juist het gebruik van geweld met het doel daar iets mee te bereiken (Cornell, et al., 1996). In de literatuur is al lang geleden de link gelegd tussen empathie en agressie (e.g. Feshbach & Feshbach, 1982; Miller & Eisenberg, 1988). Miller and Eisenberg postuleerden bijvoorbeeld dat personen die zelf de negatieve gevolgen voor anderen voelen, veroorzaakt door hun eigen agressieve gedrag, minder geneigd zijn om hun agressie voort te zetten of om agressie te vertonen in de toekomst (Miller & Eisenberg, 1988, pagina 324). Verschillende studies bevestigen deze (kleine) negatieve relatie tussen agressie en empathie in kinderen (Miller & Eisenberg, 1988; maar zie Lovett & Sheffield, 2007), adolescenten (Jolliffe & Farrington, 2004; Lovett & Sheffield, 2007) en volwassenen (Jolliffe & Farrington, 2004).

Het verhoogde niveau van instrumentele agressie kan worden opgevat als een teken van gebrekkige morele socialisatie (Blair, 2007). Een interessant model in dat opzicht is het ‘Violence Inhibition Model’ (VIM, Blair, 1995), waarin het belang van empathie voor morele ontwikkeling wordt benadrukt. Aan de basis van het VIM staat dat het leed van anderen een negatief gevoel opwekt bij degene die dit leed waarneemt. Wanneer het leed van anderen door onze eigen acties werd veroorzaakt, zullen de twee aan elkaar worden gekoppeld. Na verloop van tijd wordt die koppeling steeds sterker, waardoor zelfs het inbeelden van zo’n zelfde handeling ons al een slecht gevoel zal geven. Hierdoor zal de frequentie van dit soort gedragingen afnemen.

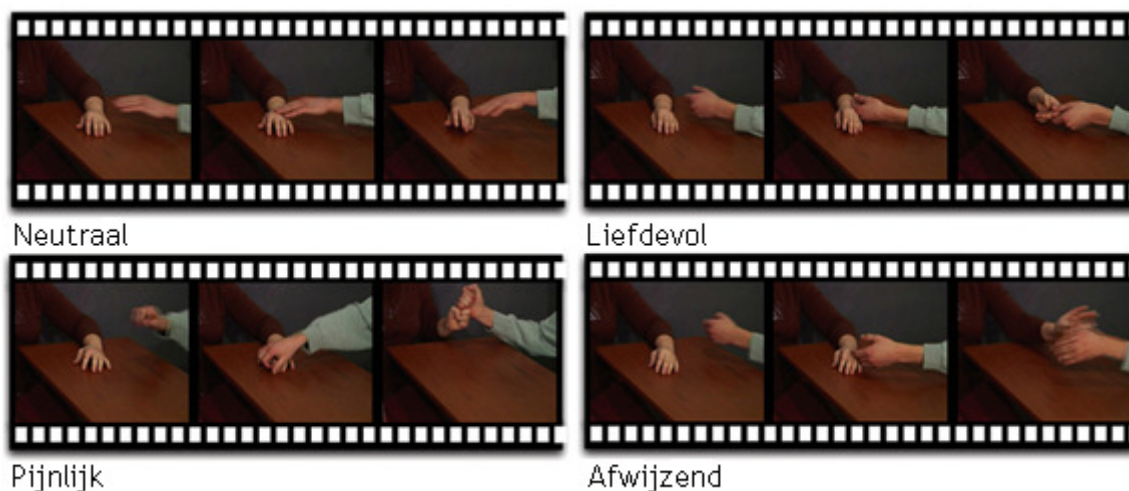
Het VIM werd door Blair (1995) ontwikkeld om de gebrekkige morele ontwikkeling van individuen met psychopathie te verklaren. Volgens Blair (1995) zijn mensen met psychopathie minder gevoelig voor het leed van anderen en daardoor zal ook de morele ontwikkeling minder sterk zijn. Bovendien stelt het model dat mensen met psychopathie ook minder in staat zijn om de koppelingen te leggen tussen bepaald gedrag en de gevolgen daarvan. De ontwikkeling van dit model heeft sindsdien niet stilgestaan en is verder gegaan onder de naam 'Integrated Emotion Systems' om nieuwe ontwikkelingen op het gebied van het onderzoek naar psychopathie te integreren met het eerdere model (Blair, 2006; Blair, et al., 2005). Een onderdeel van het oude model speelt echter nog steeds een rol, namelijk de ongevoeligheid van individuen met psychopathie voor het leed van anderen.

Met dit model wordt dus een verklaring gezocht voor hoe een gebrekkige moralisatie en instrumentele agressie kunnen voortvloeien uit een verminderde empathie voor de emoties van anderen. Het model biedt dus een verklaring voor het gedrag van deze groep mensen. Echter, in dit proefschrift hebben wij ons bezig gehouden met het onderliggende mechanisme van empathie: Hoe kan het dat we andere mensen kunnen begrijpen en waarom is dit bij mensen met psychopathie minder vanzelfsprekend. We hebben dat onderzocht door te besturen of mensen met psychopathie de 'shared circuits' voor handelingen, aanrakingen en emoties minder activeren, vergeleken met normaal ontwikkelde mensen.

HET PARADIGMA

De uitwerking van deze vraagstelling wordt beschreven in **Hoofdstuk 2** van dit proefschrift. Tijdens dit onderzoek lieten we de deelnemers korte filmpjes zien van handen die elkaar op verschillende manieren aanraken. Deze aanrakingen konden neutraal zijn of hadden een emotionele connotatie (liefdevol, pijnlijk of afwijzend). Een filmpje begon altijd met één hand in beeld, waarna een andere hand het beeld inkwam om de aanraking te initiëren. In de neutrale filmpjes werd de ene hand bijvoorbeeld aangetikt door de andere hand om de aandacht te krijgen. In de liefdevolle filmpjes werd de hand die al in beeld was gestreeld door de andere hand. De pijnlijke aanrakingen bevatten knijpen, slaan of het pijnlijk ombuigen van een vinger. De laatste soort film representeerde een afwijzende aanraking, waarbij de ene hand de ander vriendelijk probeert aan te raken, maar wordt weggeduwd door de andere hand. In Figuur 1 kun je screenshots zien van een voorbeeld van elk van deze filmtypen.

De filmpjes gebruikten we tijdens het eerste en tweede gedeelte van ons MRI onderzoek. Een belangrijk verschil tussen het eerste en tweede gedeelte, zat hem in de instructie die we aan de deelnemers gaven. We vroegen onze proefpersonen in het eerste gedeelte om naar de films te kijken, alsof ze naar een van hun favoriete films zaten te kijken. We vertelden ze niet waar ze specifiek op moesten letten en wat het doel hiervan was. Dit noemden we het Observatie experiment. Tijdens het tweede gedeelte lieten we de proefpersonen de films nog een keer zien, maar nu met een andere instructie: We wezen een van de twee handen aan tijdens het onderzoek met behulp van een pijl en vroegen nu of ze zich wilden inleven / meeleven met de aangewezen hand. Dit noemden we het Empathie experiment. Tijdens het derde gedeelte van het onderzoek lieten we de proefpersonen soortgelijke interacties meemaken in de scanner, door dezelfde aanrakingen uit te voeren met de proefleider. Dit noemden we het Ervaringsexperiment.



Figuur 1: Voorbeelden van het gebruikte filmmateriaal. Elk type film wordt weergegeven door drie representatieve frames uit een filmpje.

HET 'SHARED CIRCUITS' ONDERZOEK

We wilden hiermee een aantal dingen onderzoeken. Zoals hierboven al kort werd aangestipt, stond de volgende vraag in dit proefschrift centraal: Activeren mensen met een diagnose psychopathie de 'shared circuits' voor handelingen, aanrakingen en emoties minder vergeleken met controle proefpersonen wanneer ze mensen observeren die handelingen uitvoeren of aanrakingen en emoties ervaren? Deze vraag kunnen we met het Observatie experiment beantwoorden. Het Observatie experiment bevatte namelijk geen specifieke instructie. De gedachte hierachter was, dat dit het meest overeenkomt met het dagelijks leven: Normaal staat er ook niet iemand naast je die je attent maakt op de belangrijkste elementen uit je omgeving. Tijdens dit experiment vonden we dat er een groot netwerk in het brein minder actief was in de psychopathie groep vergeleken met de controle groep. Sterker nog, er was geen enkel hersengebied meer actief was voor de psychopathie groep. Dit netwerk van hersengebieden omvatte ondermeer 'shared circuits' voor handelingen, aanrakingen en emoties, maar ook andere gebieden.

Ten tweede wilden we onderzoeken of de verschillen tussen de twee groepen konden worden beïnvloed door specifieke instructies. Om dat te kunnen bestuderen, instrueerden we onze deelnemers om tijdens het Empathie experiment mee te voelen met de aangegeven hand. Op die manier stuurden we als het ware de aandacht naar de relevante onderdelen van de films. We zagen dat deze instructie de groepsverschillen inderdaad veranderde. Zoals hierboven beschreven vonden we tijdens het Observatie experiment geen enkel hersengebied dat meer actief was voor de psychopathie groep, vergeleken met de controle group. Echter, tijdens het Empathie experiment was het beeld veel genuanceerder. Er waren nu ook meerdere hersengebieden, die sterker geactiveerd werden door de psychopathie groep. En als we beide experimenten direct met elkaar vergeleken, dan bleek het 'activatieniveau' van een aantal hersengebieden tijdens het tweede experiment significant minder van de controle deelnemers af te wijken, vergeleken met de eerste taak. En dat terwijl er geen enkel hersengebied was dat meer ging verschillen van de controle proefpersonen. Dit betekent dus dat een instructie wel degelijk iets uitmaakt: Ook al waren er nog steeds genoeg verschillen, deze verschillen werden kleiner na instructie.

Ten derde wilden we weten of de twee groepen deelnemers van elkaar verschilden, wanneer ze soortgelijke interacties uitvoerden met de experimentator. De theorie achter 'shared circuits' is namelijk dat je je eigen gevoelens, ervaringen en handelingen 'heractiveert' wanneer je naar anderen kijkt die iets meemaken of doen. Het is dus mogelijk dat er een primair probleem met het uitvoeren van handelingen en/of verwerken van emoties en sensaties ten grondslag ligt aan een verminderde activatie van 'shared circuits'. Om dat uit te zoeken, lieten we onze deelnemers specifiek die dingen meemaken, die ze ook in de films hadden gezien. Daaruit kwam naar voren, dat beide groepen niet significant van elkaar verschilden in hersenactiviteit, wanneer ze soortgelijke interacties zelf uitvoerden.

Samengevat lijken mensen met psychopathie de 'shared circuits' voor acties, aanrakingen en emoties dus minder te activeren tijdens een passieve observatie conditie. Dit kan echter gedeeltelijk worden genormaliseerd door een gerichte instructie te geven, waarmee de aandacht wordt gevestigd op relevante onderdelen van de film. Dat zou kunnen betekenen dat mensen met psychopathie tot op zekere hoogte wel mee kunnen voelen met andere mensen, maar dat ze dat spontaan niet zo sterk doen vergeleken met controle proefpersonen. Dit komt overeen met de resultaten uit het Ervaringsexperiment. Daaruit bleek namelijk dat beide groepen niet significant van elkaar verschilden, wanneer ze soortgelijke handelingen uitvoerden: Een aanwijzing dat beide groepen deze gebieden wel kunnen aanspreken wanneer dat nodig is.

STRUCTURELE HERSENVERSCHILLEN

In hoofdstuk 3 hebben we de vraagstelling van dit proefschrift op een andere manier benaderd. In dit hoofdstuk hebben we namelijk onderzocht of er een structurele deficiëntie ten grondslag kan liggen aan de mogelijkheid van deze groep om 'shared circuits' aan te spreken. We hebben dit gedaan door de structurele hersenscans te analyseren met behulp van 'voxel-based morphometry'. Met deze techniek kunnen we bepalen of het hersenvolume van bepaalde gebieden in de ene groep afwijkt van een andere groep. We hebben de psychopathie groep op deze maat vergeleken met de controle groep, met een focus op 'shared circuits'. Bovendien hadden we de mogelijkheid binnen onze onderzoeksgroep, om dit gedeelte van de studie uit te breiden met twee additionele onderzoekspopulaties, die ook in verband worden gebracht met deficiënties in shared circuits: Autism Spectrum Stoornissen (ASS, Iacoboni & Dapretto, 2006) en schizofrenie (Gallese, 2003; Salvatore, et al., 2007). In onze data zagen we dat er vooral bij schizofrenie sprake was van een verminderd volume in deze gebieden. Ook bij psychopathie vonden we de afwijkingen vooral in 'shared circuits', al moet worden gezegd dat de hoeveelheid in totaliteit klein was. Vergeleken met de andere twee groepen vielen de verschillen in hersengrootte bij de ASS groep vooral buiten gebieden die behoren tot de 'shared circuits'. We hebben dit ook vergeleken met de literatuur, door een gestructureerde meta-analyse uit te voeren op de gepubliceerde data en vonden dat de gerapporteerde resultaten voor ASS en schizofrenie in de literatuur globaal overeenkwamen met onze data. Helaas konden we voor psychopathie geen meta-analyse doen, aangezien er nog te weinig onderzoek naar deze groep is gedaan met behulp van neuroimaging methoden.

SYNTHESE

De twee empirische hoofdstukken die hierboven worden beschreven, wijzen erop dat mensen met een psychopathie diagnose de ‘shared circuits’ voor handelingen, sensaties en emoties wel kunnen activeren, maar dit niet even consistent of sterk doen vergeleken met een controle groep. Uit **hoofdstuk 2** blijkt namelijk dat ze niet verschillen van de controle proefpersonen als ze de handelingen zelf uitvoeren en nauwelijks in ‘shared circuits’ wanneer ze zich actief proberen in te leven in de handen op het scherm (het Empathie experiment). Hierbij moet wel worden aangemerkt dat ze nog steeds van de controle proefpersonen verschillen in gebieden die somatosensorische informatie verwerken. Deze gebieden behoren tot de ‘shared circuits’. Ook in hoofdstuk 3 vonden we dat een aantal hersengebieden in somatosensorische en motorische gedeelten, een afwijkend volume hadden, vergeleken met de controle proefpersonen. Bovendien, tijdens het Empathie experiment activeerde de groep met psychopathie een aantal hersengebieden sterker, die geassocieerd zijn met het redeneren over anderen mensen (Amodio & Frith, 2006; Van Overwalle & Baetens, 2009), maar niet met spontane empathie (Van Overwalle & Baetens, 2009). Verder waren in deze groep ook hersengebieden over-geactiveerd, die betrokken zijn bij emotionele herwaardering (Ochsner et al., 2004). Het lijkt dus alsof deze groep meer cognitieve controle uitoefende tijdens deze taak, in vergelijking met de controle groep.

In **hoofdstuk 5** stellen we een model voor dat een aantal theorieën met betrekking tot psychopathie met elkaar verbindt. In dit hoofdstuk suggereren we, dat de spontane activatie van ‘shared circuits’ in psychopathie verminderd is in vergelijking met een controle groep, ten gevolge van een probleem met het spontaan richten van de aandacht op de juiste elementen in de omgeving. Dit zou te maken kunnen hebben met de amygdala. De amygdala is een klein hersengebiedje dat vaker in verband is gebracht met psychopathie. Volgens Adolphs is de amygdala belangrijk bij de detectie van saillante informatie (Adolphs, 2010) en een disfunctionele amygdala zou met dit proces kunnen interfereren. Wanneer dit inderdaad het geval is bij mensen met een diagnose psychopathie, dan betekent dit dat zij zonder duidelijke sturing van de aandacht wellicht minder goed de juiste signalen oppikken van andere mensen. Een verminderde activatie van ‘shared circuits’ hangt daarmee samen. We stellen verder voor dat dit kan worden gecompenseerd door de regulerende invloed van de prefrontale cortex (zie ook Harenski & Kiehl 2010; Ochsner, et al., 2004). Dit hangt samen met de observatie dat gedeelten van de prefrontale cortex ook meer actief waren in de psychopathie groep, terwijl ze het Empathie experiment uitvoerden. In ons model gaan we er echter ook vanuit dat een gedeelte van het verschil tussen beide groepen in de activering van ‘shared circuits’ zal moeten worden gerelateerd aan meer primaire tekorten in het ervaren van emoties.

ONDER VOORBEHOUD

Het is belangrijk om een aantal kanttekeningen te plaatsen bij de conclusies van dit proefschrift. Ten eerste is de hoeveelheid neuroimaging data met betrekking tot psychopathie nog erg klein. Dit is bovendien de eerste fMRI studie met een dergelijke vraagstelling. Daarom is het belangrijk dat we nog niet teveel ophangen aan de resultaten van dit onderzoek. Voordat we de resultaten kunnen gebruiken om bijvoorbeeld voorstellen voor nieuwe therapieën te doen, zullen we de resultaten op zijn minst moeten kunnen repliceren. Ten tweede is psychopathie is een heterogene stoornis, wat betekent dat het ene individu nogal van het andere kan verschillen, ook al hebben ze dezelfde score

op de PCL-R. Het is daarom belangrijk, dat er meer aandacht wordt besteed aan het onderverdelen in subtypen. Dit is echter een lastig probleem, omdat de onderzoeksgroepen daar over het algemeen niet groot genoeg voor zijn en in dit proefschrift is dat dan ook nog niet gebeurd.

DANKWOORD

Het is een aparte gewaarwording om na zoveel jaar ineens te zitten kluiven op het dankwoord. In de loop der tijd zijn er veel mensen direct of indirect betrokken geweest bij dit proefschrift en ik wil dan ook graag gebruik maken van de gelegenheid om ze te bedanken.

I would first like to take the opportunity to thank **Christian and Hans**. This project has been a tremendous challenge in many ways and it was great that you have given me the chance to take it on. Christian, I have great respect for your sharp mind, which has helped me formulate the ideas in this thesis and connect the different disciplines that are joined in this study. Hans, bedankt dat je deur altijd openstond voor inspirerende discussies en morele ondersteuning.

Arnold, zonder jou hadden we het project nooit van de grond gekregen. Door je jarenlange ervaring in de TBS-wereld, heb je ons meteen naar de juiste deuren weten te begeleiden. Ik heb erg veel bewondering voor de toewijding waarmee jij je inzet voor je patiënten en de verbreding van kennis. Ik hoop dat we in de toekomst samen verder kunnen werken aan de koppeling tussen neurowetenschappelijk onderzoek en de klinische praktijk.

I would also like to thank the reading committee, **André Aleman, James Blair and Eveline Crone**. There was little time to read the whole thesis and I am grateful that you were able to manage this on such short notice.

Paranimfies. Jullie ondersteuning is *bitter genootzaakt* geweest! Nu op naar een meer dan *schappelijke* afsluiting van de cyclus. **Marleen**, de luchtige en opgeruimde manier waarop je met veel dingen omgaat is heerlijk rustgevend en de openheid waarmee je lief en leed deelt buitengewoon verfrissend. **Jojanneke**, de kracht, intensiteit en overtuiging waarmee jij je dingen doet bewonder ik erg. Jij weet waar je staat! Helaas is dat nog steeds in Nederland. Voorlopig zullen we onze grappen dus nog even vleugels moeten geven. Ik kan me geen betere 'home base' voorstellen dan jullie twee.

En dan natuurlijk dank aan alle leden van het Social Brain Lab die nu nog niet voorbij zijn gekomen. **Valeria**, the first steps I took in my PhD were together with you. Thank you for the warm welcome you gave me into the lab. **Mbemba**, gelukkig heb ik je aanstekelijke lach weer terug gevonden. Heel fijn dat jij en **Anita** me zo thuis laten voelen in de States. **Jo**, thank you for your methodological insight and keeping me hydrated. Thank you, **Marc**, for the inspiring discussions on and off topic. **Luca**, gelukkig was er ook altijd iemand bereid om nerdengesprekken met me te voeren. Dank ook voor de smakelijke kooksessies en het serieus nemen van een proost. Bedankt ook **Nikola** voor de heerlijke koffie, **Idil** voor de geinige kleinigheidjes die af en toe op mijn bureau verschenen, **Christiaan, Leonardo** for knowing just about anything, **Piray, Annerose** en **Jayne** voor de leuke tijd. **Lianne**, het was fantastisch om te zien hoeveel jij binnen korte tijd voor elkaar krijgt. En sorry dat het nog steeds niet op papier staat. Ook wil ik graag **Margo** en **Jacqueline** bedanken voor de fijne samenwerking.

Anita, jij maakt daar beneden in de scanner natuurlijk genoeg mee, maar dit project is vast voor jou ook wel bijzonder geweest. Ik heb het in ieder geval erg gewaardeerd dat je zo betrokken bent geweest bij mijn project en hebt geholpen met het uitdenken van de logistieke en veiligheidsaspecten. En dan is dit ook de plek om de **mannen en vrouwen van de beveiliging van de Mesdag** te noemen. Bedankt voor de altijd plezierige en professionele begeleiding van het project. Achteraf kunnen we zeker stellen dat we daar met zijn allen voor de volle 100% in zijn geslaagd.

Marinus, Erwin, Swanny, Marlies en Ruud, bedankt voor de peptalks en de gezellige, warme sfeer die er altijd hangt in jullie groep. Ik heb me erg thuisgevoeld bij de onderzoeksafdeling, ook al kon het grootste deel van het werk helaas niet bij jullie worden uitgevoerd. Verder wil ik ook graag de **onderzoeksafdeling van Veldzicht** bedanken voor al hun belangeloze ondersteuning, met natuurlijk in het bijzonder **Irma**.

Lieve **Marte**, voor het eerst sinds lange tijd zijn we uit elkaar. Ergens had ik verwacht dat ik je hier in Bethesda wel weer door de gangen zou zien lopen, want dat is toch zoals het altijd gaat met ons? Helaas ben ik je hier nog niet tegengekomen. Ik ga je erg missen.

Verder wil ik iedereen van het nic bedanken die ik nog niet genoemd heb: **Ana, Branislava, Dave, Diana, Edith, Esther, Jan-Bernard, Janine, Katrien, Katharina, Marten, Martijn, Peter, Ramona, Richard en Ruud**. Ik ga de ongedwongen - loop maar binnen sfeer - op het nic erg missen. Er zijn heel wat problemen opgelost bij het koffieapparaat. Met een speciaal bedankje aan **Hedwig**, voor al die gezelligheid op het bankje. En natuurlijk **Remco**, voor de onmisbare discussies over de juiste (als die al bestaat) manier van het analyseren van neuroimaging data.

Op de gang in het nic is ook nog iets moois ontstaan in de vorm van de **Dolma Dames, Anne-Marthe, Leonie, Lisette, Marte, Jojanneke en Marleen**. Niet meer te herkennen aan de huidige vorm van activiteiten, maar geëvolueerd uit het moeizame en langdurige handwerk dat gepaard gaat met het maken van de beroemde pakketjes rijst. Ik hoop dat we de traditie kunnen voortzetten en nog lang 'dolma's' blijven draaien, bij voorkeur op dinsdag of donderdag. En natuurlijk ook bedankt voor alle hulp!

Annelies, een van de beste ongeplande uitstapjes van mijn PhD was 'het ADOS project'. Ik ken niet veel mensen die zo oprecht geïnteresseerd zijn in anderen als jij. Dat betekent dat ik niet alleen veel van je geleerd heb op het gebied van ASS, maar ook nog eens regelmatig mijn verhaal aan je kwijt kon. Bedankt daarvoor.

Petra en Simone, bedankt ook voor jullie inbreng aan het 'ADOS-project'. Zonder jullie hadden we het nooit voor elkaar gekregen, maar nog belangrijker, ik heb veel geleerd van jullie ervaren klinische blik.

Al met al lijkt het de afgelopen maanden alsof het proefschrift het enige is dat telt op deze wereld. Gelukkig heb ik in de aanloop naar de afronding ook nog dingen naast het wetenschappelijke werk gedaan en zelfs samen met mensen die niet door dezelfde werkgever werden betaald. Lieve **vrienden**, bedankt dat jullie er zijn. Ik hoop dat jullie me in de komende maanden weer terug kunnen begeleiden naar de echte wereld. Ik kan daar denk ik wel wat hulp bij gebruiken. Ik wil hier

Matty nog even extra bedanken voor de hele tastbare bijdrage aan dit boek: de geweldige kaft. Als de inhoud van het boek je niet interesseert, dan is het nog altijd een prachtexemplaar geworden voor aan de muur.

Theo en **Gebbe**, mijn lieve kleine broertjes. Ik weet dat ik altijd op jullie kan rekenen, ook al is de fysieke afstand nu even te groot om snel te overbruggen. Ik maak wel een lijstje van iedereen die hier naar tegen me doet, dan ligt dat klaar zo gauw jullie een keer de oversteek wagen. **Gebbe** en **Theo** natuurlijk niet zonder **Chantal** en **Suus** en gelukkig maar. Lieve schoonzusjes, bedankt ook dat jullie er zijn, samen met jullie zijn we een completere familie.

Papa en **mama**. Bedankt dat jullie altijd voor me klaarstaan. Zonder jullie ondersteuning waren een heleboel dingen veel lastiger geweest en was er helemaal geen dankwoord, laat staan proefschrift geweest. Verhuur mijn zolderkamertje voorlopig nog maar niet aan een ander, want misschien ga ik de hutspot met klapstuk wel teveel missen.