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OFFENDERS WITH MENTAL DISORDER: PSYCHOSOCIAL AND NEUROBIOLOGICAL ASPECTS

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Cover illustrate cortical thickness from study III, by Simon Fristedt Eskildsen
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To the three men in my life
Robert, Nikolaj and my dad

ABSTRACT

The main hypothesis of this thesis is that certain functions, or symptoms, in mentally disordered offenders are connected to biological correlates. There is no specific diagnosis that explains antisocial or violent behaviour. Among offenders some functions or symptoms are considered more common, such as impulsivity and reduced empathy. To date, biological factors related to antisocial and violent behaviour are still not fully understood. This is particularly true in the field of brain imaging, where research-findings are mixed and sometimes contradictory. Biological mechanism associated with antisocial and violent behaviour may have an impact on several forensic psychiatric areas, such as diagnostic assessments, provision of treatment options, risk assessment, and treatment evaluation. Therefore, increased knowledge of these biological factors will be important on many levels in forensic psychiatry and the criminal justice system. In this thesis mentally disordered offenders are studied, using a multi-dimensional approach, with parallel investigation of behaviour and peripheral physiology as well as brain structure and function. The findings imply that there are specific subgroups of offenders. These subgroups differ in crime scene behaviour, psychosocial functioning, and emotional processing, reflected by peripheral physiological reactivity as well as cerebral emotional processing.

In **study I**, crime scene behaviour was studied and the results suggest subgroups of offenders, with respect to differences in psychosocial factors and crime scene behaviour. In **study II**, emotional reactivity was investigated by measuring peripheral physiological reactivity in response to negative and neutral pictures. In this study, healthy controls and mentally disordered offenders, with different degrees of antisocial behaviour but without psychopathy, were studied. The offenders showed significant lower physiological reactivity in comparison to the controls. Moreover, the attenuated emotional reactivity was a characteristic shared by the offenders overall, thus antisocial behaviour was not a differential factor. In **study III**, cerebral structural changes were investigated. Cortical thickness was compared between a group of mentally disordered offenders with lack of empathy and healthy controls. The offender group showed thinner cortex in the frontal lobes bilaterally. Also, a negative correlation was found between scores on the psychopathy checklist and cortical thickness in the frontal lobes bilaterally, the right temporal lobe, and right hemisphere, suggesting that these areas are of importance in psychopathy. In **study IV**, emotional reactivity, reflected by cerebral functioning, was assessed with fMRI, during presentation of fearful and neutral facial expressions. Mentally disordered offenders were compared to healthy controls, moreover, two subgroups of offenders were also compared, the psychopathy group and the autism spectrum disorder group. The results indicated higher cerebral activity in specific brain areas in the mentally disordered offenders, implying altered perception and processing of fearful facial expressions in these subjects. Also, there were differences between the subgroups in the communication between the amygdala and other parts of the limbic system, suggesting that processing of fearful facial expressions differ in the two groups.

The results from this thesis suggest that biological factors, in addition to social and psychological factors should be considered in order to advance the understanding of

different mechanism underlying antisocial and violent behaviour. Future studies are needed to confirm some of the findings, to further increase knowledge about these biological factors.

SVENSK SAMMANFATTNING

Hypotesen i denna avhandling är att vissa funktioner och symptom hos psykiskt störda lagöverträdare kan kopplas till biologiska korrelat. Det finns ingen enskild diagnos som kan förklara antisocialt eller våldsamt beteende. Bland lagöverträdare finns dock vissa drag som förekommer ofta, så som impulsivitet och brist på empati. Det är i dagsläget inte helt klarlagt på vilket sätt biologiska mekanismer ligger bakom antisocialt och våldsamt beteende. Detta gäller särskilt inom forskningsfältet hjärnabbildning, där resultaten är blandade och ibland till och med motsägelsefulla. Ökad kunskap om kopplingar mellan biologiska mekanismer och antisocialt och våldsamt beteende kan ha betydelse både för rättspsykiatri och kriminalvården, mer specifikt inom områden såsom diagnostik, val av behandling, riskbedömningar och utvärdering av behandlingar. I denna avhandling studeras psykiskt störda lagöverträdare utifrån flera olika nivåer, dels beteende och fysiologi, men också hjärnans struktur och funktion. Fyndet indikerar att det finns undergrupper bland lagöverträdare. Undergrupperna skiljer sig åt vad gäller brottsplatsbeteende, psykosocialt fungerande och känslomässig bearbetning, vilket avspeglas både i perifer fysiologisk reaktivitet och i hjärnans sätt att bearbeta känslomässiga stimuli.

I **studie I** studerades brottsplatsbeteenden och resultaten tyder på att det finns undergrupper av förövare som skiljer sig åt vad gäller psykosociala faktorer och brottsplatsbeteende. I **studie II** undersöktes känslomässig reaktivitet, genom att mäta perifer fysiologisk respons, under det att deltagarna tittar på negativa och neutrala bilder. Deltagarna utgjordes av en grupp friska kontroller och en grupp psykiskt störda lagöverträdare med olika grad av antisocialt beteende, men utan psykopati. Gruppen lagöverträdare delades även upp i två undergrupper med avseende på grad av antisocialitet. Lagöverträdarna uppvisade signifikant lägre fysiologisk respons i jämförelse med de friska kontrollerna. Vidare var den nedsatta känslomässiga reaktiviteten karakteristiskt för hela gruppen med lagöverträdare, det vill säga, antisocialt beteende var inte en särskiljande faktor. I **studie III** undersöktes hjärnans struktur. Hjärnbarkens tjocklek jämfördes mellan en grupp psykiskt störda lagöverträdare med brist på empati och friska kontroller. Lagöverträdarna uppvisade tunnare hjärnbark i pannloberna på bägge sidor. Det fanns också ett negativt samband mellan grad av psykopati och hjärnbarkens tjocklek i bägge pannloberna, höger tinninglob och hela höger hjärnhalva, vilket tyder på att dessa områden är av vikt för psykopati. I **studie IV** undersöktes känslomässig reaktivitet i hjärnan hos psykiskt störda lagöverträdare och friska kontroller med hjälp av fMRI, medan deltagarna tittade på bilder med rädsla och neutrala ansikten. Sedan jämfördes två undergrupper av lagöverträdarna, en grupp med psykopati och en grupp med autism spektrum störning. Resultaten visade att lagöverträdarna hade högre hjärnaktivitet i vissa områden, vilket tyder på att bearbetning av rädsla ansikten krävde en större ansträngning hos dessa individer. Därutöver hittades skillnader mellan de två undergrupperna (av lagöverträdare) med avseende på kommunikation mellan amygdala och andra delar i det limbiska systemet, vilket tolkades som att känslomässiga bearbetningen skiljer sig åt mellan dessa grupper.

Resultaten från denna avhandling tyder på att biologiska faktorer, tillsammans med sociala och psykologiska faktorer, bör tas i beaktande för att till fullo kunna förstå de mekanismer som ligger bakom antisocialt och våldsamt beteende. Framtida studier är nödvändiga för att bekräfta fynden i denna avhandling, och på så sätt få en ökad kunskap om korrelation mellan dessa biologiska faktorer och antisocialt och våldsamt beteende.

LIST OF PUBLICATIONS

- I. **Wahlund K** and Kristiansson M. Offender characteristics in lethal violence with special references to antisocial and autistic personality traits. *Journal of Interpersonal Violence*, 2006, Vol 21, No. 8, pp 1081-1091
- II. **Wahlund K**, Sorman K, Gavazzeni J, Fischer H and Kristiansson M. Attenuated subjective ratings and skin conductance responses to neutral and negative pictures in non-psychopathic mentally disordered offenders with various diagnoses. *Psychiatry Research*, 2010, Vol 180, No. 1, pp 30-34
- III. **Howner K**, Eskildsen FS, Fischer H, Dierks T, Wahlund L-O, Jonsson T, Kristoffersen-Wiberg M and Kristiansson M. Frontal cortical thinning in mentally disordered offenders. *Submitted manuscript*.
- IV. **Howner K**, Fischer H, Dierks T, Federspiel A, Wahlund L-O, Jonsson T, Kristoffersen-Wiberg M and Kristiansson M. Brain processing of fearful facial expressions in mentally disordered offenders. *Submitted manuscript*.

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LIST OF ABBREVIATIONS

ACC	Anterior cingulate cortex
ADHD	Attention deficit/hyperactivity disorder
ANOVA	Analysis of variance
ANS	Autonomic nervous system
APD	Antisocial personality disorder
AS	Asperger syndrome
ASD	Autism spectrum disorder
ASDI	The Asperger Syndrome Diagnostic Interview
BET	Brain extraction tool
BOLD	Blood oxygen level dependent
BPD	Borderline personality disorder
CD	Conduct disorder
CR	Conditioned response
CS	Conditioned stimulus
CSF	Cerebrospinal fluid
C/U	Callous and unemotional traits
dACC	Dorsal anterior cingulate cortex
DLPFC	Dorsolateral prefrontal cortex
DSM III-IV	Diagnostic and statistical manual of mental disorders III-IV
DSM-5	Diagnostic and statistical manual of mental disorders 5
EDA	Electrodermal activity
EPI	Echo planar imaging
FACE	Fast accurate cortex extraction
fMRI(-BCI)	Functional magnetic resonance imaging (Brain-Computer Interface)
FOV	Field of view
FTD	Frontotemporal dementia
GM	Gray matter
GMV	Gray matter volume
HC	Healthy controls
HFA	High functioning autism
IAPS	International affective picture system
ICC	Intra-class correlation
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10 th revision
IES	Integrative emotion system
IQ	Intelligence quotient
MFC	Medial frontal cortex
MNS	Mirror neuron system
MPFC	Medial prefrontal cortex
MP-RAGE	Magnetization-prepared rapid acquisition gradient echo
MRI	Magnetic resonance imaging
μS	Micro Siemens
OFC	Orbitofrontal cortex

PAG	Periaqueductal gray
PCL-R	Psychopathy Checklist Revised
PCL-SV	Psychopathy Checklist Screening Version
PDD-NOS	Pervasive developmental disorder – not otherwise specified
PET	Positron emission tomography
PFC	Prefrontal cortex
PPI	Psychopathy personality inventory
rACC	Rostral anterior cingulate cortex
RH	Right hemisphere
ROI	Region of interest
SAM	Stand alone monitor
SBU	Statens beredning för medicinsk utvärdering
SCID-I	Structured Clinical Interview for the DSM-IV, axis I
SCL	Skin conductance level
SCR	Skin conductance response
SPECT	Single photon emission computed tomography
STG	Superior temporal gyrus
T	Tesla
TE	Echo time
TI	Inversion time
TR	Repetition time
UR	Unconditioned response
US	Unconditioned stimulus
VBM	Voxel based morphometry
VIM	Violent inhibition mechanism
VTC	Volume time course
WAIS-R	Wechsler adult intelligent scale-revised
WHO	World Health Organization
WM	White matter

1 INTRODUCTION

Over the past few years, several violent crimes, committed by mentally disordered offenders in Sweden, have attracted great media attention. Different mechanisms operate behind violent behaviour. Previous studies have pointed out a complex system of biological and social risk factors underlying antisocial and violent behaviour (Raine, 2002b). Whether these risk factors eventually lead to antisocial and violent behaviour in any single individual depends on a large set of possible interactions which are still largely under-researched (Raine, 2002b). Specific symptoms or functions may, regardless of diagnosis, be related to violent behaviour. Accordingly, there are different motives and different triggers for violent behaviour such as hatred, jealousy, perceived insult, fantasy, distortions of reality, or the urge to gain money or a superior position. Despite a strong consensus on the complex causes of violent behaviour, general and forensic psychiatry are often limited to referring violent behaviour to specific psychiatric diagnoses defined in diagnostic manuals such as the DSM-IV (American Psychiatric Association, 1994, 2000). According to the DSM-IV, subjects have to fulfil a number of criteria in order for a certain diagnosis to apply. Clinically, two subjects assigned the same diagnosis could present very differently, as they may not share the same criteria. For example, in order to be assigned the diagnosis Borderline Personality Disorder, BPD, a subject has to fulfil five out of nine different criteria. Therefore, in practice, two BPD patients may only really share one of the specified criteria. It would probably be more interesting to consider functional differences such as intentions and motives that control and trigger different types of offenders. Such differences could be explored with regards to factors such as impulse control and lack of empathy. Criminal investigative analyses (Hazelwood & Warren, 2000; Meloy et al., 2000) and case studies (Kristiansson, 1995), have already suggested differences in motives and triggers underlying violent behaviour.

In this thesis different subgroups of mentally disordered offenders are studied, using a multi-dimensional approach, with parallel investigation of behaviour and peripheral physiology as well as brain structure and function.

2 BACKGROUND

2.1 EMOTIONS

There is no precise scientific definition of the concept emotion, but there is a consensus that at least three different systems are involved in an emotional state; 1) subjective feeling, 2) physiological reactivity and 3) behavioural expression (Mauss et al., 2005). Emotions are commonly considered either in a dimensional way or as discrete characters, i.e. a set of basic emotions.

In the dimensional model of emotions, the most common dimensions are valence (positive or negative) and arousal (high or low) (Russell, 1979; Russell & Carroll, 1999; Watson et al., 1999). According to this line of thinking, excitement is connected to positive valence and high arousal, while fear is connected to negative valence and high arousal. Sadness is associated with negative valence and low arousal, and calmness is associated with positive valence and low arousal. Sometimes other emotional dimensions are used such as approach/withdrawal (Davidson et al., 1990) or reward/punishment (Rolls, 1999).

When describing emotions in discrete characteristics, each emotion is treated as a separate phenomenon. Darwin stated that there are basic emotions, which are manifested in all mammals. In his work “The Expression of the Emotions in Man and Animals”, Darwin applied his observations to the facial and bodily expressions of cats, dogs and infants, whose emotions were expressed through their nonverbal behaviour (Darwin, 1979 based on the 1872 edition). Human faces are full of information and emotional facial expressions are important cues to people around us, giving information about potential threats. Paul Ekman studied emotions through facial expressions which further developed the idea of basic emotions (P. Ekman, 1973). The six emotions commonly considered basic are: happiness, surprise, sadness, disgust, anger, and fear. When conducting his research, Ekman travelled around the world and showed that these six basic emotions were much alike in different cultures all over the world (P. Ekman, 1973). Tomkins further suggested that biologically given affect programs control emotional reactions (Tomkins, 1962, 1963).

The statement that emotional facial expressions are alike in different cultures have been questioned later on, for example Russell et al. have reported that Japanese subjects often mistakes fearful faces for surprised ones (Russell et al., 1993). One fMRI study in Japanese and Caucasian subjects, observing Ekman's fearful facial expressions, showed that the two study groups activated different areas in the brain. The Caucasians responded to fearful faces in a more direct emotional way, while the Japanese did not attach an emotional valence to the faces (Moriguchi et al., 2005). Therefore cultural specificity should be taken into account when designing emotional tasks using faces as stimulus material.

In 1884, William James stated that certain stimuli can trigger emotional bodily reactions. It is the perception of these reactions that constitutes the conscious experience of an emotion. That is; when we see a bear, it elicits a physiological

response e.g. our heart rate increases and blood rush to our limbs, the so called ‘fight or flight response’. According to the theory, it is the automatic response which makes us instinctively run away, that tells us that we are afraid. James stated that emotions are no more than the experience of physiological changes that occur in response to specific stimuli (James, 1884). Carl Lange extended this theory by developing what has later been called the James-Lange theory. This theory proposes that physiological reactions precede the conscious experience of emotions.

In 1927, the James-Lange theory was challenged by Cannon and his co-workers. Cannon and Bard performed animal studies and their results indicated that separating the viscera (the internal organs of the body, such as the heart and lungs) from the central nervous system did not change emotional behaviour. The results also indicated that the autonomic nervous system is unable to differentiate between various emotional states, and that bodily changes are too slow to generate emotions. In contrast to the James-Lange theory, the Cannon–Bard theory suggests that an elicited stimulus *simultaneously* evokes a physiological reaction and a conscious experience of emotion (Bard, 1928; Cannon, 1927).

Even though this line of thinking has been criticised in contemporary research, there is a general consensus among researchers that emotional response can be distinguished, at least partly, with regards to autonomic activity (P. Ekman et al., 1983). Moreover, in Cannons animal experiments, the animals in which the viscera were disconnected from the brain, displayed a reduced emotional intensity (Cannon, 1927). In summary, most contemporary cognitive neuroscientists and researchers in this field agree on a close interaction between the central and autonomic nervous system (Adolphs, 2010; Critchley, 2005; Kreibig, 2010; Sequeira et al., 2009).

2.1.1 The emotional brain

In 1937, James Papez proposed a circuit theory of the brain and emotions. He suggested a specific network responsible for processing emotions. This network consisted of the hypothalamus, anterior thalamus, cingulate gyrus, and hippocampus. This was called Papez circuit by Paul MacLean (MacLean, 1949, 1952). According to MacLean, the emotional network also includes the amygdala, orbitofrontal cortex (OFC), and parts of the basal ganglia. This was called the limbic system and has been extensively investigated ever since. It is believed to play a prominent role in various emotional contexts, but has, as a concept, been debated over the years (Brodal, 1982; Kotter & Meyer, 1992; LeDoux, 1991). There is not one consistent definition of what constitutes the limbic system; different researchers have different definitions. Also, some researchers refer to the ‘limbic system’ without specifying of which parts it is constituted. This discrepancy can partly be explained by a developing research field, in which some of the structures, which originally were thought to be part of the limbic system, have been found to have a more diverse or specific function. For instance, results from brain research show that the hippocampus is strongly connected to memory function.

The limbic system is closely connected to the autonomic nervous system. Some of the most important structures for emotional processing in the brain are the amygdala,

anterior cingulate cortex (ACC), medial prefrontal cortex (MPFC), OFC, and the insula. A large meta-analysis of 106 functional imaging studies (PET and fMRI) of emotions, performed by Murphy et al., showed good evidence for regional specialization of three discrete emotions: fear in the amygdala, anger in the OFC and disgust in the insula (Murphy et al., 2003).

2.1.2 Amygdala

The amygdala is a key structure in emotional processing. It is an almond shaped structure located in the medial temporal lobe adjacent to the anterior portion of the hippocampus. The amygdala is composed of a number of nuclei that are reciprocally connected to the hypothalamus, hippocampus, and thalamus. The basolateral nuclei of the amygdala receive afferent information and the central nucleus has efferent projections to the stria terminalis, which innervates the hypothalamus, nucleus accumbens, brain stem, thalamus, and rostral cingulate gyrus (Kandel et al., 1995). Sensory information reaches the basolateral complex of the amygdala through two separate pathways (Gazzaniga, 2009; LeDoux, 1996). The cortical pathway is the most well known and provides the amygdala with well defined information from the primary sensory areas. Sensory information projects to the thalamus which then sends this information to the sensory cortex for a more exact analysis. The information is then projected to the amygdala. The other pathway, the subcortical pathway, is much faster and sometimes referred to as “the quick but dirty way”. Sensory information projects to the thalamus, which in turn sends a signal directly to the amygdala. This is a crude signal indicating whether the stimulus is dangerous or not, without any cortical influences (Gazzaniga, 2009; Kandel, et al., 1995). Although the amygdala seems specialized in negative stimuli it also responds to positive stimuli, but in somewhat more limited circumstances (Gazzaniga, 2009). It plays a role in some learning tasks in which rewarding stimuli are associated with neutral stimuli (Gallagher, 1992; Johnsrude et al., 2000).

Bilateral damage to the amygdala in Rhesus monkeys gives rise to Klüver-Bucy syndrome, also called psychic blindness. In experimental lesion studies, monkeys have shown lack of fear and a tendency to approach objects that would normally elicit a fear response. This, however, has not been observed in humans with bilateral amygdala damage. Damage to the amygdala in humans seems to give rise to a number of other symptoms, such as agnosia of faces and loss of ability to identify fear in human faces.

The amygdala is also important for emotional learning. Fear conditioning is a form of classical conditioning in which the subject learns to predict aversive events. An aversive stimulus (e.g. an odour or electrical shock) is associated with a neutral stimulus (e.g. a light or a picture of a human face), resulting in the expression of fear responses to the originally neutral stimulus. This is done by pairing the neutral stimulus, called “conditioned stimulus” (CS), with the aversive stimulus, the “unconditioned stimulus” (US), in the acquisition stage. Eventually the neutral stimulus alone can elicit the state of fear. The natural fear responses to the aversive stimulus before the acquisition stage, is called the “unconditioned response” (UR). After the acquisition stage the neutral stimulus, which alone can provoke the state of fear, is called “conditioned response” (CR). Lesions in the amygdala do not usually block the

UR to the aversive stimulus, indicating that the involvement of the amygdala is not necessary to exhibit a fear response. However, the ability to acquire and express a CR to the neutral CS that is paired with the aversive US is blocked in amygdala lesions.

2.1.3 Anterior Cingulate Cortex (ACC)

Lesion studies in both animals and humans have demonstrated a role of the ACC in emotions (Kennard, 1955; Tow & Whitty, 1953). Recent neuroimaging research has indicated that the ACC also is activated during cognitive tasks. In a seminal article by Bush et al. (2000), it is suggested that the ACC can be subdivided in two major parts; the dorsal cognitive division (dACC) and the rostral-ventral affective division (rACC) (Bush et al., 2000). The dACC is activated in cognitive tasks, including monitoring competition, complex motor control motivation and error detection (Bush et al., 1999; Bush, et al., 2000; Drevets & Raichle, 1998; Picard & Strick, 1996). The rACC is primarily involved in emotional processing and it is connected to the amygdala, periaqueductal gray (PAG), nucleus accumbens, hypothalamus, anterior insula, hippocampus and the OFC (Devinsky et al., 1995). The subdivision of the ACC is based on results from affect-related tasks. Different activations in the two parts of the ACC have been demonstrated by two versions of the stroop task, involving cognitive interference and emotional words respectively (Bush, et al., 1999; Whalen, Bush, et al., 1998).

2.1.4 Medioprefrontal cortex (MPFC)

The MPFC seems to be activated in different emotional states, suggesting general emotional processing in this area (Phan et al., 2002). This region is activated in different emotions, both negative and positive, and mixtures of these emotions, and also by different types of emotional stimuli, such as emotional films, pictures and recalls (Lane, Reiman, Ahern, et al., 1997; Lane, Reiman, Bradley, et al., 1997; Reiman et al., 1997). Worth mentioning is that this region is not always distinctly anatomically and functionally separated from the OFC.

2.1.5 Orbitofrontal cortex (OFC)

The OFC is activated when observing angry faces or listening to angry prosody (Blair et al., 1999; Grandjean et al., 2005), which indicates its involvement in the basic emotion anger. Focal OFC lesions may be specifically associated with changes in aggressive behaviour in humans (Blair, 2001; Blair & Cipolotti, 2000; Brower & Price, 2001). There is neuropsychological and neuroimaging literature suggesting that the OFC also is important for response reversal (Cools et al., 2002; Rahman et al., 1999; Rolls et al., 1994). Response reversal involves changing a response to a stimulus as a function of a change in contingency; i.e. learning to withhold a response that is now punished though previously it had been rewarded (Rolls, 1996).

2.1.6 Insula

The anterior insula is essential for detection as well as experience of disgust (Phillips et al., 1998). It is also an important area for interoception (A. D. Craig, 2002; Saper, 2002). One interesting study, performed by Rizzolatti and colleagues, analyzed the neural response during observation of others experiencing disgust and firsthand

experience of disgust. They found that the same portion of the anterior insula was activated in both conditions. This provides additional evidence for the insula to be a neural correlate of disgust identification and experience. Moreover, it suggests that understanding the emotions of others may require simulating ones own emotions (Wicker et al., 2003).

2.1.7 Autonomic nervous system (ANS)

As discussed in a previous paragraph, the ANS is an important component in emotional activity and reactivity. It has been demonstrated that there are descending influences, specifically from prefrontal and limbic structures (cingulate, medial temporal, and insula) and amygdala on autonomic control mediated by hypothalamic and brainstem centers (Asahina et al., 2003; Mangina & Beuzeron-Mangina, 1996). The ANS involves involuntary functions such as heart rate, blood pressure, breathing and activation of sweat glands (Critchley, 2002, 2005). The main function is to maintain a stable internal environment inside the body. The hypothalamus is closely connected to ANS, and the hypothalamus itself is closely connected to the limbic structure which explains physiological reactions to emotional stimuli (Lännergren, 1996). There are two main branches of the ANS, the sympathetic and the parasympathetic. The sympathetic system reacts in emergency situations, for example in a threatening situation, the heart starts pounding, breathing becomes rapid and shallow, muscles tense and blood pressure rises, all preparing the body for fight or flight. When the danger is over, the parasympathetic branch is activated, in order to return the body to basic functioning; which is called the 'rest and digest state'.

2.1.8 Measuring emotions

2.1.8.1 Stimuli

Emotional facial expressions are important cues for interaction between people, and one of the strongest emotional stimuli (Hariri et al., 2002; Kolb, 2000). From an evolutionary perspective, being able to perceive an emotional facial expression rapidly is crucial, in order to quickly identify potential threats. Research has shown that negative stimuli are scanned and perceived faster than positive ones. Negative stimuli signal potentially lethal threat, and must be processed at a faster rate. Fearful faces give rise to higher activity in the amygdala compared to neutral faces (Breiter et al., 1996). All emotional facial expressions will activate the amygdala, but fearful faces are the strongest activator (Murphy, et al., 2003). Fearful facial expressions that are presented subliminally – so quickly that the subject is unaware of the fearful expression- and then masked with neutral expressions will still result in amygdala activation (Whalen, Rauch, et al., 1998). In the study of emotions, the use of human facial expressions as a stimulus is common. A specific neural network for processing human faces has been suggested (Haxby et al., 2002). This network consists of brain regions processing static information, such as the shape and size of the face (including inferior occipital gyrus, lateral fusiform gyrus, and superior temporal sulcus), and areas specific for other aspects of facial perception. In this network, the amygdala has a specific role in processing emotional facial expression.

Another way to provoke emotions is to use pictures with affective content (see study II). The International Affective Picture System (IAPS) is a large set of standardized, emotionally-evocative, internationally accessible images in colour that includes contents across a wide range of semantic categories, (Bradley et al., 1993; Lang et al., 1999).

2.1.8.2 Skin conductance response (SCR)

Electrodermal activity (EDA) is under control of the sympathetic branch of the ANS and is considered a useful measurement of arousal (Bradley & Lang, 2000). EDA is measured by passing a small current through a pair of electrodes attached to the skin. When sweat fills the pores, there is a more conductive path through the relatively electrically resistant outer layer of the skin. If a constant voltage is applied, the skin resistance will vary with sweat gland activity, and the conductance can be determined. (Santerre & Allen, 2007). EDA can be measured by skin conductance level (SCL) or skin conductance responses (SCR). SCL represents the tonic level of skin conductance at rest and reflects sustained attention or baseline activity at rest, while SCR reflects rapid and transient reactions to internal or external affective events (Santerre & Allen, 2007). The amplitude of SCR increases linearly as ratings of arousal (regardless of valence) increase (Bradley & Lang, 2000). This has been shown with emotional pictures (Winton et al., 1984) and emotional words (Manning & P., 1974). Lang et al. also showed that 80% of subjects showed a positive correlation between arousal reports and SCR amplitudes (Lang et al., 1993).

Low autonomic arousal has been considered a biological correlate for antisocial and criminal behaviour (Babcock et al., 2005; Raine et al., 1999; Raine et al., 1990a, 1990b). Although the findings are equivocal (Lorber, 2004) studies have generally shown low autonomic reactivity in antisocial populations (Lorber, 2004; Raine, et al., 1999; Raine et al., 2000; Verschuere et al., 2007).

2.2 BRAIN IMAGING

Modern brain imaging techniques offer the possibility not only to study the anatomy of the brain but also to study neuronal processing underlying emotional and cognitive processing. At present, magnetic resonance imaging (MRI) is the most common way of imaging the structure and function of the brain. In structural studies, volumes in different areas of the brain can be investigated with various techniques such as segmentation, manual outline (guided by certain protocols depending on which structure is being measured), semi-automatic combination of manual and automatic segmentation, the stereological Cavalieri principle (Barta et al., 1997), voxel-based morphometry (VBM), and measurement of cortical thickness. Brain functioning can be studied with different techniques such as positron emission tomography (PET), single photon emission computed tomography (SPECT), or by magnetic resonance imaging (MRI).

PET is a nuclear medical imaging technique which produces a three-dimensional image or map of functional processes in the body. The system detects pairs of gamma rays

emitted indirectly by a positron-emitting radioisotope which is introduced into the body attached to a metabolically active molecule or substance (proteins, drugs etc.).

SPECT is a nuclear tomographic imaging technique which enables the study of e.g. perfusion in the brain, either in resting state or during an active task. The basic technique requires injection of a gamma-emitting radioisotope into the bloodstream of the patient and is less versatile compared to PET.

MRI works by using the magnetic properties of the hydrogen atom. The hydrogen atom behaves as a magnetic dipole, when placed in a strong magnetic field. During MRI, a subject is placed in such a strong magnetic field and a radio pulse of a specific frequency is sent in which will affect the alignment of the hydrogen atoms. When the pulse stops, the protons will try to return to their original positions, which will emit energy that can be captured and registries as a signal. In functional magnetic resonance imaging (fMRI), the neural activity in the brain is indirectly measured by the so called Blood Oxygen Level Dependency (BOLD)-technique (Ogawa et al., 1993). When a specific area in the brain is activated, the ratio between oxygenated and deoxygenated haemoglobin changes, and because oxygenated and deoxygenated haemoglobin have different magnetic properties, this change gives rise to a disturbance in the magnetic field. This disturbance will in turn give rise to an increased signal, the BOLD-signal. The functional images will then be co-registered with anatomical images, in order to map out the exact location of the activation site. It is a non-invasive method and requires no radioactive substances, making it attractive for research purposes.

When designing an fMRI-experiment there are at least two phases; the control phase and the stimuli phase. These two phases should be similar except for the specific stimuli that the task is aiming to test. For example, if the aim is to study processing of fearful facial expressions, the control phase is a neutral face and the stimuli phase is a fearful face. When analysing the fMRI-data, all activity that is generated during the control phase (when the subject views neutral faces) is withdrawn from the activation in the brain during the stimuli phase (when the subject views fearful faces), leaving only the activation responsible for processing fearful facial expression. An fMRI-experiment can involve either a block-design or an event-related design. In a block-design, multiple stimuli of the same sort are used in a block, for example multiple neutral faces in the control phase/block and multiple fearful faces in the stimuli phase/block. Between each block, there is a baseline phase with, for example, a white fixation cross on a black screen, in order to allow the brain to go back to a low level attention state before the next phase. In a block design, it is important that all the stimuli in the block are of equal value, as they are treated equally in the analysis. The block design has higher statistical power compared to the event related design. In an event-related design, the different conditions (stimuli, control, and baseline conditions) are presented one at a time in randomized order, avoiding habituation. It also makes it possible to analyse the different conditions separately.

2.3 AGGRESSION AND VIOLENCE

In contemporary research, two forms of aggression and violence are recognised; affective (also referred to as impulsive or reactive) and predatory (also referred to as instrumental or premeditated) (McEllistrem, 2004; Meloy, 1988, 2006). These forms of aggression and violence are triggered differently. Even though aggression and violence are related, it is important to distinguish between them in order to fully understand how they are expressed in specific behaviours. Aggression is necessary for survival and is therefore not inappropriate *per se* (Valzelli, 1981). Affective aggression is commonly referred to as an emotionally charged hostile reaction to a perceived threat or dangerous situation (Berkowitz, 1983). Predatory aggression, on the other hand, involves goal-driven behaviour with specific intended consequences (Bandura, 1983). According to Volavka (1999), violent behaviour is defined as overt and intentional physically aggressive behaviour against another person and develops as a result of complex interactions between neurobiological and environmental factors (Volavka, 1999). Aggression does not necessarily initiate violence; however, aggression is a necessary component of all acts of violence (Meloy, 1988).

The World Health Organization (WHO) declares violence a worldwide public health problem (WHO, 2002). According to their statistics, in the year 2000, approximately 1,6 million people died as a result of violence. Half of these committed suicide, 20% lost their lives due to armed conflicts and nearly one third died through homicide (WHO, 2002). The Scientific Assessment of Health Technology (in Swedish: Statens beredning för medicinsk utvärdering, SBU) has published a report on risk assessment which proposes that current knowledge on predicting violence on group level is far more advanced than the knowledge of individual risk factors (SBU, 2005). Individual risk factors for violence are emphasised in the clinical context. In the academic literature, numerous risk factors have been associated with violent behaviour. It is widely accepted that substance abuse disorders (alcohol and drugs) co-vary with violent behaviour (Volavka, 1999). Furthermore, it is a consensus that major mental disorders such as schizophrenia or mood disorders carry an elevated risk of violent acts; however it is important to keep in mind that severe mental illness on its own is not a robust predictor of future violence (Elbogen & Johnson, 2009). Major mental disorders are frequently co-morbid with substance abuse which elevates the risk of violent behaviour (Elbogen & Johnson, 2009; Fazel et al., 2009; Steadman et al., 1998; Swanson et al., 1997).

2.3.1 Affective aggression

In mammals, affective aggression is a natural response to frustration or threat (real or perceived), and is therefore not inappropriate *per se*. The goal is to get rid of the potential threat, to maintain internal homeostasis and to promote self or species preservation. Affective aggression is acted out instantly as a direct response to provocation or frustration, such as in the case of an argument that progresses over from verbal to physical harm. It is mediated by a neural circuit that is shared with other mammalian species, such as rats and cats (Gregg & Siegel, 2001; Panksepp, 1998), which runs from the amygdala, via the hypothalamus and further to the PAG. The system is organized in a hierarchical fashion. Regions of the frontal cortex, in particular the OFC, ventrolateral and medial frontal cortex (MFC) are involved in regulating and

modulating the subcortical circuit mediating affective aggression (Grafman et al., 1996; Gregg & Siegel, 2001; Panksepp, 1998).

One process that modulates affective aggression is the computation of expectations of reward and identifying if these expectations have been violated (Rolls, 1999). When an expected reward is absent, this leads to frustration, which is a trigger for affective aggression (Berkowitz, 1983). Since medial, orbital and ventrolateral frontal cortices are involved in resolving these types of situations and in decision making, lesions in these areas will give rise to more frequent frustration. Physiologically, affective aggression is preceded by intense autonomic arousal manifested by a pounding heart, rapid shallow breathing, elevated blood pressure and muscle tension, preparing the body for fight or flight. The OFC is involved in controlling and inhibiting impulsive actions, and lesions in this area may result in disinhibited aggressive behaviours (Grafman, et al., 1996; Volavka, 1999).

2.3.2 Predatory aggression

Predatory aggression, on the other hand, is usually planned and goal directed and is not preceded by heightened autonomic arousal (Glenn & Raine, 2009; Meloy, 1988). It can be a response to a provocation but is, in that case, usually acted out as revenge after a clear cool off period. In animals, predatory aggression and violence is used to hunt prey for food and survival. Humans can also be regarded as “cold blooded” predators aiming to get rewards such as money, sex, drugs, or power. Predatory aggression often underlies crimes such as serial murders or rape (Silva et al., 2004).

Research suggests that predatory aggression and violence is strongly connected specifically to psychopathy (Barratt & Felthous, 2003; Barratt et al., 1999; R. J. Blair, Mitchell, D., Blair, K., 2005; Cornell et al., 1996; Williamson et al., 1987). Importantly however, psychopathic subjects also display affective aggression which is reflected by two items in the Psychopathy Checklist Revised (PCL-R); impulsivity and poor behaviour control (Hare, 1991, 2003). Subjects with Asperger syndrome (further explained in section 2.7) can also sometimes act in a predatory way, for instance by stalking other people as a means of ‘communication’ (Stokes et al., 2007).

2.3.3 Brain imaging and violence

Raine et al. have performed several PET-studies on groups of convicted murderers with mental disorders. One of these studies showed that glucose metabolism was selectively reduced in the prefrontal lobes of the subjects during a continuous performance task (Raine et al., 1997). When sub-grouping the subjects with respect to childhood abuse or neglect, subjects with *no* history of early psychosocial deprivation had lower prefrontal glucose metabolism compared to normal controls and compared to subjects who had been victims of childhood deprivation (Raine, Phil, et al., 1998). This result indicates that violent behaviour can stem from either neurobiological alterations or childhood neglect and victimization. In an additional analysis of the same material, the authors sub-grouped the participants based on the type of violence they had committed (impulsive or predatory). The results indicated that the offenders who had used impulsive violence had lower prefrontal glucose metabolism in comparison with the normal controls. This was not the case however for the offenders who had used

predatory violence. Therefore, the authors proposed that offenders who are prone to using predatory violence have a more normal frontal lobes functioning (Raine, Meloy, et al., 1998). It is worth noting that the subjects in the study had a range of different psychiatric disorders, such as substance abuse, which could have confounded the findings.

2.4 EMPATHY

Empathy is a complex construct encompassing many aspects. There are probably as many definitions of empathy as there are researchers in this field (de Vignemont & Singer, 2006). However, most researchers agree upon at least three different core components (M. H. Davis, 1996; Decety, 2002; Decety & Jackson, 2004; Eisenberg, 2000; Lamm et al., 2007);

- 1) affective empathy, an emotional response to another person, which often means sharing that person's emotional state,
- 2) cognitive empathy, which usually refers to taking the perspective of the other person and
- 3) self-awareness and monitoring mechanism that modulates inner states

Another important finding in empathy research is the discovery of the mirror neuron system (MNS).

2.4.1 Mirror neuron system (MNS)

The MNS was discovered by accident two decades ago, in 1991. When studying primates, Rizzolatti and colleagues found an unexpected set of neurons in the ventral premotor cortex of the monkey. The distinct characteristics of these neurons were that they discharged both when the monkey performed a goal-directed hand movement and when it merely observed these hand movements performed by the experimenter (Dipellegrino et al., 1992). This discovery provided a neural basis for imitation and how learning by observation can take place. The neurons were termed "mirror neurons" (Rizzolatti & Craighero, 2004). Even though the MNS is mostly motor, it can help us understand the mechanism for certain social and emotional behaviours, such as imitation (Iacoboni & Dapretto, 2006). The MNS is also involved in pain. Singer et al. compared neural responses when a subject experienced pain and when the subject observed a loved one receiving similar painful stimulus, and found that the brain activity in pain pathways overlapped regardless of who received the painful stimulus (Singer et al., 2004). In the same study, two structures that connect the MNS with the limbic system were proposed; the insula and the ACC (Singer, et al., 2004). These findings imply that the MNS is of importance in the mechanism behind empathy.

2.4.2 Affective empathy

Affective empathy includes the ability to share another person's affective state (Decety & Jackson, 2004). It includes perception of emotional facial expressions and an internal bodily response from the ANS. Being presented with a stimulus, such as a crying child, usually evokes a reaction from the ANS, inducing high arousal, in order to experience

emotions and affects. Two more primitive aspects of affective empathy are mimicry and emotional contagion. Mimicry is defined as the tendency to automatically mimic and synchronize facial expressions, vocalizations, posture, and movements with those of another person. In doing so, the individual will resonate emotionally with the other person (Hatfield, 1994). Studies using facial electromyography demonstrate that when an observer perceives another person's emotional facial expression, such as a smile or fear, the corresponding emotional facial expression will appear in the observer (Dimberg & Ohman, 1996). Emotional contagion is a rapid and automatic process which is manifested already in infants (Nummenmaa et al., 2008). This can be demonstrated by infants who start crying when they hear other infants cry. Emotional contagion is a simple expression of affective sharing without cognitive elaboration or conscious awareness (Decety & Jackson, 2004). It is suggested to be a primitive form of sympathy (R. J. Blair, 2005) or a component in the development of empathy (Preston & de Waal, 2002).

2.4.3 Cognitive empathy

Cognitive empathy, or theory of mind, includes the ability to “put oneself in another person's shoes”, to be able to change perspective and regard a situation from different angles (M. H. Davis, 1996). Mentalizing, the ability to represent mental states, is crucial for theory of mind development. In a mature empathic response, observers must be able to separate themselves from others and have some minimal mentalizing ability (Zahn-Waxler, 1990). The development of a separation between self and others is functionally linked to that of executive functions (Russell, 1996). These are the processes that serve to monitor and control thoughts and actions including self-regulation, planning cognitive flexibility, response inhibition, and resistance to interference (Shallice, 1988).

2.4.4 Self-awareness and modulating

The ability to separate self from others, which is a fundamental basis for a mature empathic response, requires self-awareness. Self-awareness begins early in life. Martin and Clark (1982) performed a study of 1-day-old babies' reactions to audiotapes of neonatal crying, the crying of an 11 month old, and the newborn's own crying. The babies showed emotional contagion by crying when hearing other babies cry. However, they did not respond to the sound of their own crying, which indicates that there is some self-other distinction already functioning from birth (Martin & Clark, 1982). Children begin to recognize their own mirror image in 18-24 months of age and to display self-conscious emotions such as shame or embarrassment (Lewis et al., 1989). Empathy is not an all-or-nothing response. It can be modulated. We empathize with others to varying degrees (Hein & Singer, 2008). Different factors modulate the empathic response; a) intensity of the displayed emotion; the more intense emotion display by the target, the higher the empathic response shown (Avenanti et al., 2006; Saarela et al., 2007), b) features of the empathy target, e.g. we tend to empathize more with people we find likeable (Singer et al., 2006), and c) the situational context, e. g. if we are convinced that pain is part of a treatment in order for it to be successful, the empathic brain response is reduced (Lamm, et al., 2007).

2.4.5 Measuring empathy

Measuring empathy is a challenge. At present, the most common way to assess empathy is using self report scales. Several different scales have been developed, aiming to assess different aspects of empathy. Generally, different scales focus on either the affective or cognitive aspect, while some scales focus on both components. The four most common scales in use today are; *the Hogan Empathy Scale* (Hogan, 1969), which focuses on the cognitive aspects of empathy, *the Questionnaire Measure of Emotional Empathy* (Mehrabian & Epstein, 1972) which attempts to measure affective empathy, *the Interpersonal Reactivity Index* (M. H. Davis, 1980, 1983) which was constructed to measure both the affective and the cognitive aspects, and *the Empathy Quotient* developed by Baron-Cohen and Wheelwright (2004) which also includes items intended to capture both cognitive and affective aspects of empathy (Baron-Cohen & Wheelwright, 2004). There are sometimes problems when using self-report scales. It is for instance difficult to use them in psychopathic subjects, and one reason is that a part of the disorder is pathological lying. How can their self-report answers be trusted?

2.4.6 Lack of empathy

Lack of empathy could manifest itself as impaired cognitive empathy, impaired affective empathy, or impairments in both cognitive and affective empathy. The results of numerous studies indicate that lack of empathy is common in violent offenders (Eisenberg, 2007), and is associated with antisocial behaviour (Miller & Eisenberg, 1988). Two developmental disorders which have been specifically connected to lack of empathy are autism spectrum disorder (ASD) and psychopathy.

ASD includes impairments in mentalizing, emotional reciprocity, communication, and social interaction (American Psychiatric Association, 1994, 2000), all suggested to be involved in empathy. Moreover, impairments in perceiving emotional facial expressions have been suggested in the disorder (Adolphs et al., 2001; Hubl et al., 2003; Schultz et al., 2000). There are also findings suggesting impairment in the MNS in children with ASD (Dapretto et al., 2006; Theoret et al., 2005). In contrast to individuals with ASD, psychopathic subjects often present a good, though superficial, ability to understand social signals (Dolan & Fullam, 2004). Lack of empathy is one of the characteristics of psychopathy. In the psychopathy checklist revised (PCL-R) and the psychopathy checklist screening version (PCL-SV) "lack of empathy" is one of the specific items that is assessed and scored. Subjects with psychopathy seem to manifest an intact cognitive empathy, however lack of affective empathy seems to be specific in these subjects (Blair, 2006; R. J. Blair, Mitchell, D., Blair, K., 2005).

2.5 PSYCHOPATHY

In 1809, the French physician Phillippe Pinel introduced the term: "Mania sans délir" or "Insanity without delirium". The concept was further developed in "The Mask of Sanity" by Hervey M. Cleckley, first published in 1941 (Cleckley, 1976). The title of the book refers to the mask of normality that Cleckley suggested concealed an underlying mental disorder of what he considered as the psychopathic personality.

According to Cleckley psychopathic individuals can be charming, glib, and verbal. They do express feelings verbally, however they lack a deeper understanding or grounding of the affects. In contemporary research, shallow affects are considered a pronounced trait in the psychopathic disorder. Based on a series of case studies, Cleckley proposed 16 characteristics of psychopathy including the following: superficial charm, absence of delusion and other signs of irrational thinking, lack of anxiety, unreliability, untruthfulness, lack of remorse, inadequately motivated antisocial behaviour, failure to learn by experience, pathologic egocentricity, poverty of emotions, lack of insight, unresponsiveness in interpersonal relations, and failure to follow any life plan (Cleckley, 1976).

Based on Cleckley's clinical descriptions and his own clinical experiences, Robert Hare developed the Psychopathy Checklist (PCL) and the Psychopathy Checklist Revised (PCL-R), which today are the most commonly used assessment instruments for psychopathy (Hare, 1991, 2003). The concept of psychopathy can be considered either in a categorical way or in a dimensional way on a continuous scale with different degrees of psychopathy (Guay et al., 2007; Walters et al., 2007). At present, psychopathy does not exist as a DSM-IV diagnosis. Quite often psychopathy is confused with antisocial personality disorder (APD), which is a diagnosis in DSM-IV (American Psychiatric Association, 1994, 2000). In the DSM-5, however, the personality disorders will be reconsidered and antisocial personality disorder is recommended to be reformulated to antisocial/psychopathic type (www.dsm5.org).

2.5.1 Pseudopsychopathy

Damages in the frontal lobes can give rise to "pseudopsychopathy" or acquired sociopathy. One famous historical case is Phineas Gage, a railway construction worker in Vermont, who in 1848 experienced an accidental explosion blowing a tamping iron through his head and destroying most of the frontal part of his frontal lobe. After the accident, Gage could read, walk, and talk as before, but his personality had changed. Before the accident, he had been a most capable and efficient foreman, however, after the accident, he became impatient and obstinate, and he was unable to plan ahead. His friends said he was "no longer Gage" (Macmillan, 1986)." This famous case has been well quoted and used as evidence for the distinct role of the frontal lobes in personality, despite there have been some uncertainties regarding it, e.g. we do not really know much about Gage's life before the accident or the last years of his life. The role of the frontal lobes in personality has since then been demonstrated in numerous other brain lesion studies.

Another example showing the connection between frontal lobes and personality is patients suffering from frontotemporal dementia (FTD), in which the frontal lobes are damaged by a chronic neurodegenerative disorder. These patients usually show severe changes in their personality and often suffer from disinhibition (Mendez et al., 2005). Disinhibited patients can make inappropriate (sometimes sexual) comments or perform inappropriate acts (Mendez, et al., 2005). It is not unusual that patients with FTD sometimes get into trouble with the police because of inappropriate behaviour such as shoplifting. Also, tumours in the frontal lobe can give rise to disinhibited behaviour.

These examples of pseudopsychopathy indicate that the frontal lobes are connected to the deviant behaviour and symptoms presented by psychopathic subjects.

2.5.2 The core concept of psychopathy

The temporal lobes, including the limbic system and the amygdala, are also suggested to be important for the development of psychopathy. It is widely accepted among researchers in the field that impairment in emotional processing is the core trait in the psychopathic personality and dysfunction in the amygdala has been suggested as one of the core neural correlates of psychopathy (Blair, 2003, 2006; R. J. Blair, Mitchell, D., Blair, K., 2005). Impairments in the amygdala could lead to deficient emotional learning which, in turn, could be one of the causes behind the development of psychopathy (Blair, 2003, 2006; Blair et al., 2006). Additionally, a large set of studies have shown that individuals with psychopathy fail to react to threatening stimuli, leading to a “cool behaviour” in emergency situations (Birbaumer et al., 2005; Patrick et al., 1993; Patrick et al., 1994; Raine, 1996; Raine, et al., 2000). The mechanism behind this behaviour is not clarified, but it has been suggested that it could be due to a dysfunctional or slow autonomic nervous system or an inhibitory mechanism stemming from other parts of the brain.

At present several different theories on the etiology of psychopathy prevail (these will be presented further on). Herba et al postulate that the deficient affective processing emerges at a very young age and contributes to the development of the other aspects of psychopathy. *“If an inability to experience emotions as others do and to empathize with the emotions experienced by others, were present early in childhood, it would limit learning requiring an emotional response or the recognition of emotional responses. Such a deficit could in turn contribute to the development of an arrogant and deceitful interpersonal style”* (Herba et al., 2007). Children and adolescents can be diagnosed with Conduct Disorder (CD), which encompasses callous and unemotional traits (C/U). CD with C/U is sometime considered a precursor to the development of psychopathy in adulthood (Barry et al., 2000; Enebrink et al., 2005; Frick et al., 2003). In psychopathy, some core deficits can be identified as of special interests. There are numerous research findings supporting impairments in the processing of fear-related stimuli in psychopathic subjects (Blair, 2006). The most common impairments are in:

- 1) aversive conditioning (Flor et al., 2002; Lykken, 1957)
- 2) generating automatic responses to anticipated threat (Hare, 1982; Ogloff & Wong, 1990)
- 3) passive avoidance learning (Lykken, 1957; Newman & Kosson, 1986)
- 4) response reversal (Mitchell et al., 2002; Newman et al., 1987)

In addition, psychopathic subjects also have difficulties with empathic responding (R. J. Blair, 2005; Blair, 2008). They show impairments in recognition of and autonomic responding to sad and fearful facial and vocal expressions (Blair et al., 2001; Blair et al., 2002).

The low fear theory proposes that, as psychopaths do not experience fear, their behaviour is not modulated by emotions. This theory was tested in three different ways

in 1957 by Lykken. He believed that psychopathic subjects suffered from deficit in fear conditioning, and he could show this by a questionnaire, electrodermal hyporeactivity during classical aversive conditioning, and poor passive avoidance of shock (Lykken, 1957). His findings have been replicated particularly the attenuated autonomic responses (Herpertz et al., 2001; Lykken, 1995; Patrick, et al., 1994).

Autonomic reactivity to social stimuli is also a core component in *the somatic marker hypothesis*, proposed by Damasio (Damasio, 1996). This hypothesis suggests that prefrontal damage leads to impaired decision-making abilities, reflecting an incapability to activate autonomic somatic states linked to the anticipation of reward and punishment. The hypothesis is based on the assumption that optimal decision making depends on the generation and interpretation of signals from the autonomic system, generated by cues from the amygdala, MFC, and OFC. Patients with damage to the OFC and/or amygdala show abnormalities in autonomic reactivity to emotional stimuli similar to those with psychopathy (Mitchell, et al., 2002). One neuro-psychological finding supporting this hypothesis is that subjects with psychopathy mimic the gambling behaviour of patients with OFC lesions in the Iowa gambling task (a psychological task thought to simulate real-life decision making (van Honk et al., 2002).

The response modulation hypothesis, developed by Newman and colleagues (Patterson & Newman, 1993), is based on specific deficit in executive functioning, autonomic processing of contextual cues during goal-directed behaviour, and selective attention (Pham et al., 2003). According to this hypothesis, the poor performance of psychopathic subjects on the passive avoidance task is related to their inability to shift attention from the goal of responding to gain reward to the peripheral punishment information (Lorenz & Newman, 2002; Newman & Kosson, 1986).

The violent inhibition mechanism (VIM), proposed by Blair (1995), is based on animal studies showing that distress cues of a victim play a central role in limiting aggressive behaviour by an attacker (Blair, 1995). In the same way, fearful or sad facial expression should act as cues to trigger empathy and inhibit the perpetrator from inflicting harm on the victim. However, individuals who are unable to recognize or react to these facial expressions may also be unable to terminate an attacking behaviour. Psychopathic subjects are considered to display deficient emotional learning. Moreover, distress cues in victims do not seem to trigger empathy in psychopathic perpetrators. The VIM is supported by studies showing selective impairment in the processing of sad and fearful facial expressions in psychopathic adults (Dolan & Fullam, 2006) and children with psychopathic tendencies (Blair, et al., 2001). Blair later expanded this VIM theory at both the cognitive and neural levels, resulting in *the integrative emotion system (IES)* (R. J. Blair, Mitchell, D., Blair, K., 2005). The IES represents a neuro-cognitive model of the interactions of the systems involved in emotional processing (Blair, 2004).

2.5.3 Assessing psychopathy

At present, the most commonly used assessment instrument for psychopathy is the Psychopathy Checklist Revised, (PCL-R), developed by Robert Hare (Hare, 1991, 2003). PCL-R consists of 20 items. At the assessment, every item is rated on a 3-point

scale (0=Absent, 1=Possible/partial, 2=Present), and the maximum score is 40 (20 x 2). The common cut off score for psychopathy is ≥ 30 points, even though, in some studies, lower cut off scores have been used (see table 3.1 and table 3.2). PCL-R has a two-factor structure; factor one and factor two. In factor 1, personality traits are scored, such as superficial charm, grandiose sense of self-worth, shallow affect, lack of remorse, and lack of empathy. In factor 2, behaviour and life-style items are scored, such as impulsivity, poor behavioural control, parasitic lifestyle, juvenile delinquency, and criminal versatility. PCL-R has been criticized for mixing personality traits with lifestyle and behaviour. Scoring relies on an interview with the subject as well as access to additional file information, such as criminal records, in order to complement the interview data. It is also possible to perform a retrospective PCL-R rating, based on case file information (Grann et al., 1998). The PCL-R is appropriate for adult offenders and forensic patients (S. D. Hart & Hare, 1989; S. D. Hart et al., 1988).

Another rating scale, derived from the PCL-R is the psychopathic checklist screening version (PCL-SV). This is a screening instrument, used to screen psychopathic traits in non-criminal subjects (S. D. Hart et al., 1995). PCL-SV consists of 12 items, divided into two subscales, factor 1 and factor 2. The maximum score is 24, cut off score for definite psychopathy is 18, and cut off score for probable psychopathy is 13. There is a high correlation between PCL-R and PCL-SV (Cooke & Michie, 1999; Guy & Douglas, 2006). The PCL-SV is appropriate for all adult populations (Brown et al., 1992).

Referring to the PCL-R, it is possible to sub-divide psychopaths into primary psychopaths with more pronounced psychopathic personality traits, scoring high on factor 1, and secondary psychopaths; who display antisocial behaviour and lifestyle, and score higher on factor 2 (Lykken, 1995; Skeem et al., 2007).

2.5.4 Brain imaging and psychopathy

Modern brain imaging studies of psychopathy have pointed to evidence for deviations in structure and function in both frontal and temporal lobes. Common problems in this research field are heterogeneous study populations, differences in the methods used and the selection of appropriate control groups. All these factors contribute to the sometimes contradictory results (Dolan, 2010; Muller, 2010; Wahlund & Kristiansson, 2009).

Yang et al. have performed a structural MRI study on “successful” psychopaths (meaning psychopathic subjects who have not been convicted of a crime) compared to “unsuccessful” psychopaths (psychopathic subjects who have been convicted). They found reduction in prefrontal gray matter volume (GMV) in the unsuccessful psychopaths (Yang et al., 2005b). In an additional study of the same material, the right and the left hippocampus volumes were compared and they found that the unsuccessful psychopaths showed an exaggerated structural hippocampal asymmetry (Right > Left) relative both to successful psychopaths and control subjects (Raine et al., 2004).

Numerous studies have shown alterations in the amygdala and temporal lobes in psychopathic subjects. The shallow affects and low autonomic arousal seen in

psychopathy indicate that these parts are also affected. Functional brain imaging studies have shown inconsistent results. Some studies have demonstrated reduced activity in the amygdala and the limbic system, (Birbaumer, et al., 2005; Veit et al., 2002) while other studies have shown increased activation in the same areas (Muller et al., 2003; Schneider et al., 2000). In two fMRI-studies using an aversive differential condition paradigm, psychopathic subjects did not display the same activation in the limbic-prefrontal circuit as control subjects (Birbaumer, et al., 2005; Veit, et al., 2002). In the studies demonstrating hyper activity in the limbic system in psychopathic subjects, the findings have been suggested to reflect the requirement of additional efforts to process emotional stimuli in psychopathic subjects (Muller, et al., 2003; Schneider, et al., 2000). An alternative network for emotional stimuli in psychopathic subjects has also been suggested (Kiehl et al., 2001). In a SPECT-study, psychopathic subjects differed from non-psychopathic ones in the pattern of relative cerebral blood flow during processing of emotional word, which indicates that it is more demanding for psychopathic subjects to process emotional words (Intrator et al., 1997). In another fMRI study with abstract and concrete words, the psychopathic offenders showed lower activity in the right anterior superior temporal gyrus and surrounding cortex for abstract words (Kiehl et al., 2004).

There are also studies investigating psychopathic traits in community populations. In some of these studies, the psychopathic personality inventory (PPI) has been used which is an instrument developed to assess psychopathic traits in the general population (Lilienfeld & Andrews, 1996). Subjects scoring high on the PPI presented brain activation suggesting a more cognitive way of processing emotional stimuli (Gordon et al., 2004). In another fMRI study the subjects played “Prisoner’s dilemma”, a game testing trust and the ability to cooperate with co players. Subjects scoring high on the PPI defected more often and compared with low-scoring subjects, they also showed weaker activation in the OFC when choosing to cooperate and showed weaker activation within the DLPFC and rACC when choosing to defect. In this game, the subjects scoring high on the PPI had less activation in their frontal lobes, the amygdala and rACC compared to those scoring low on the PPI (Rilling et al., 2007). These findings suggest that, whereas subjects scoring low on the PPI have emotional biases toward cooperation that can only be overcome by exerting cognitive control, subjects scoring high on the PPI have the opposite bias towards defection which likewise only can be overcome by cognitive effort.

2.6 ANTISOCIAL PERSONALITY DISORDER (APD)

Antisocial personality disorder (APD), Dissocial personality disorder in ICD-10 (WHO, 1993), is characterised by disregard for, and violation of, the rights of others, as well as aggressive and criminal behaviour (American Psychiatric Association, 1994, 2000). Quite commonly, it is confused with psychopathy. They are not interchangeable concepts, even though they have a number of overlapping symptoms. The DSM-IV criteria of APD mainly regard criminal and socially deviant behaviour (American Psychiatric Association, 1994, 2000). As discussed in the previous section, psychopathy, however, is further characterised by callous and unemotional traits (see Factor 1 in PCL-R, (Hare, 1991, 2003)). In prison samples, the prevalence of APD is

higher than the prevalence of psychopathy. In North America, studies have reported a prevalence of APD of between 50-75% in prison populations (Cote & Hodgins, 1990; Hare, 1983), while the prevalence of psychopathy was between 25-30% in USA and Canada (Cooke & Michie, 1999; Hare et al., 1991). Higher prevalence of both APD and psychopathy is generally found in North American compared to European prison and forensic samples (Cooke & Michie, 1999; Hare, et al., 1991; Raine, 1985; Stålenheim & Von Knorring, 1996). In a large review study of surveys in general prison populations in western countries (23 000 subjects), the prevalence of ASD was 47 % (Fazel & Danesh, 2002). In the upcoming revision of DSM-5, however, the personality disorders will be reconsidered, and, in the draft of DMS-5 it is recommended that antisocial personality disorder is reformulated to antisocial/psychopathic type (www.dsm5.org).

2.6.1 Brain imaging and APD

Findings from brain imaging studies in violent offenders with APD are inconsistent. Moreover, it is hard to draw firm conclusions as almost all studies are conducted by very limited number of research groups (Dolan, 2010) (see table 3.1 and table 3.2).

Dolan et al. studied brain volumes of the frontal and the temporal lobes in APD compared to healthy controls. They discovered a 20% smaller temporal volume but no significant frontal reduction in brain volume in the APD group (Dolan et al., 2002a). Later, work by Barakati et al (2006) confirmed reduced temporal lobe volumes rather than reduced frontal lobe volumes in violent men with APD (Barkataki et al., 2006). Raine et al used high resolution MRI and found reduced GMV in the PFC in APD compared to both healthy controls and subjects with substance abuse but without APD (Raine, et al., 2000). In the same study, they were also able to show lower skin conductance activity during stress task in the subjects with reduced PFC volumes, compared to the subjects with intact PFC GMV (Raine, et al., 2000). This finding suggests that prefrontal deficit may account for the reported difficulties in fear conditioning and autonomic responsiveness in antisocial populations. Using VBM, Tiihonen et al (2008) reported reduced GMV in the OFC, frontopolar cortex and superior temporal gyrus (STG), but increased white matter (WM) volume in posterior brain areas in APD compared to healthy controls (Tiihonen et al., 2008).

In an fMRI-study on APD subjects, a differential aversive classical conditioning paradigm was applied with odours as US and faces as CS. Different effects were found in the amygdala and dorsolateral PFC during acquisition. Controls showed decreased signal while the APD-group unexpectedly showed increased signal. The interpretation of this finding was that the APD needed an additional effort to form negative emotional association; a pattern of processing that may correspond to their characteristic deviant emotional behaviour (Schneider, et al., 2000). Kumari (2006) used fMRI to test working memory in schizophrenic patients and APD. The APD subjects, relative to healthy subjects, showed activation deficit in the left frontal gyrus, ACC, and precuneus (Kumari et al., 2006).

2.7 AUTISM SPECTRUM DISORDERS (ASD)

Autism spectrum disorder (ASD) is a group of neurodevelopment disorders. ASD commonly includes Autism, Aspergers syndrome (AS) and Pervasive Developmental Disorder – not otherwise specified (PDD-NOS).

In 1938, Hans Asperger used the term *autistic psychopaths* when describing children in his practice who lacked nonverbal communication skills, demonstrated limited empathy, and were physically clumsy (Asperger, 1944). Around the same time Leo Kanner introduced *early infantile autism*, describing 11 children with striking behavioral similarities (Kanner, 1943). It was in the late 1960s that the disorder Autism was separated from mental retardation, schizophrenia, and other developmental disorders. In 1980s Lorna Wing defined a symptom triad which was common for all autistic subjects. The “Wings triad” comprises 1) impaired or lack of social interaction, 2) impaired or lack of social communication, 3) restricted and repetitive patterns of behaviour, interests, and activities. These are the core symptoms in all autism spectrum disorders, and the foundation for the diagnoses in ICD-10 (WHO, 1993), and DSM-IV (American Psychiatric Association, 1994, 2000). In 1981 Wing also published a paper: *Asperger's Syndrome: a Clinical Account*, in which she discusses Asperger’s earlier research and introduced the term Aspergers syndrom (AS) (Wing, 1981). The diagnosis Autism was included in DSM-III in 1978, while AS was included in DSM-IV 1994, and ICD-10 in 1993. In DSM-5 there will be only one overall diagnosis, Autism or Autism spectrum disorder (www.dsm5.org).

In autism, overt symptoms gradually develop after the age of six months and are manifested two or three years later (S. J. Rogers, 2009). Autistic infants show less attention to social stimuli, smile at, and look at others less often (Volkmar et al., 2005). About 30-50% of the subjects with autism do not develop enough natural speech to meet their daily communication needs (Noens et al., 2006). In AS, the language development is not affected, even though it is quite common that these subjects have unusually pedantic and formal speech. The intellectual ability is also intact in AS. In some cases, AS is referred to as *high functioning autism* (HFA), which denotes a condition unaccompanied by mental retardation and with normal language development. The amount of overlap between HFA and AS is disputed. Some researchers argue that the two are distinct diagnostic entities; others argue that they are indistinguishable (Klin, 2006). HFA is not a diagnosis in the DSM-IV (American Psychiatric Association, 1994, 2000) or the ICD-10 (WHO, 1993). The diagnosis PDD-NOS, sometimes labelled *atypical autism*, is used when a subject does not fulfil criteria for any of the other diagnoses, but clearly has symptoms related to ASD.

The core features in ASD comprise severe and sustained impairment in social interaction and communication, as well as development of restricted, repetitive patterns of behaviour, interest, and activities (American Psychiatric Association, 1994, 2000). Lack of empathy is also a pronounced trait in these conditions, and, as will be discussed in this section, subjects with ASD have deficits in both affective and cognitive empathy. The constellation of impairments in socialization, imagination, and communication in these subjects has been hypothesized to result from a biologically caused deficit in the ability to represent mental states, i.e. theory of mind, leaving them

with degrees of mind-blindness, also referred to as *the mind-blindness theory* (Baron-Cohen et al., 1985; Leslie, 1987). Across a range of tasks this theory has been able to predict the pattern of impairments. Children with ASD tend to believe that other individuals always are truthful and they may be surprised to discover that people not always say what they mean (Baron-Cohen, 2009). A typical 4-year-old child passes the false belief test, recognizing when someone else has a mistaken belief about the world (Wimmer & Perner, 1983), while most children with ASD are delayed in passing this test (Baron-Cohen, et al., 1985). Individuals with ASD commonly find tasks requiring theory of mind very difficult (Baron-Cohen, et al., 1985). While mind reading is obviously one component of empathy, true empathy also requires an emotional response to another person's state of mind, affective empathy (M. H. Davis, 1996). Many people with ASD also report that they are puzzled by how to respond to another person's emotions (Grandin, 1996). For example, they may be able to see that someone is crying, deduce that they are sad or upset, but not know why, or, how to comfort them. Even though disturbance of facial perception is not a core symptom, it is often impaired in these subjects. In comparison to healthy individuals, who commonly focus on the eye-region when looking at human faces, individuals with autism seem to focus on other parts of the face, for example on the mouth (Klin et al., 2002). Impairment in facial perception and the similarities to subjects with amygdala damage leads one to believe that the amygdala may be one of the key structures involved in the mechanism underlying the disorder (Adolphs, et al., 2001; Schultz, et al., 2000). ASD is correlated to chronically high arousal level i.e. larger baseline autonomic activity than controls (Hirstein et al., 2001; Kennedy et al., 2006; Ming et al., 2005).

2.7.1 Brain imaging and ASD

Structural imaging studies have shown differences in brain volumes in specific areas in individuals with ASD as compared to control subjects. For example, reduced size of lobus VI and VIII of the vermis in cerebellum have been shown (Stanfield et al., 2008). The volume of the amygdala has also been studied, however, with contradictive findings. However, a recent meta-analysis, reported that age was an important factor and that enlargement of the amygdala was present in younger subjects, however not in elderly patients (Stanfield, et al., 2008). Voxel based whole-brain analyses have shown significant localised gray matter reduction within the fronto-striatal and parietal networks and decreases in the ventral and superior temporal gray matter volumes (Boddaert et al., 2004; McAlonan et al., 2005). Cortical thickness measurements have shown both increased cortical thickness (Hardan et al., 2006) and cortical thinning in autistic subjects (Hadjikhani et al., 2006).

Functional neuroimaging studies, using both fMRI and PET, have identified key areas of the "social brain" (MPFC, temporal parietal junction, ACC, insula, and amygdala) which are specifically activated during mind reading tasks. These areas are hypoactive in the autistic subjects during mind reading tasks (Baron-Cohen et al., 1999; Castelli et al., 2002; Frith & Frith, 2003). Such neuroimaging studies provide a biological correlate to the psychological difficulties that have been reported. Neural mechanism underlying the impairment in facial perception has been studied in functional imaging studies. Reduction in areas typical for facial processing and higher activation in areas typically associated with object perception have suggested alternative pathways for face

processing as compared to controls (Critchley et al., 2000; Hubl, et al., 2003; Pierce et al., 2001; Schultz, et al., 2000). Even if there are numerous studies on subjects with ASD, there are no imaging studies focusing on antisocial or violent individuals with ASD.

2.7.2 ASD in forensic settings

The prevalence of ASD in criminal and forensic settings has been debated. As these diagnostic entities were quite recently defined, it has been proposed that the number of subjects with ASD in forensic psychiatric settings is underestimated. Even though the majority of subjects diagnosed with ASD are not offenders, it has been shown that they are more prevalent in forensic samples than in general community samples (Haskins & Silva, 2006; Kristiansson & Sorman, 2008; Scragg & Shah, 1994; Siponmaa et al., 2001). One of the first studies setting out to investigate the prevalence of males with Asperger syndrome in a forensic setting was performed at Broadmoor hospital, one of three special maximum secure forensic psychiatric hospitals in England. The prevalence in the hospital population was found to be 1.5-2.3%, which was considered approximately three times higher compared to the prevalence in the general population (Scragg & Shah, 1994). In Sweden, a retrospective study of juvenile delinquents undergoing forensic psychiatric assessments was performed and the researchers found a prevalence of about 3 % with Aspergers syndrome and 12 % with PDD-NOS (Siponmaa, et al., 2001). These figures have later been replicated in a prospective study in a forensic psychiatric context (Soderstrom et al., 2004).

3 SUMMARY OF THE RESEARCH FIELD

Table 3.1 and table 3.2 present an overview of the research field. Brain imaging studies performed in mentally disordered offenders from 1994-2010 have been included, as well as some studies in community samples with subjects either diagnosed with psychopathy or with psychopathic personality traits. Structural imaging studies are listed in table 3.1 and functional brain imaging studies are listed in table 3.2.

3.1 STRUCTURAL IMAGING STUDIES

Table 3.1 Structural imaging studies

Authors	Subjects	Method	Results
Glenn, Yang, et al. (2010) [‡] USA	24 PSY community (PCL-R >23), 24 HC (PCL-R ≤14)	sMRI	no group differences in the volume of ACC
Glenn, Raine, et al. (2010) [‡] USA	22 PSY community (20m/2f, PCL-R >23), 22 HC (20m/2f, PCL-R ≤ 18)	sMRI	PSY ↑striatum volumes
Boccardi et al. (2010) [*] Finland	26 offenders with APD and type 2 alcoholism (12 high PSY ≥30 PCL-R, 14 med-PSY), 25 HC	sMRI	PSY, APD: no changes in overall size, but different distribution of hippocampus volume vs HC
Yang, Raine, Narr, et al. (2009) [‡] USA	27 PSY community (PCL-R >23), 32 HC (PCL-R ≤15)	sMRI	PSY: ↓AMY bilat, correlations between ↓AMY volumes and higher PCL-R scores
Yang, Raine, Colletti, et al. (2009) [‡] USA	27 PSY community (PCL-R >23), 32 HC	Cortical thickness	PSY: GM thinning in right frontal and temporal cortices
Tiihonen, et al. (2008) [*] Finland	26 offenders with APD and type 2 alcoholism, 25 HC	VBM	APD: ↑WMV bilat occipital, parietal, left cerebellum, ↓GMV bilat OFC, postcentral gyri, frontopolar cortex
Muller, Ganssbauer, et al. (2008) Germany	17 PSY offenders (PCL-R >28), 17 HC	VBM	PSY: ↓GMV in frontotemporal and right STG

Authors	Subjects	Method	Results
de Oliveira-Souza et al. (2008) Brazil	15 PSY (8m/7f, PCL-SV mean 17,8), 15 HC (8m/7f, PCL-SV mean 0,4)	VBM	PSY: ↓GMV frontopolar, OFC, anterior temporal cortices, STS and insula
Narayan et al. (2007) ^a UK	14 APD+history of violence, 12 Sz+history of violence, 15 Sz + no history of violence, 15 HC	Cortical thickness	Violence associated with thinner cortex in BA 10-12 and 32, most in RH. APD: cortical thinning in inferior mesial frontal cortex
Barkataki, et al. (2006) ^a UK	13 APD+history of violence, 13 Sz+history of violence, 15 Sz with no history of violence, 15 HC	sMRI	APD vs HC: ↓whole brain volume and temporal lobe, ↑putamen volume, All Sz: ↑lateral ventricle volume, Sz with violence: ↓whole brain and hippocampal volumes, ↑putamen size
Yang et al. (2005a) [□] USA	12 pathological liars (11m/1f), 16 APD (15m/1f), 21 HC (15m/6f)	sMRI	In liars: ↑WMV prefrontally, and ↓prefrontal grey/white ratios compared with APD and HC
Yang, et al. (2005b) [□] USA	16 unsuccessful PSY (PCL-R>23), 13 successful PSY (PCL-R>23), 23 HC (PCL-R ≤14)	sMRI	PCL-R score neg correlated with GMV prefrontally. In unsuccessful PSY: ↓prefrontal GMV vs HC
Raine, et al. (2004) [□] USA	16 unsuccessful PSY (PCL-R>23), 12 successful PSY (PCL-R>23), 23 HC (PCL-R ≤14)	sMRI	Unsuccessful PSY: structural hippocampus asymmetry (R > L) relative to both successful PSY and HC
Raine et al. (2003) [□] USA	15 community PSY with APD (PCL-R >23), 25 HC	sMRI	PSY: ↑WMV in CC, ↑functional interhemispheric connectivity vs HC
Dolan et al. (2002b) [^] UK	24 violent offenders with PD (18 PSY, 6 non-PSY, assessed by SHAPS), 19 HC	sMRI	No group differences in frontal or temporal lobe volumes

Authors	Subjects	Method	Results
Dolan, et al. (2002a) [^] UK	18 PSY violent offenders with APD (PSY assessed by SHAPS), 19 HC	sMRI	APD: ↓temporal lobe volumes, but no frontal lobe changes
Laakso et al. (2002) ⁺ Finland	24 violent offenders with APD and type 2 alcoholism (PCL-R), 33 HC	sMRI	APD vs HC: no differences after controlling for education and duration of alcoholism. No correlation between volumes and degree of psychopathy
Laakso et al. (2001) ⁺ Finland	18 violent offenders with APD and type 2 alcoholism (PCL-R)	sMRI	Negative correlation between PCL-R scores and volume of posterior hippocampus bilateral
Raine, et al. (2000) [¤] USA	21 community APD, 26 substance abuse, 34 HC, 21 psychiatric controls	sMRI	APD vs HC: ↓prefrontal GMV, ↓autonomic activity during stressor

PSY=psychopathy, PCL-R=psychopathy checklist revised, HC=healthy controls, sMRI=structural magnetic resonance imaging, ACC=anterior cingulate cortex, APD=antisocial personality disorder, AMY=amygdala, GM=gray matter, VBM=voxel-based morphometry, WMV=white matter volume, GMV=gray matter volume, OFC=orbitofrontal cortex, STG=superior temporal gyrus, STS=superior temporal sulcus, PCL-SV=psychopathy checklist screening version, Sz=schizophrenia, BA=Brodmann area, RH=right hemisphere, R=right, L=left, CC=corpus callosum, PD=personality disorder, SHAPS=Special Hospital Assessment of Personality and Socialization inventory. *same study sample, ¤study samples drawn from the same study population (108 community volunteers drawn from five temporary employment agencies in Los Angeles), ^ overlapping study samples, + overlapping study samples, ¢ overlapping study samples

3.2 FUNCTIONAL IMAGING STUDIES

Table 3.2 Functional imaging studies

Authors	Subjects	Method	Task	Result
Sommer et al. (2010) Germany	14 PSY forensic patients (PCL-R>28), 14 non-PSY forensic patients (PCL-R<15)	fMRI	cartoon stories (understanding that emotional states of others depend on fulfilment of their intention)	PSY: ↑OFC, medial frontal cortex and tempo-parietal areas. Non-PSY: ↑MNS, bilat supramarginal and superior frontal gyrus
Dolan & Fullam (2009) UK	12 Sz + high PSY (PCL-SV mean 12.4), 12 Sz + low PSY (PCL-SV mean 8.4)	fMRI	Facial expressions (anger, disgust, fear, sad)	High PSY (fear): ↓AMY right, High PSY (disgust): ↑AMY right
M. C. Craig et al. (2009) UK	9 offenders with PSY (PCL-R>25), 9 HC	DT-MRI	Resting state	PSY: ↓FA in the UF Correlation between antisocial behaviour and anatomical differences in the UF
Fullam et al. (2009) UK	24 controls (PPI)	fMRI	Simple Deception Paradigm	Lies ↑VLPFC. PPI correlated with activation in areas implicated in deception and social cognition
Muller, Sommer, et al. (2008) Germany	10 PSY offenders (PCL-R>28), 12 HC	fMRI	Emotional Simon Paradigm	PSY: no PFC activation through emotion and cognition integration, ↓STG
Rilling, et al. (2007) USA	30 students (15m/15f, PPI)	fMRI	Prisoners Dilemma task	High PPI: defected more often, more likely to not cooperate; ↓AMY + OFC when cooperate, ↓DLPFC, rACC when defected
Joyal et al.(2007) Finland	12 violent offenders with APD+Sz +SUD, 12 violent offenders with only Sz, 12 HC	fMRI	go/no-go task (impulse control)	Sz+APD+SUD: ↓fronto basally during go/no-go task than Sz and HC. ↑frontal motor, premotor and ACC than in Sz-only

Authors	Subjects	Method	Task	Result
Kumari, et al. (2006) UK	10 violent APD, 13 violent Sz, 12 non-violent Sz, 13 HC	fMRI	the 'n-back'-task (working memory task)	APD vs HC: ↓left frontal gyrus, ACC and precuneus
Deeley et al. (2006) UK	6 PSY (PCL-R >25) community, 9 HC	fMRI	Implicit emotional processing with faces (happy, fear, neutral)	PSY (happy): ↓fusiform and extrastriate cortex, PSY (fear): ↓fusiform
Birbaumer, et al. (2005) Germany	10 PSY offenders (PCL-R Factor 1> 10,5), 10 HC	fMRI	Aversive conditioning, CS: neutral faces US: painful stimuli	HC: ↑AMY, OFC, insula, and ACC during acquisition, PSY: no activity in this circuit
Gordon, et al. (2004) USA	20 students (high PSY and low PSY, using PPI)	fMRI	Recognition task requiring attention to affect or identity of target stimuli	Group differences in affect task in PFC and AMY. No differences in identity task
Kiehl, et al. (2004) [^] Canada	8 PSY offenders (PCL-R >28), 8 HC	fMRI	Lexical decision task with abstract and concrete words and pseudowords	PSY ↓right anterior superior temporal gyrus and surrounding cortex for abstract stimuli
Muller, et al. (2003) Germany	6 PSY offenders (PCL-R >30), 6 HC (PCL-R <10)	fMRI	Emotional processing using IAPS-pictures (neutral, negative, and positive)	PSY (neg): ↑right PFC and right AMY, ↓right subgenual cingulate, temporal gyrus, left dorsal cingulate, and parahippocampus. PSY (pos): ↑left OFC, ↓right medial frontal and temporal
Soderstrom et al. (2002) Sweden	32 violent offenders (PCL-R)	SPECT	Resting state	PCL-R factor 1 neg correlation with fronto- temp perfusion
Veit, et al. (2002) Germany	4 PSY offenders, 4 social phobia, 7 HC	fMRI	Aversive conditioning, CS: neutral faces US: painful pressure	PSY: ↓OFC, insula, ACC, right AMY vs HC and social phobia

Authors	Subjects	Method	Task	Result
Kiehl, et al. (2001) [^] Canada	8 PSY offenders (PCL-R > 28), 8 offenders (PCL-R < 23), 8 HC	fMRI	Affective memory task with neutral and negative words	PSY ↓ affect-related in the AMY, parahippocampus, hippocampus, ventral striatum, ↑ frontotemporal cortex bilat. in affective stimuli
Schneider, et al. (2000) Germany	12 APD, 12 HC	fMRI	Aversive conditioning, CS: faces, US: odour	APD: ↑ AMY and DLPFC during acquisition, while HC ↓
Raine, Phil, et al. (1998) [*] USA	12 psychosocial deprivation, 26 without psychosocial deprivation, 41 HC	PET	Continuous Performance Task (testing selective attention and impulsivity)	Without psychosocial deprivation: ↓ rCMRG in PFC vs with psychosocial deprivation and HC
Raine, Meloy, et al. (1998) [*] USA	9 affective, 15 predatory, 41 HC	PET	Continuous Performance Task	Affective: ↓ bilat PFC, ↑ RH subcortical, and ↓ RH PFC/subcortical ratios. Predatory: PFC function more like HC and ↑ right subcortical
Raine, et al. (1997) [*] USA	41 (39m/2f) murderers pleading NGRI, 41 HC	PET	Continuous Performance Task	Murderers: ↓ rCMRG in PFC, superior parietal gyrus, CC. Asymmetry (left < right) in AMY, thalamus, medial temporal lobe
Intrator, et al. (1997) USA	8 PSY patients (PCL-R > 25), 9 non-PSY patients, 9 HC	SPECT	Lexical decision task with neutral and emotional words	PSY: ↑ rCBF frontotemporal in the emotional condition
Seidenwurm et al. (1997) USA	7 violent subjects, 9 HC	PET	Resting state	↓ rCMRG in temporal lobe compared to HC

Authors	Subjects	Method	Task	Result
Kuruoglu et al. (1996) Turkey	40 alcohol-dependent (15 with APD), 10 HC	SPECT	Resting state	↓rCBF in alcoholic patients. APD ↓frontal perfusion
Volkow et al. (1995) USA	8 violent psychiatric patients, 8 HC	PET	Resting state	Pat: ↓rCMRG medial temporal and PFC vs HC
Goyer et al. (1994) USA	17 Personality disorders, 43 HC	PET	Resting state	inverse correlation between aggression and rCMRG in PFC
Raine et al. (1994) [*] USA	22 (20m/2f) murderers pleading NGRI, 22 HC	PET	Continuous Performance Task	Murderers: ↓rCMRG in lateral and medial PFC vs HC

fMRI=functional magnetic resonance imaging, PSY=psychopathy, OFC=orbitofrontal cortex, MNS=mirror system neurons, DT-MRI=diffusion tensor magnetic resonance imaging, FA=fractional anisotropy, UF=a ventral anterior associative bundle that connects the anterior temporal lobe with the OFC, APD=antisocial personality disorder, STG=superior temporal gyrus, Sz=schizophrenia, SUD=substance abuse disorder, ACC=anterior cingulate cortex, US=unconditioned stimulus, CS=conditioned stimulus, PPI=psychopathic personality inventory, AMY=amygdala, DLPFC=dorsolateral prefrontal cortex, IAPS=international affective picture system, SPECT=single photon emission computed tomography, PET=positron emission tomography, rCBF =regional cerebral blood flow, CC=corpus callosum, rCMRG=regional cerebral metabolic rates of glucose, PFC=prefrontal cortex, HC=healthy controls, NGRI=not guilty by reason of insanity, m=male, f=female. ^{*} overlapping study samples, ^ overlapping study samples

4 AIMS

The hypothesis of this thesis was that certain functions or symptoms in mentally disordered offenders can be connected to biological correlates. The overall aim was to study mentally disordered offenders in a multi dimensional approach, by parallel investigation of behaviour and peripheral physiology, as well as brain structure and function. This may lead to better understanding of the underlying neural mechanisms associated with antisocial and violent behaviour in mentally disordered offenders.

The specific aims for the different papers were:

Study I – The aim was to assess the relationships between personality traits, lifetime psychosocial functioning, and crime scene behaviour in offenders who have committed lethal violence. This was applied with specific focus on autistic and antisocial personality traits.

Study II – The aim was to investigate autonomic reactivity in response to emotional stimuli in mentally disordered offenders with various degrees of antisocial behaviour, but without psychopathy.

Study III – The aims were to assess cerebral structural changes in a group of offenders with lack of empathy and to assess whether there was a correlation between degrees of psychopathy and circumscribed structural changes in the brain.

Study IV – The aim was to investigate the neural underpinning of emotional facial perception and whether this differ in two groups of offenders, psychopathic offenders and offenders with autism spectrum disorder, in comparison to a healthy control group.

5 MATERIAL AND METHODS

5.1 SUBJECTS

All offenders in the four studies included in this thesis were recruited from the forensic psychiatric assessment unit in Stockholm. In this unit offenders are undergoing court ordered forensic psychiatric assessments before sentencing (see appendix). The assessment includes a Structured Clinical Interview for DSM-IV, (SCID I), (First, Gibbon, et al., 1997) with the aim to confirm and/or exclude diagnoses according to DSM-IV (American Psychiatric Association, 1994, 2000). Furthermore, the assessment includes the Wechsler Adult Intelligence Scale-Revised, WAIS-R (Wechsler, 1981) performed by a psychologist. When applicable, a PCL-R rating according to Hare, (Hare, 1991, 2003) is also performed.

Healthy controls (HC) were either staff or students at the department of forensic psychiatry (Study II, HC1) or individuals recruited through advertisement at Karolinska University Hospital in Huddinge, Sweden (Study III – IV, HC2).

Since the majority of violence crimes are performed by males, all study subjects (both offenders and HC) in this thesis are male.

5.1.1 Study sample in study I

All male subjects, who had committed lethal violence (homicide or manslaughter) between 1996 – 2001, and were assigned a main diagnosis of either antisocial personality disorder (APD) or autism spectrum disorder (ASD), were included. The material was divided into one ASD group (n=8) and one APD group (n=27). The APD group was further subdivided into two groups according to which kind of violence the offenders had used, either impulsive (APDi) (n= 14) or controlled (APDc) (n=13). The subdivision was performed based on information from the forensic psychiatric assessment report regarding type of crime and violence used. This was scored from 1 (strongly controlled) to 4 (strongly impulsive) (Raine, Meloy, et al., 1998). Subjects with score 1 and 2 were assigned to the APDc sub group and subjects with scores 3 and 4 were assigned to the APDi sub group. The offenders were 15-71 years old.

5.1.2 Study sample in study II

Inclusion criteria for study II were offenders with various diagnoses who had committed different kinds of crimes. Sixty one male subjects, 19-57 years old were included; 41 offenders with various diagnoses but without psychopathy and 20 healthy non-criminal controls (HC1). Exclusion criteria for participation in the study were; difficulties in reading and understanding Swedish, acute state of psychosis or acute compulsory psychiatric treatment at the time of assessment, or heavily sedating medication.

To ensure that the sample did not contain any psychopathic offenders; two independent raters conducted a file-based retrospective PCL-R rating (Hare, 1991, 2003), based on

the forensic psychiatric assessment reports. File-based PCL-R ratings have been shown to be reliable in earlier studies (Grann, et al., 1998).

The offenders were divided into two subgroups in order to study whether they differed in SCR in relation to the control group and in relation to one another;

- An antisocial subgroup ($n = 16$) consisting of subjects leading an antisocial life style, who had antisocial traits or fulfilled the criteria for APD.

- A non-antisocial subgroup ($n = 25$) consisting of subjects with various psychiatric diagnoses, not leading an antisocial life style.

5.1.3 Study sample in study III and IV

In study III and IV, inclusion criteria was subjects who were undergoing a forensic psychiatric assessment and assigned either a main diagnosis of psychopathy (PSY), according to Hare, PCL-R >30 (Hare, 2003) or autism spectrum disorder (ASD) (American Psychiatric Association, 2000). Exclusion criteria for participation in the study were; difficulties in reading and understanding Swedish, acute state of psychosis or acute compulsory psychiatric treatment at the time of assessment, or heavily sedating medication.

All subjects underwent an interview that included the Structured Clinical Interview for DSM-IV (SCID I) (First, et al., 1997; First, Spitzer, et al., 1997), Asperger Syndrome Diagnostic Interview, (ASDI) (Gillberg et al., 2001), and Psychopathy Check List Screening Version (PCL-SV) (S. D. Hart, et al., 1995). As the HC2 group consisted of non-offenders it was not possible to check their records (i.e. their self-reported criminality had to be relied upon), we chose to use the PCL-SV (which can be used without file-based information). The PCL-SV has a high correlation with the Psychopathic Checklist-revised (PCL-R) (Guy & Douglas, 2006) and is recommended for use in non-criminal subjects. The PCL-SV rating was assessed by two independent raters. In study III we used the PCL-SV scores to correlate number of psychopathic traits with cortical thickness. In study IV, the PCL-SV was used to make sure those subjects in the ASD and the HC2 did not have high numbers of psychopathic traits.

5.1.4 Summary of the study samples

Table 5.1 Description of the study samples.

Subjects	N	Age median (range)	PCL-scores mean (SD)
Study I			
APD (APDi+APDc)	27	32 (19-71)	-
APDi	14	38.5 (19-71)	-
APDc	13	25 (19-35)	-
ASD	8	23.5 (15-55)	-
Study II			
Antisocial offenders	16	33 (19-45)	21.7 ^a (5.2)
Non-antisocial offenders	25	39 (19-57)	12.2 ^a (6.4)
HC1	20	34 (24-57)	-
Study III+IV			
Offenders (ASD+PSY)	14	28.5 (18-40)	15.1 ^b (5.5)
ASD	7	32 (18-40)	10.6 ^b (3.5)
PSY	7	28 (18-33)	19.7 ^b (2.1)
HC2	12	26 (21-46)	0.5 ^b (0.5)

^aPCL-R score ^bPCL-SV score

APD=offenders with antisocial personality disorder, i=impulsive, c=controlled, ASD=offenders with autism spectrum disorder, HC=healthy controls (sample 1 and 2), PSY=offenders with psychopathy, N=number of study subjects, PCL=psychopathy checklist.

5.2 PROCEDURE

5.2.1 Study I

Study I was retrospective and the material consisted of file based data collected from forensic psychiatric assessments. Variables from the following three main categories were collected:

- 1) Background factors; if the subject was born in Sweden, if the subject's biological parents had a mental disorder or substance abuse, parents' separation during childhood, experience of physical and/or sexual abuse, early onset of alcohol and/or drug abuse (before age 15 years), early onset of criminal behaviour (before age 15 years), level of education, and previous admissions to child and adolescent psychiatry.
- 2) Demographic factors; contact with the mental health care system within the 5 years preceding the crime, previous suicide attempt, presence or absence of any physical illness (hepatitis was noted in particular), presence of other psychiatric diagnoses and intellectual level (IQ < 85, IQ = 85-115, IQ > 115).

- 3) Crime analysis; if the crime scene was a public place, relationship to victim, if the subject was intoxicated with alcohol or drugs at the time of the crime, and how the lethal violence was inflicted on the victim (gun, knife, or other, including blunt violence, strangulation, and poisoning).

These variables were compared between groups, firstly the comparison APD-group versus ASD-group was performed, followed by the APDi-group versus the APDc-group.

5.2.2 Study II

Skin conductance responses (SCR) were collected from the subjects while they viewed fifty pictures with emotional content (25 neutral and 25 negative) from the International Affective Picture System (IAPS; (Lang, et al., 1999)). The pictures were presented in a fixed randomized order, during a time frame of 6 seconds each. Following each picture, the subject was instructed to rate the pictures on a 1-9 scale according to arousal and valence. Arousal was rated with respect to experienced emotional intensity, from very calm (1) to very excited (9). Valence was rated from very unpleasant (1) to very pleasant (9).

SCRs were collected by a pair of silver/silver chloride electrodes (8 mm diameter), filled with electrode cream (Minograf electrode cream, SIEMENS-ELEMA AB), placed on the hypothenar eminence of the non-dominant hand, using sticky electrode collars. SCRs were measured during stimulus presentation and registered with Psylab SC5, in combination with Psylab Stand Alone Monitor, SAM instruments (www.psylab.com). The system constantly delivered 0.5 V and measured SCR with a sampling rate of 40 Hz. Responses were scored manually and defined as the maximum increase of the first uninterrupted SCR starting within a 1-4 s time interval following stimulus onset.

5.2.3 Study III+IV

The MR-scans were performed at Karolinska University hospital, Huddinge, using a Siemens Avanto 1.5 T whole body MRI system, with a 12-channel matrix head coil. The subjects were placed supine in the scanner wearing headphones to reduce noise from the machine. To minimize head motion, all subjects' heads were fixated with a vacuum pillow.

All subjects performed the Ekman-study (study IV) inside the scanner and then a structural sequence was collected (study III-IV). In the Ekman-study, the stimuli comprised photographs of human facial expressions from the standardized Ekman and Friesen face set (P. Ekman & Friesen, 1976). The task used a blocked design which consisted of alternating blocks of fearful faces (36 sec) and neutral faces (36 sec). Each block consisted of 15 different faces, presented for 2 seconds each, followed by a fixation cross for 400 ms. The 'face-blocks' were interspersed with 18 sec 'baseline-blocks' with a white fixation cross on a black screen (see Fig 5.1). As an attention control an on-line gender identification task was employed, where subjects were asked to identify the sex (male or female) of the face by means of pressing buttons. The subjects viewed the pictures through a mirror on the head coil and the pictures were

presented with a projector on a screen inside the scanner room. Mean reaction time and accuracy according to the sex discrimination task were used as a proxy for attention to the faces.

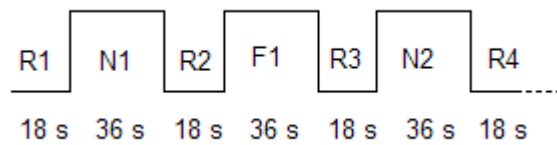


Figure 5.1 The experimental block design with 36 sec of stimuli block with fearful faces (F), 36 sec control blocks with neutral faces (N) and 18 sec of baseline blocks with fixation cross (R).

5.3 MRI AQUISITION (STUDY III-IV)

5.3.1 Structural MRI

For structural data, we used a 3D magnetization-prepared rapid-acquisition gradient echo (MP-RAGE) sequence. A total of 176 sagittal slices were acquired with the following parameters: repetition time (TR) = 2300 ms, inversion time (TI) = 1100 ms, echo time (TE) = 3.93 ms, slice thickness = 1 mm, field of view (FOV) = 256 mm x 256 mm, Matrix = 256 x 256, isotropic voxel size = 1 mm³.

5.3.2 Functional MRI (fMRI) (Study IV)

Functional imaging was performed using a T2*-weighted gradient echo planar imaging sequence (EPI) -mosaic sequence (TR = 3000 ms, TE = 50 ms, slice thickness = 5 mm, gap between slices = 0.5 mm, FOV = 220 mm, matrix size = 64 x 64, voxel dimension = 3.4 mm x 3.4 mm x 5 mm, 30 coronal slices, covering the whole brain). In total, 114 volumes were collected in the functional experiment.

5.4 MRI-ANALYSIS (STUDY III)

5.4.1 Cortical thickness

MRI data were linearly and nonlinearly registered to a common model using the ICBM152 (Mazziotta et al., 2001) as standard space. A brain mask was created by iteratively fitting a deformable surface to the brain meninges using an algorithm similar to the brain extraction tool (BET) by Smith 2002 (Smith, 2002) (figure 5.2.A). The voxels inside the brain mask were classified into white matter (WM), gray matter (GM), and cerebrospinal fluid (CSF) using a fuzzy clustering algorithm producing fuzzy classification images used for further processing (figure 5.2.B). Fast Accurate Cortex Extraction (FACE) was used to calculate cortical thickness (S. F. Eskildsen & Ostergaard, 2006; S.F. Eskildsen et al., 2005). FACE generates topologically correct surfaces of the WM in each hemisphere of the cerebrum (figure 5.2.C-D). These surfaces are iteratively deformed to the WM/GM and GM/CSF boundary of the cortex respectively. Each hemispheric surface consists of approximately 100.000 vertices, and from each of these a cortical thickness measurement is calculated as the distance between the WM/GM boundary and the GM/CSF boundary perpendicular to the

cortical surface. The thickness measurements were divided into the main lobes, based on a digital brain atlas in standard space that accompany the MRIcro software package (Rorden & Brett, 2000). From this parcellation, lobe-wise thickness averages were calculated.

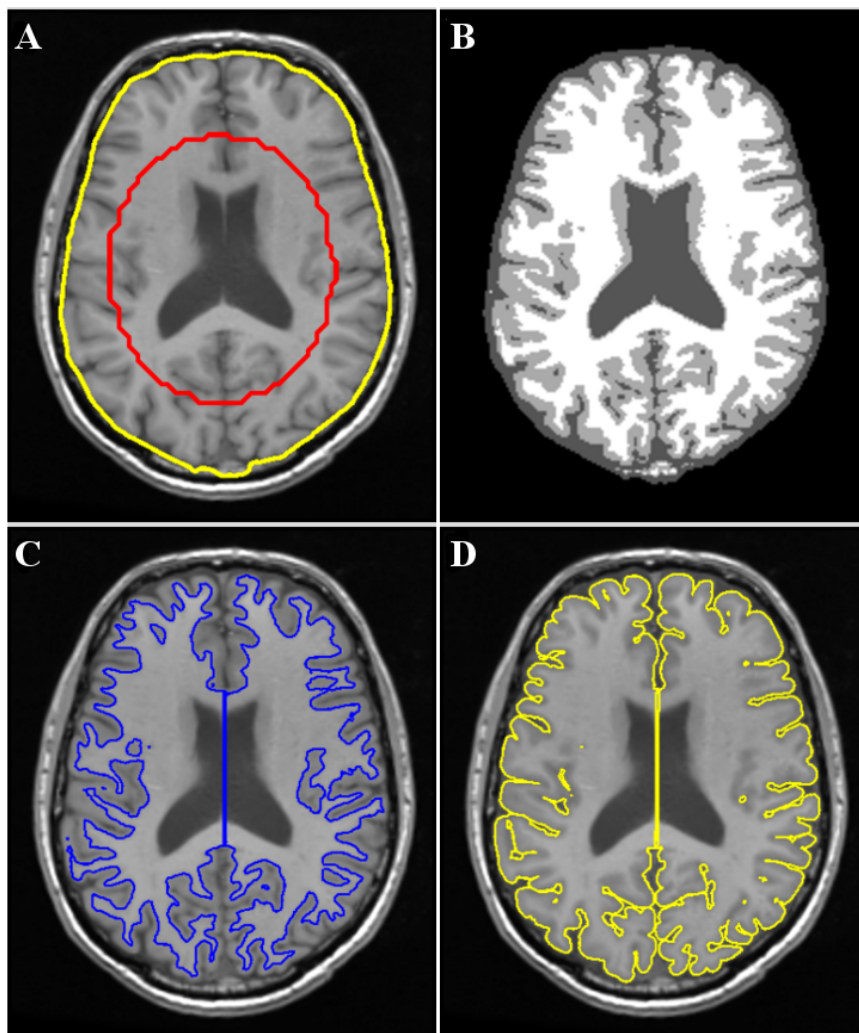


Figure 5.2 Extraction of the cortical boundaries. (A) Spatially aligned MRI data with initial (dark contour) and final (bright contour) brain extraction contour superimposed. (B) Brain tissue classified as WM, GM, and CSF. (C) WM surface superimposed on the MRI data. (D) GM surface superimposed on the MRI data.

5.5 FMRI-ANALYSIS (STUDY IV)

In each fMRI run the first three volumes were discarded to allow for T2* equilibration effects. Image time-series analysis was performed using Brain voyager, BVQX 1.9. Pre-processing is important in the fMRI-analysis and contains several steps. First there was a correction of slice scan times in order to compensate for the fact that the images are taken sequentially at slightly different time points. The slice scanning order was ascending interleaved. Movement of the subject is unavoidable in fMRI-experiments and a major concern, as the high spatial resolution in fMRI sequences is sensitive to motion artifacts. In order to minimize motion, we used a vacuum pillow during the

experiment. As breathing and swallowing are motions that the subject cannot voluntarily suppress for any length of time, a 3D motion correction was performed using trilinear/sinc interpolation in order to improve the quality of the data. To remove unwanted components of a time series without damaging the signal of interest, we applied a temporal filter removing linear trend. The images of each subject were then co-registered to the 3D anatomical volume, normalized into Talairach space (Talairach, 1988), and hereby resampled into 3 mm isotropic voxels. The resulting volume-time course files (VTC) were then spatially smoothed with a Gaussian filter of 8 mm full-width at half maximum for the group analyzes.

We chose the following anatomical regions of interest (ROIs), from the model for facial perception by Haxby (Haxby, et al., 2002); inferior occipital gyrus, superior temporal sulcus, lateral fusiformis gyrus, insula, hippocampus, parahippocampus, cingulate gyrus, and amygdala. Within these predefined areas, we used a threshold level of $p < 0.001$ (uncorrected), in line with many other studies in the field. As the amygdala has been shown in many studies to be of major importance for fearful facial processing (Murphy, et al., 2003), we used a threshold of $p < 0.05$ (uncorrected) in this circumscribed ROI.

Firstly we applied individual analysis investigating BOLD-activation associated specifically with the processing of the emotional cues in fearful faces (i.e. fearful faces > neutral faces). This was done by applying a fixed effects model with condition-specific stimulus boxcar functions, convolved with a gamma-kernel to model the hemodynamic response behaviour. Three predictors were entered into the design matrix: fearful faces, neutral faces, and baseline (looking at a white fixation cross on a black screen). The outputs of the model were beta values for the different conditions.

Between-group analyses were performed between (1) the HC2 and the offenders and (2) between the two subgroups of offenders (ASD vs PSY). Random effects models were used for the group analyses. The between-group analyses were calculated in the following steps: firstly all individual VTCs were created for the contrast fearful faces > neutral faces, then a two-tailed t-test was performed between the HC group and the offender group, and finally the same procedure was performed between the ASD and the PSY groups.

5.5.1 Functional co activation

The functional co-activation analysis was performed in the following steps: first functional ROIs in the right and the left amygdala in the offender group were defined based on the group contrast fearful faces > neutral faces, consisting of 8 voxels located around the peak activation voxel in each of the two regions (mean Talairach localization: $x = 21, y = -11, z = -11$; $x = -19, y = -7, z = -13$). Individual beta values from these specific ROIs were then collected. The difference between the beta values for the fear condition minus the beta value for the neutral condition for each subject was used as a measurement of the amygdala reactivity to fearful expressions. From the between group analyses (ASD vs PSY), we found five regions (table 6.2) where the two offender groups differed from each other within the network for the processing facial expressions (Haxby, et al., 2002). In all these five regions, we defined functional

ROIs, as described above, for the amygdala and extracted beta values from these ROIs as well. We then correlated amygdala reactivity with activity in these specific ROIs, using Pearson's correlation, on each side separately (right and left), within each of the two groups (ASD and PSY).

5.6 STATISTICS

5.6.1 Study I

The Mann-Whitney U-test or the Chi-square test was used to facilitate comparisons between groups. The Chi-square test was corrected for numbers less than 10 in any cell using the V^2 (Kendall, 1979). A p-value of less than 0.05 was considered significant.

5.6.2 Study II

All demographic variables and scores of the PCL-R were tested with the Chi-square test, the Fischer's exact test or the Mann-Whitney-U test. The confidence interval was set at 95% and the level of statistical significance of differences was $p < 0.05$.

Inter-rater reliability for the PCL-R ratings was computed for 22 of the 41 offenders by using the intraclass correlation coefficient (ICC);(Shrout & Fleiss, 1979). The ICC was calculated using a two-way mixed effects model. The single measure ICC was 0.79 (95% CI = 0.56-0.91, $n = 22$) for the total score of the PCL-R. Three separated two-tailed t-tests showed significant differences between the two offender groups (antisocial versus non-antisocial) for total PCL-R scores ($t = 4.39$, $df = 39$, $P < 0.001$).

To investigate group effects on SCRs and subjective ratings, we used 2×2 (neutral and negative pictures \times HC1 and offenders) ANOVA, and 2×3 (neutral and negative pictures \times HC1, antisocial and non-antisocial offenders) ANOVA. To reduce skewness, SCRs on individual trials were square-root transformed before averaging.

Two measures of SCRs were performed; magnitude, which includes all responses across stimuli, and amplitude, which excludes non-responses (Dawson et al., 2000), here defined as responses below $0.01 \mu\text{S}$. In order to rule out group differences based on differences in actual responses, the analyses based on magnitude were repeated with amplitude measurement of the SCRs (i.e., excluding non-responses). The outcome was similar to the findings based on magnitude responses, subsequently; the analyses for amplitude were excluded from the result section. To reduce inter individual error variance of SCRs magnitude, a range correction was performed, in which each subject's response was expressed as a proportion of that subject's largest response, which was given the value 1 (Lykken, 1972).

At the time of the assessment, the offenders used a variety of medications. For statistical analysis, medication was coded as a dichotomous variable. The t-tests of the difference in mean SCRs (magnitude) for neutral and negative pictures showed no significant differences between participants. In addition, separate mixed 2×2 ANOVAs of ratings and SCRs with picture category as within-subject factor and medication and

offender group as between-subject factors, controlling for age, showed no significant effects ($F_s < 1$). Therefore, medication was eliminated from further analyses.

5.6.3 Study III-IV

All demographic variables and scores of the PCL-SV were tested with the Chi-square test, the Fischer's exact test or the Mann-Whitney-U test. The confidence interval was set at 95% and the level of statistical significance of differences was $p < 0.05$.

Inter-rater reliability for the PCL-SV ratings was computed using the ICC (Shrout & Fleiss, 1979). The single measure ICC was 0.98 (95% CI = 0.96-0.99 $n = 25$) for the total score of the PCL-SV. Two-tailed t-tests showed significant differences between the HC2 group and the offenders for total PCL-SV scores ($p < 0.0001$). The same analysis was performed between the two subgroups of offenders (PSY vs AUT) for total PCL-SV scores ($p < 0.0001$).

In study III, bivariate regression analysis was performed to test correlation between PCL-SV scores and cortical thickness in the different lobes. As the distribution of PCL-SV scores was positively skewed, we performed a square root transformation of the variable, but since the result remained stable, we present the non-transformed variable here.

Regarding the behavioural data in study IV (mean reaction time and accuracy according to the sex discrimination task), comparison between groups was performed using two-tailed t-test.

5.7 ETHICS

Study I was approved by the ethic committee at the former Huddinge university hospital (274/02). As study I was a retrospective register study we did not obtain the informed consent of all the subjects, which was in accordance with the ethical approval which had been granted.

Study II-IV was approved and conducted in accordance with the ethical guidelines established by the Regional Ethic Committee at the Karolinska Institutet in Stockholm (2006/925-31/3, 2007/1042-323). After description of the study, written informed consent was obtained from all subjects.

6 RESULT AND DISCUSSION

6.1 PSYCHOSOCIAL FACTORS AND CRIME SCENE BEHAVIOUR (STUDY I)

The main finding in Study I was that there are different subgroups among homicide offenders, revealed in both differences in psychosocial factors and crime scene behaviour. All subjects in the ASD group were born in Sweden, compared to 60% in the APD group. Subjects in the ASD group were less intoxicated at the time of the crime and were less likely to use knives or guns, compared to the APD group. Subjects in the APDi group were older than subjects in the APDc group. Also, they were more likely to have suffered physical abuse during childhood, to have established psychiatric contacts, and to have made suicide attempts, compared to subjects in the APDc group. In addition, there was a higher incidence of substance abuse in biological parents of subjects in the APDi group. In the APDi group, subjects were more likely to use knives as homicide weapons, in contrast to subjects in the APDc group who were more likely to use guns.

No statistical differences were found in the following variables: separated parents, level of education, early onset of alcohol and drug abuse, early onset of criminal behaviour, admission to child and adolescent psychiatry, co morbidity of other DSM-IV diagnoses, relationship to victim, and public crime scene.

6.1.1 Discussion

The results suggest that differences in psychosocial factors and crime scene behaviour are related to different subgroup among homicide offenders. These results are in line with those presented by Meloy (2000) regarding stalkers (Meloy, et al., 2000) and Hazelwood (2000) in the sexually violent offender (Hazelwood & Warren, 2000), which differentiated between impulsive and more controlled or ritualistic crime scene behaviour and related this to differences in psychosocial factors. The current results may also be relevant for the concept of *affective and predatory violence* (McEllistrem, 2004; Meloy, 1988). The different types of violence can be related to different personality traits, such as antisocial or autistic traits. In the current study, subjects in the APDc group may be more prone to use predatory violence.

Some of the current findings deserve to be elaborated on. Subjects in the APDi group were more inclined to use self-destructive behaviour (i.e. suicide attempts) compared with subjects from the other groups. In addition, in the APDi group, there was a tendency toward being intoxicated with alcohol, at the time of the crime, more often than in the APDc and ASD groups, as an example of the more impulsive behaviour. It is conceivable that this impulsivity could be a phenotypic expression related to a disturbance in the serotonergic system and in the prefrontal regions. That would be in line with results from studies investigating biological variables (Mantere et al., 2002) and associations between brain function and decision making (R. D. Rogers et al., 1999). The tendency toward early disruptive behaviour in the APDi group may also be consistent with the same hypothesis. Attention deficit/hyperactivity disorder (ADHD) is

often seen in the background history of APDi participants. ADHD has also been related to a polymorphism in the serotonin transporter promoter region that may be associated with impulsivity (Retz et al., 2002). The subjects in the APDi group were significantly older than those in the APDc group and the ASD group. One possible mechanism is that an ADHD-related condition during childhood and youth makes subjects in the APDi group abuse central stimulants such as amphetamine, which may actually make them less impulsive. However, when they become older they often start to abuse alcohol, which may reduce their impulse control and lead to an increased risk of violent acts. In ASD subjects, it may be that their difficulties in social interactions will become marked in youth and early adulthood, resulting in risk of violent behaviour at an earlier stage as compared to APDi participants. Many subjects in the APDc group (81%) were intoxicated at the time of the crime; however, the crimes were still described as planned and controlled in the forensic psychiatric reports, possibly suggesting that these offenders also have a tendency toward a more controlled abuse pattern compared to APDi offenders.

One interesting observation was that the methods of murder seemed to reflect the different traits of the three groups. In the APD groups, the act of killing was more instrumental than in the ASD group. In the ASD there were different methods, such as intoxication and strangulation, which might reflect more odd motives than in the APD group. In the APDc group the use of a gun was the most common method, which could be related to more predatory violence. Knives were the most common weapons in the APDi group, possibly reflecting an impulsive affective act of violence.

6.1.2 Limitations

The current results must be cautiously interpreted because of the relatively small sample size and the retrospective design. Classifying participants into impulsive and controlled subgroups solely based on information retrieved from forensic psychiatric reports might seem to be a methodological weakness. Although, the Swedish penal code requires this information to be included in Swedish forensic psychiatric reports, so in this way, the information can be regarded as highly reliable. Moreover, the members of the forensic psychiatric teams were unaware of the present study, at the time of the assessments, so no conflict of interest has been present.

6.1.3 Conclusion

In study I, homicide offenders with antisocial traits differed from homicide offenders with autistic traits, with regards to offending behaviour. Moreover, two different subgroups of APD offenders emerged; those inclined to use impulsive offending (APDi) and those inclined to use controlled offending behaviour (APDc). Subjects in the APDi group were more likely to have been subjected to more traumatic events during childhood, compared to the APDc group. These results may have implications for understanding specific mediators of violence at crime scene and may also have applications in risk and need analysis and risk management, including monitoring.

6.2 PHYSIOLOGICAL REACTIVITY TO EMOTIONAL STIMULI (STUDY II)

Negative pictures elicited larger SCRs and were rated as more arousing and aversive compared to neutral pictures among the whole study sample. The HC1 showed larger SCRs and rated the pictures as more aversive compared to the aggregated offender group. Comparisons of the HC1 with the two sub groups of offenders showed lower SCRs in the antisocial and the non-antisocial groups. There were no significant differences between the two offender groups (antisocial and non-antisocial) on any measurements.

6.2.1 Discussion

Differences in emotional response were found between the HC1 and the offender groups, but not between the two subgroups of offenders. Therefore, the results of the present study suggest that levels of antisocial traits may not be a differentiating factor with regard to emotional reactivity. It has been suggested that low physiological arousal per se predisposes antisocial individuals to commit crimes (Raine, 2002a). According to the stimulation seeking theory, antisocial individuals may be driven to commit crimes as a way to increase their arousal level thus compensating for an unpleasant physiological state caused by hypoarousal (Raine, 2002a). Furthermore, in the low fear theory, it is argued that inherent hypoarousal facilitates criminal actions (Raine, 2002a). Our results suggest that low levels of autonomic reactivity as an underlying factor for criminal behaviour may generalize to non-antisocial mentally disordered offenders as well. Another important aspect worth noting is that hypoarousal may be limited to aversive pictures specifically or, it may reflect a general attenuation of reactivity (Benning et al., 2005). Although our study setting was limited to neutral and negative pictures, the results may be indicative of a general affective attenuation in the offenders. Differences in emotional reactivity between the controls and offenders could be due to offenders failing to allocate attention resources to the emotional stimuli, which has been proposed by earlier research (Bergvall et al., 2001; Raine & Jones, 1987). Another possibility is that the lower SCRs are associated with fewer somatic markers (Damasio, 1996) and thus lower subjective ratings, possibly leading to behaviour and decision making being less influenced by bodily sensations. Our finding of attenuated emotional reactivity as a common trait in mentally disordered offenders with various diagnoses warrants future studies with larger groups and additional physiological measures.

6.2.2 Limitations

The HC1 were not assessed with regard to intellectual capacity or psychopathic traits. It is important to keep in mind, however, that the present study was conducted in a forensic psychiatric context, prior to sentencing. This is a setting in which a substantial number of offenders can be expected to display a level of intelligence below average (in our sample, 25% of the offenders had an intellectual capacity below average). Moreover, for the purpose of the present study, psychopathic offenders were excluded by retrospective PCL-R rating. Given these circumstances, it was not considered fruitful to match the offender groups to a group of non-criminal control subjects with full-time jobs and a high level of social functioning.

6.2.3 Conclusion

The present study includes a unique population specifically recruited from the forensic psychiatric system, providing new knowledge about different subgroups of mentally disordered offenders. In contrast to the HC1, two subgroups of mentally disordered offenders, but without psychopathy, showed a general attenuation of arousal reactivity, as measured by SCRs and subjective ratings to pictures. In addition, both subgroups showed similar attenuated emotional reactivity to neutral and negative pictures. Therefore, in the present study, antisocial behaviour was not a differentiating factor for emotional reactivity. Our findings suggest that attenuated reactivity to neutral and negative pictures might be a general feature in mentally disordered offenders without psychopathy.

6.3 CEREBRAL STRUCTURAL CHANGES (STUDY III)

The offender group had thinner cortex bilaterally in the frontal lobes and in the whole right hemisphere (RH). There was also a tendency towards thinner cortex in the right temporal lobe (Table 6.1).

Table 6.1 Cortical thickness average in mm. Mean values \pm standard deviation.

Region	HC2	Offenders	T-value	p-value	Df
Frontal lobe, L*	2.39 \pm 0.19	2.22 \pm 0.23	2.078	0.049	24
Frontal lobe, R*	2.37 \pm 0.20	2.19 \pm 0.22	2.215	0.037	24
Temporal lobe, L	2.68 \pm 0.16	2.56 \pm 0.22	1.157	0.129	24
Temporal lobe, R	2.73 \pm 0.14	2.58 \pm 0.24	1.898	0.071	21.5 ^a
Parietal lobe, L	1.96 \pm 0.19	1.88 \pm 0.15	1.191	0.245	24
Parietal lobe, R	2.04 \pm 0.16	1.92 \pm 0.17	1.852	0.076	24
Occipital lobe, L	1.83 \pm 0.17	1.83 \pm 0.13	0.002	0.998	24
Occipital lobe, R	1.83 \pm 0.14	1.80 \pm 0.11	0.610	0.547	24
Hemisphere, L	2.26 \pm 0.17	2.15 \pm 0.18	1.647	0.113	24
Hemisphere, R*	2.30 \pm 0.15	2.16 \pm 0.18	2.083	0.048	24

df = degrees of freedom, HC = healthy controls, L = left side, R = right side.

* p<0.05 ^aequal variances not assumed

6.3.1 Correlation between cortical thickness and PCL-SV scores

When correlating PCL-SV scores with differences in cortical thickness across the two study groups (offenders and HC2), significant negative correlations between PCL-SV scores and cortical thickness were found in the right temporal lobe ($r = -0.44$), the right frontal lobe ($r = -0.44$), the left frontal lobe ($r = -0.41$), as well as in the whole RH ($r = -$

0.43). There were no significant correlations between PCL-SV-scores and cortical thickness in the other lobes.

6.3.2 Discussion

These findings are in line with previous results in antisocial and psychopathic subjects (Muller, 2010; Wahlund & Kristiansson, 2009; Yang, et al., 2009; Yang, et al., 2005b). Reduced grey matter in the frontal lobes has been described in both antisocial subjects (Raine, et al., 2000) and in “unsuccessful” psychopaths (Yang, et al., 2005b). Two studies VBM also showed reduced grey matter in the frontal lobes in subjects with psychopathy (de Oliveira-Souza, et al., 2008; Muller, et al., 2008).

The offenders had thinner cortex in the whole right hemisphere (RH) compared to HC2. Previous studies have demonstrated subjects with damage in the RH show impairment in the capacity for affective recognition, which supports the RH-hypothesis (Borod et al., 1998; Yang, et al., 2005b), implying that social behaviour and compliance with social norms is mediated by the RH. Comparison between right and left unilateral lesions in the ventromedial prefrontal cortices (VMPC), suggests that the RH-lesion patients had a more profound disturbance of social and interpersonal behaviours than the left hemisphere (LH)-lesion group (Tranel et al., 2002). Put together, our findings of thinner cortex in the frontal lobes and in the RH in these offenders could relate to the emotional pathology, associated with lack of empathy, described in both autistic and psychopathic subjects. There was a tendency towards thinner cortex also in the right temporal lobe in the offender group. The lack of significance may be related to a type II error since the sample size was small. Several structures in the temporal lobes are important for emotional processing and learning. Also, some of these structures, e.g. the amygdala and the insular cortex, have been suggested to be part of cortical networks involved in empathy development (Singer et al., 2009). Thus, the lack of empathy seen in these forensic psychiatric populations could also be due to less than optimal neural functioning in these nodes.

The finding of negative correlation between PCL-SV scores and cortex thickness in the right temporal lobe and bilaterally in the frontal lobes is in line with a previous study by Yang et al. (2009) that showed a negative correlation between cortical thickness and scores in the affective subscale of PCL-R (Yang, et al., 2009). This negative correlation suggests that these areas could have specific roles in the behavioural profile exhibited by psychopathic offenders, in whom lack of empathy is one of the more pronounced characteristics.

Early animal studies on rats have shown that environmental factors can affect the developmental of cortical thickness; rats which were exposed to an enriched environment exhibited an increased cortical thickness in the brain compared to rats which were placed in isolation without stimuli (Diamond et al., 1964). It also seems possible to increase the gray matter in humans through physical and mental training; this has been shown for motor activities, such as learning to juggle (Draganski et al., 2004; Driemeyer et al., 2008), extensive studying (Draganski et al., 2006), memory tasks (Engvig et al., 2010), and second language learning (Stein et al., 2010). Studies on subjects that meditate have shown increased cortical thickness in regions connected to

attention, interoception and sensory processing (Lazar et al., 2005). In the prison system, there is an increased use of offender programs with focus on social learning and cognitive behavioural therapy. Could repeated sessions of applied social learning have an impact on cortical thickness in cerebral regions involved in e.g. impulse control and emotional learning in these criminal populations? Moreover, in offenders with specific developmental disorders, further research should be performed in order to clarify whether changes in cortical thickness, after new pedagogic intervention tools, is correlated to relapse in violence.

6.3.3 Limitations

The sample size was small and it was not possible to control for education and socioeconomic status in comparison to the HC2. Further, we were not able to test the HC2 with WAIS-R and it cannot be excluded that IQ could have influenced the results (Narr et al., 2007). Finally, some offenders had a history of drug and alcohol misuse prior to arrest. As they were remanded in custody, all of the offenders had been free from drugs and alcohol for at least 6-10 weeks prior inclusion. As these were subjects undergoing forensic psychiatric assessment, one should be cautious about generalizing to other groups of offenders and psychiatric patients. Having been referred for forensic psychiatric assessment, it is conceivable that the studied subjects had more psychiatric problems than the average offender in the prison system.

6.3.4 Conclusions

This study investigated cortical thickness in a group of offenders undergoing forensic psychiatric assessment. Thinner cortex was shown in the frontal lobes and in the RH in the offenders, compared to subjects in the HC2 group. A negative correlation was also evident between psychopathy-scores, assessed with the PCL-SV, and cortical thickness in the frontal lobes, the right temporal lobe, and in the RH across the two study groups. Regional cortical thinning in the frontal and temporal lobes could reflect neural underpinnings related to deficient emotional processing and deranged empathic development, which are common clinical traits in offenders. Whether the findings are causes or consequences of the antisocial behaviour is still unknown.

6.4 CEREBRAL PROCESSING OF EMOTIONAL STIMULI (STUDY IV)

The main finding of study IV was that the whole offender group demonstrated increased neuronal (BOLD) activity, compared to the HC2 group, within the network involved in perceiving and processing emotional facial information (Haxby, et al., 2002); bilateral amygdala, cingulate gyrus, and left hippocampus. When comparing the two subgroups of offenders, PSY vs ASD, the two groups differed in five regions. Functional co-activation analyses revealed that the two subgroups differed qualitatively in the network processing of emotional facial expressions. Behavioural data did not differ between groups.

6.4.1 Neuronal activity (fMRI-BOLD response)

The whole offender group, compared to HC2 had higher activation in the amygdala, bilaterally, the left hippocampus, as well as in the medial cingulate cortex, bilaterally

(Table 6.2). In a comparison between the two subgroups of offenders (ASD vs PSY), there were two regions in which the PSY group had significantly higher activation than the ASD group; the ACC (Fig 6.2) and the insula on the left side (Table 6.2). The ASD group, on the other hand, had higher activation in the right insula, the left cingulate cortex, and the left fusiform gyrus (Table 6.2).

Table 6.2 Between group comparisons in the contrast fear>neutral, p <0.001 (uncorrected), with Talairach coordinates (x, y, z)

Region	BA	Hemisphere	X	Y	z	No of voxels	T-value
<i>Offenders>HC2</i>							
Amygdala		L	-19	-7	-13	118	2.22
Amygdala		R	21	-11	-11	126	2.18
Cingulum	24	R	21	0	34	7	3.85
Cingulate gyrus	23	L	-23	23	27	44	3.93
Parahippocampus-Hippocampus		L	-43	-33	-5	22	3.89
<i>HC2>Offenders</i>							
No areas							
<i>PSY>ASD</i>							
Insula	13	L	-39	-7	-5	24	4.36
ACC	24	L	-4	27	17	19	4.40
<i>ASD>PSY</i>							
Insula	13	R	34	-25	0	258	4.61
Fusiform gyrus	18	L	-7	-91	-14	26	4.37
Cingulate gyrus	23	L	-15	-13	31	7	4.45

BA=Brodman's areas, ACC=anterior cingulate cortex, HC2=healthy controls, PSY=offenders With psychopathy, ASD=offenders with autism spectrum disorder

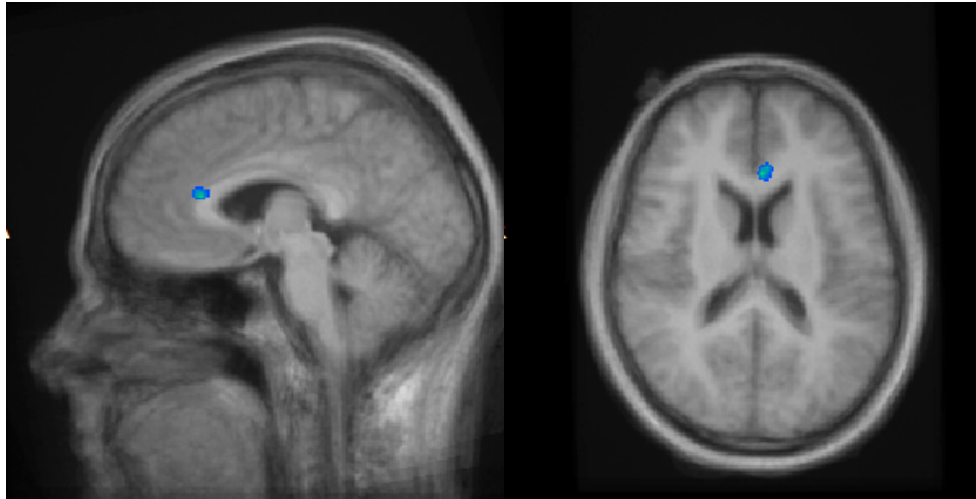


Figure 6.2 Between-group analyses (PSY>ASD) in the contrast fearful>neutral faces in ACC (mean TAL-coordinates: -4, 27, 17), p -value<0.001 (uncorrected). This region was correlated with amygdala in the PSY-group. PSY=psychopathic offenders, ASD=offenders with autism spectrum disorder, ACC=anterior cingulate cortex

6.4.2 Functional co activation

In the PSY group, there was a correlation between the amygdala and the ACC on the left side ($r^{xy} = 0.97$, $p < 0.001$), which was not found in the ASD group ($r^{xy} = 0.327$, $p = 0.475$) (fig. 3.3). No other correlations with amygdala reactivity were significant in either of the two groups.

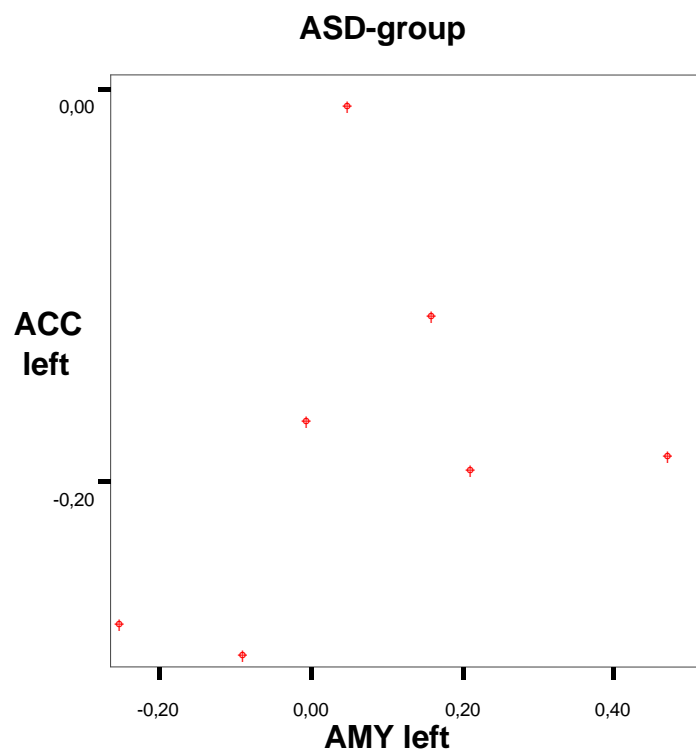
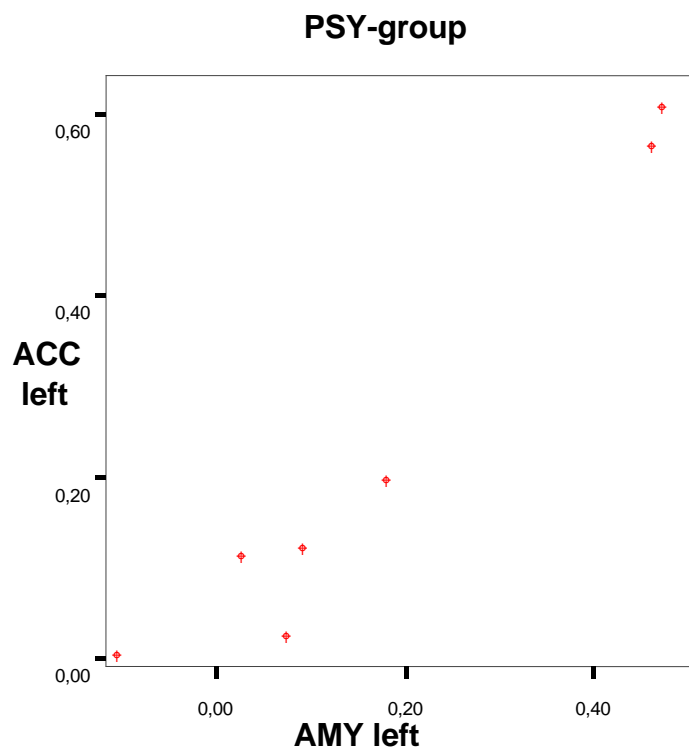


Figure 6.3 Functional co-activation; correlation between reactivity in the amygdala (AMY) and in the anterior cingulate cortex (ACC) on the left side in the PSY group, but no significant correlation in the group of offenders with ASD. PSY=psychopathic offenders, ASD=autism spectrum disorder.

6.4.3 Discussion

In other studies investigating cerebral activation patterns, applying brain imaging techniques in antisocial subjects, impairments in the frontal lobes (Raine, et al., 2000), the limbic system (Kiehl, et al., 2001; Laakso, et al., 2001), and suggested impairment in the balance between these two systems have been described (Muller, et al., 2003; Raine, Meloy, et al., 1998; Schneider, et al., 2000). Previous studies have reported both hypoactivity (Birbaumer, et al., 2005; Kiehl, et al., 2001) and hyperactivity (Muller, et al., 2003; Schneider, et al., 2000) in the amygdala and the limbic system. Hyperactivity in amygdala in the current offender group could be related to alteration in the way emotional facial expressions are processed in this specific group. The enhanced amygdala activity may be related to an ambiguity in the processing of the emotional face signals (M. Davis & Whalen, 2001). If so, this ambiguity is related to enhancing cognitive processing associated with perception of fearful faces in the offender group, which could explain the activations also in more cognitive regions, such as the medial cingulate gyrus and the hippocampus.

In the contrast ASD vs PSY, we observed differential activations in both the insular cortex (left vs right) and cingulate gyrus. Hence, ASD and PSY seem to have differential activation patterns within these two cortical regions during perception of fearful faces. The insular cortex, especially the right side, has been connected to visceral representation of autonomic arousal (A. D. Craig, 2002; Saper, 2002). As the ASD-group activated the right insula more than the PSY-group, this could reflect that exposure to fearful facial expressions is associated with more bodily arousal in the ASD-group compared to the PSY-group. This reasoning is in line with earlier studies, showing that psychopathic subjects have lower autonomic responses during exposure to emotionally relevant information (Birbaumer, et al., 2005; Hare, 1965; Herpertz, et al., 2001; Lykken, 1957; Patrick, et al., 1994; Raine, 1996). The PSY-group had higher activation in the ACC compared to the ASD-group which could be connected to the possible inhibition of amygdala reactivity. The ASD-group, on the other hand, had higher activity in the posterior cingulate gyrus, Brodmann area 23. The posterior cingulate cortex has been connected to both emotional processing and memory-related functions (Maddock, 1999; Maddock et al., 2003; Pavlovic, 2010). Accordingly, the higher posterior cingulate activation in the ASD-group could reflect altered emotional or memory related processing of fearful facial information compared to the PSY-group. These brain activation differences could be related to dysfunction in the neural underpinning of perception of fearful faces.

The strong correlation between amygdala reactivity and ACC reactivity in the PSY group on the left side was not found in the ASD group. This suggests that the amygdala activation in the two offender groups may differ qualitatively, even though there were no quantitative differences. The ACC influences emotional processing (Bush, et al., 2000) and previous research has suggested a role of the ACC in modulating the amygdala activity (Das et al., 2005). The amygdala – ACC correlation could reflect a marked ACC influence on fearful emotional facial processing in the amygdala, resulting in the disturbed fearful facial processing pattern often seen in psychopathic populations (Deeley, et al., 2006; Hastings et al., 2008). However, the findings of the present study do not permit speculations regarding the direction of the connectivity.

The behavioural relevance of the findings is unclear. Facial processing most certainly influences our decision making in various situations and might also be an important factor in the development of empathy. Lack of empathy is a common trait in offenders (Eisenberg, 2007). Both PSY and ASD have been associated with reduced empathic ability. Empathy is a construct consisting of many aspects; for example affective and cognitive empathy. While cognitive empathy or theory of mind requires mentalizing, affective empathy includes the ability to interpret emotional facial expressions. In ASD cognitive empathy is affected, which has not yet been found in PSY. Blair discussed these two disorders and their differences regarding empathic ability. He points out their different dysfunctions regarding empathy deficit and suggests that a “fine cut” between ASD and PSY can be made in both the amygdala and in the different aspects of empathy, affective, and cognitive empathy (R. J. Blair, 2005; Blair, 2008). Future studies should investigate brain activation patterns to facial expressions in criminal and non criminal subjects with autistic and psychopathic traits and compare this with measures of different dimensions of empathy.

6.4.4 Limitations

Some study limitations should be mentioned. Firstly, the sample size in the subgroups was small, which increases the risk of type II error. Secondly, five of the offenders and one of the controls were taking medication at the time of inclusion. Due to the clinical setting, it was not possible to withdraw all medication. Finally, the use of HC2 as a comparison group to the offenders involves some problems. In comparison to the offenders, the HC2 group consisted of non-criminal subjects who had completed high school education and probably had a different socioeconomic background and different socioeconomic status.

6.4.5 Conclusions

The present study investigated the neural underpinnings of emotional facial perception in two groups of offenders, with either ASD or PSY, and healthy controls. In summary, our findings indicate altered neural processing of fearful facial expressions in the offender group compared to the HC2 group, within the neural network involved in processing emotional facial information. Moreover, the two subgroups of offenders differed from each other in functional communication (direct or indirect) between the amygdala and ACC, both located within the face processing network.

6.5 GENERAL DISCUSSION

There is no single diagnosis in the DSM-IV that explains antisocial or violent behaviour. Among mental disordered offenders the diagnoses varies, but some symptoms are considered more common than others, such as impulsivity and reduced empathy. Psychiatric illness can be described either in a categorical way, or in a dimensional way. When considering psychiatric illness from a categorical perspective, we use diagnoses (i.e. either you receive a diagnosis or not). In the other dimensional perspective, different degrees of a symptom or function are described. It is also possible to consider psychiatric illness from both perspectives. That is, you can have more or

less of psychopathic traits (the dimensional way of thinking), but after a certain number of traits, you fulfil the diagnosis psychopathy, and now it is considered a construct (categorical perspective). It could be argued that maybe there are certain changes in the brain that are common for all subjects with a higher degree of, for example psychopathy, but in a subject who fulfil the psychopathy disorder there are additional changes, not seen in a subject with fewer psychopathic traits.

In this thesis we are using both perspectives in the different studies. In study I we use the categorical way of subdivide the material in different diagnostic groups. The results suggest different subgroups in the APD group, which differ from each other in both psychosocial factors and crime scene behaviour. In study II, antisocial behaviour is considered as a dimension, and instead of studying specific diagnoses the focus was on emotional reactivity in offenders with different degrees of antisocial behaviour. The findings indicated that antisocial behaviour was not a differentiating factor for emotional reactivity. In study III we consider lack of empathy as a common trait among the offenders included. The focus was on cerebral structural changes and the main finding was that the offenders had thinner cortex in the frontal lobes bilaterally. Psychopathy was regarded in a dimensional way, when correlating scores on the PCL-SV and cortical thickness in the brain. There was a negative correlation between scores on the PCL-SV (i.e. degrees of psychopathy) and cortical thickness in the right temporal lobe, frontal lobes and in the whole RH, suggesting that these areas are of importance in psychopathic development. In study IV all offenders share the common trait lack of empathy. However, the offender group was also divided in two sub groups, ASD and PSY, because the hypothesis implicated that their reduced empathic ability may differ from each other. The offender group had higher amygdala activation compared to controls, which was interpreted as a greater effort in these offenders to process fearful facial expressions. When comparing subjects in the ASD group with those in the PSY group the results suggests differences in the connections between amygdala and ACC. The PSY subjects had a positive correlation between activity in the amygdala and the ACC on the right side. This finding could reflect an ACC inhibition on the amygdala response, which would be in line with the clinical observation of shallow affects among psychopathic subjects. Both physiological arousal and processing of emotional facial expressions are of importance in affective empathy. The current findings are in line with impairment in affective empathy and could be the biological correlates to impairment in different aspects of emotional processing in the mentally disordered offenders in these studies.

When conducting studies in the forensic psychiatry context certain problems or challenges emerge. In table 3.1 and table 3.2 the inconsistency of findings in this research field is revealed. One problem is that these subjects often are affected by more than one condition, i.e. co-morbidity is very common, and many subjects suffer from substance abuse disorders. In order to circumvent this problem, in study III and IV, we had very strict inclusion criteria, aiming to include subjects with clearly defined psychiatric traits and to not include subjects with co-morbidity. Therefore, the sample size in these studies is limited.

7 CONCLUSIONS

- There are differences in psychosocial factors and crime scene behaviour between homicide offenders with antisocial personality disorder and autism spectrum disorder. Moreover, antisocial offenders with prevailing impulsive offending differs in various domains from those offenders assigned a diagnosis of antisocial personality disorder presenting controlled offending behaviour.
- The autonomic reactivity in response to emotional stimuli is reduced in mentally disordered offenders compared to healthy controls. In addition, both subgroups of offenders show similar attenuated emotional reactivity to neutral and negative pictures. Therefore, antisocial behaviour is not a differentiating factor for emotional reactivity.
- There are structural changes in mentally disordered offenders, reflected by thinner cortex in the frontal lobes. There is also a negative correlation between structural changes in the brain and amount of psychopathic traits, reflected by scores on a psychopathy checklist.
- Perception and processing of fearful emotional facial expressions differ in direct or indirect communication between the amygdala and ACC in the psychopathic offenders compared to the autism spectrum disordered offenders. The whole offender group also differ from the healthy controls in the neural processing of fearful facial expressions.

The findings in this thesis imply that there are differences, reflected in psychosocial, physiological, and neurological functioning in mentally disordered offenders. The emotional processing differs, both in physiological reactivity and brain functioning, implying biological differences in mentally disordered offenders.

8 FUTURE RECOMMENDATIONS

The findings in this thesis imply that there are subgroups of offenders. These subgroups differ in crime scene behaviour, psychosocial functioning, and emotional processing, reflected by peripheral physiological reactivity as well as cerebral emotional processing. These differences may be important to take into account when investigating and assessing these offenders. Biological factors which are considered to be linked to antisocial and violent behaviour have an impact on several forensic psychiatric areas; diagnostic assessments, providing treatment options, risk assessment, and treatment evaluation.

In diagnostic assessments, some psychiatric dysfunctions can be difficult to evaluate, e.g. callous and unemotional trait (C/U). This trait can be problematic to assess in an interview situation or in a self-report scale. Therefore, increased knowledge about underlying biological factors might be helpful, for instance; C/U traits have been related to blunted heart rate reactivity (Lorber, 2004). Moreover, there are brain imaging studies that suggest that there are structural and functional correlates to pathological lying (Lee et al., 2002; Yang, et al., 2005a). As the results of study I imply, there is also heterogeneity within certain psychiatric diagnoses, suggesting subgroups within certain diagnoses. By taking biological factors into account the specificity of diagnostic assessments could be improved.

The improvement in diagnostic identification could also lead to improvements in the selection of specific treatments. In cancer-treatment, somatic markers are already used in order to choose the most effective chemotherapeutic agent. In psychiatry it has been shown that in depressed patients, pretreatment baseline prolactin levels can predict responses to antidepressant treatments (Porter et al., 2003). Still largely hypothetical, there is evidence from studies in general medicine as well as in other fields of psychiatry that support the possibility that biological parameters may also be useful for forensic psychiatry (Popma & Raine, 2006). In forensic psychiatric practice, and in the criminal justice system, the biological profile could help in selecting the most suitable treatment for each offender.

In addition, evaluation of different treatment approaches could also be improved with increased knowledge of different biological factors. To study a biological profile before and after treatment may be a useful measure of treatment outcome. A new use of imaging technique is Brain-Computer Interfaces based on fMRI (fMRI-BCI) which allows volitional control of anatomically specific regions in the brain (Sitaram et al., 2007). Studies on emotional processing using fMRI-BCI have shown effect on volitional control of the ACC (Weiskopf et al., 2003) and right anterior insula (Caria et al., 2007). In one study, subjects were trained to self-regulate their amygdala activation by a strategy of self-induced sadness. The results indicated that their emotional ratings correlated with amygdala activation (Posse et al., 2003). A real-time fMRI system for the specific treatment of psychopathic offenders is currently under development, in which the offenders are trained to self-regulate their BOLD-activity in localized brain areas implicated in the disorder, such as, anterior insula and amygdala. Could this be a possible way of training the emotional processing deficit seen in these subjects?

Risk assessments could also be improved by increased knowledge of biological correlates of behaviour. It is possible that a certain biological profiles could be used to assess risk of recidivism and predict treatment outcome, even though no study to date has tested this hypothesis (Popma & Raine, 2006). Considering biological profiles as complements to the known static and dynamic risk factors could help in improving risk assessments in the future.

Even though this sounds appealing and hopeful, one must keep in mind that it is hypothetical. It is still unknown which biological factors that are causes or consequences of antisocial and violent behaviour. Moreover, it is important to keep in mind that brain imaging research is still new field. There is not yet a full understanding of the significance of activation in the brain. When an area is activated, is it really activation or is it perhaps inhibition of another area? Inter-individual differences are also a major concern in brain imaging studies.

However, in the present thesis we have investigated additional biological correlates of emotional reactivity. This offers a multi dimensional approach, by parallel investigation of behaviour and peripheral physiology as well as brain structure and function. Combining several measurements offers a richer understanding of emotional reactivity. If a clear trend in reactivity emerges in the different tests, it may be of importance.

If structural and functional differences are found in the brains of offenders, should that influence the concept of free will and responsibility for one's actions? Could images of the brain be used in court as evidence? It is not the purpose of this thesis to speculate about this. In line with the results, however, the thesis does propose that, in order to learn more about the underlying mechanisms of antisocial and violent behaviour, all different factors, social, psychological and biological, should be considered. Future studies are needed, in order to increase knowledge about biological factors related to antisocial and violent behaviour.

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APPENDIX

Mentally disordered offenders

According to the Swedish Criminal Code, a defendant who has committed a crime under the influence of a severe mental disorder must primarily be sentenced to other penalty than prison, often meaning inpatient compulsory psychiatric treatment, often combined with special court order restrictions. All psychotic states, severe depression with strong intention to commit suicide and severe personality disorders or neuropsychiatric disorders, combined with marked compulsiveness or impulsivity with psychotic features, are considered severe mental disorders. Certain cases of dementia and severe mental retardation may also qualify as severe mental disorders.

Psychopathy, on the other hand, would not be considered a severe mental disorder. In Sweden, if the court suspects that the defendant may have been under the influence of a severe mental disorder at the time of the crime, it may request a forensic psychiatric assessment. A major forensic assessment is performed once the court has found evidence for the crime but before conviction. Defendants remanded in custody are transferred to a forensic psychiatric assessment unit where they are assessed which usually takes four weeks. The assessment is performed by a forensic psychiatric team consisting of a forensic psychiatrist, a psychologist, a forensic medical social investigator, staff from the ward, and staff from the occupational therapy department. The forensic psychiatrist is in charge of the forensic court report which is based on the separate assessments made by the all the co-workers in the team. In Sweden, at the time the studies were performed, approximately 650 major forensic psychiatric assessments were performed every year, and of these, approximately 280 per year were performed in the assessments unit in Stockholm. Ten percent of inmates are female, and of the remaining 90% who are male, approximately 5% have marked psychopathic traits (i.e. PCL-R score >30) and a further 10% are diagnosed with ASD.