

Classification and treatment of antisocial individuals:

From behavior to biocognition

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Abstract

Antisocial behavior is a heterogeneous construct that can be divided into subtypes, such as antisocial personality and psychopathy. The adverse consequences of antisocial behavior produce great burden for the perpetrators, victims, family members, and for society at-large. The pervasiveness of antisocial behavior highlights the importance of precisely characterizing subtypes of antisocial individuals and identifying specific factors that are etiologically related to such behaviors to inform the development of targeted treatments. The goals of the current review are (1) to briefly summarize research on the operationalization and assessment of antisocial personality and psychopathy; (2) to provide an overview of several existing treatments with the potential to influence antisocial personality and psychopathy; and (3) to present an approach that integrates and uses biological and cognitive measures as starting points to more precisely characterize and treat these individuals. A focus on integrating factors at multiple levels of analysis can uncover person-specific characteristics and highlight potential targets for treatment to alleviate the burden caused by antisocial behavior.

Keywords: psychopathy; antisocial personality; treatment; cognitive endophenotype; computational psychiatry; multimodal neuroimaging; RDoC; biological and cognitive fingerprinting.

Highlights

- Antisocial personality and psychopathy are severe personality conditions.
- Inconsistencies in the characterization of these conditions plague research.
- Over-reliance on scoring behavior may account for these failures.
- These conditions account for the majority of failed treatment efforts.
- Biocognitive approach provides better classification and treatment options.

1. Introduction

Antisocial behavior is a heterogeneous construct that encompasses a wide range of traits and behaviors. Two subtypes of antisocial offenders, those with antisocial personality traits and psychopathy, are at significantly greater risk than other offenders for diverse substance use disorders and elevated criminal activity. Individuals with an antisocial personality (e.g., diagnosed with antisocial personality disorder), present in about 50-80% of the prison population, often display excessive reward seeking, intense hostility and reactive aggression, and poor impulse control. In contrast, psychopathic individuals, who comprise of approximately 15-25% of the prison population, are characterized by difficulty establishing genuine relationships, minimal and superficial affective experience, an impulsive behavioral style, and a chronic antisocial lifestyle that entails great costs to society as well as for the affected individual (e.g., incarceration).

The behaviors of these subtypes of antisocial individuals lead to several adverse consequences that affect society. For example, the financial damage resulting from psychopathic behavior is estimated at \$400 billion in the USA alone (Kiehl and Buckholtz, 2010). A similar pattern exists in European countries, such as the Netherlands, where treatment costs of a single antisocial offender in forensic psychiatric facilities amount to €160.000 a year. By comparison, the average costs of treating type 2 diabetes (without other complications) has been estimated at only \$1.700-\$2.100 a year (Brandle et al., 2003). The emotional and financial costs of these disorders create a real need for identifying and developing treatment programs that will target these disorders. Unfortunately, as reflected by their high risk of recidivism, antisocial and psychopathic individuals account for the majority of failed treatment efforts within the penal system.

In this review, we will discuss the **classification (i.e., clustering of individuals with similar characteristics into homogeneous groups)** and treatment of adult individuals characterized by antisocial behavior, such as antisocial personality and psychopathy. First, we will provide an historical overview emphasizing various key developments that helped shape modern views on antisocial personality and psychopathy. This overview will elucidate the many sources of conceptual divergence related to the operationalization of these constructs and highlight how the current lack of conceptual precision has been (at least partly) caused by the focus on observable behavior rather than underlying mechanisms. Second, we will review the effectiveness of various treatment approaches that have been used to target antisocial behavior and, in this context, discuss the implications of the lack of clarity in the operationalization of antisocial personality and psychopathy. Third, we will discuss three major approaches that aim to redefine diagnostics and treatment in psychiatry in general, but can also be used to re-characterize antisocial personality and psychopathy by incorporating information from biology (e.g., genetics, brain, and physiology), cognitive functioning, and clinical observations. Finally, we go a step further and propose how to combine elements from these three approaches to obtain profiles for classification consisting of biological and cognitive (i.e., biocognitive) dimensions, **while minimizing the reliance on behavioral observations**. Ultimately, by combining information at several levels of analysis we can help improve the description of different types of antisocial individuals and can facilitate the development of novel therapeutic interventions that are tailored to fit the biological and cognitive characteristics of these individuals.

2. Antisocial personality and psychopathy

2.1 Early views on antisocial personality and psychopathy

The existence of individuals engaging in disruptive and antisocial acts can be found in writings dating back a few thousand years (Yildirim and Derksen, 2015). Around the 19th century, the high prevalence of antisocial behavior in some psychiatric populations caught the attention of psychiatrists who began to attribute the patients' erratic behaviors to deviant mental functioning (for an overview see Hoppenbrouwers et al., 2016). For example, Pinel (1806) described psychiatric patients that showed no obvious incapacities in rational thinking, but still exhibited antisocial behavior. He attributed the antisocial behavior to uncontrollable impulses and instinctive fury. Rush (1812) described individuals that were rational thinkers, yet they engaged in severely immoral and antisocial actions that he attributed to biological impairments that reduced their moral faculties. Rush believed that there was a causal link between antisocial behavior, personality characteristics and hereditary biological factors. A century later, Cleckley wrote an influential book called "The Mask of Sanity" (1941), in which he described an antisocial personality style that later evolved into what is now known as psychopathy, based on his observations of psychiatric inpatients. Cleckley described psychopathy as a severe form of emotional pathology masked by a façade of good mental health. He proposed sixteen specific diagnostic criteria for the condition that spanned disruptive features (e.g., lack of anxiety, shallow affect, superficial relationships with others, and impulsive behavioral deviance) and features that promoted psychological stability (e.g., social self-assurance and persuasiveness). While Cleckley clearly highlighted both maladaptive and adaptive features of psychopathy, other clinicians placed greater emphasis on callousness and a predatory aggressive style in their operationalization of psychopathy (e.g., McCord and McCord, 1964). The tension between the presence of maladaptive and adaptive features of psychopathy characterizes the complex nature of this

disorder and the potential difficulty in distinguishing psychopathy from antisocial personality.

Unfortunately, discussions about the conceptualization of psychopathy and its differentiation from other antisocial disorders were further complicated by the introduction of the Diagnostic Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 1952). The first edition of the DSM included the construct Sociopathic Personality Disturbance, in which antisocial behavior was considered in the light of the individual's social and cultural background. This classification disappeared in the 3rd edition of the DSM (American Psychiatric Association, 1980). The DSM-III introduced the diagnosis of Antisocial Personality Disorder (ASPD) (e.g., antisocial behavioral tendencies that combine conduct disorder with adult antisocial behavior), which is still included in the most recent version of the DSM (American Psychiatric Association, 2013).

The evolution of the DSM classification scheme (from Sociopathic Personality Disturbance to ASPD) increasingly placed an emphasis on observable, behavioral, criteria for the diagnosis (Arrigo and Shipley, 2001). As a consequence, the DSM discarded the fact that there were multiple types of antisocial individuals (e.g., psychopathic vs. non-psychopathic) that differed in many ways, and collapsed them into a single group based on similarities in behavioral tendencies (e.g., impulsive actions and aggression). This development added more fuel to the controversy about the etiology of antisocial behavior and the classification of individuals prone to engaging in disruptive and deviant social acts. Many have criticized the lack of differentiation between subtypes of antisocial individuals, especially that between those with antisocial personality and psychopathy (Hare et al., 1991; Lykken, 2006; Millon et al., 1998). Nevertheless, the ASPD diagnosis still remains dominant in clinical settings.

It is also worth mentioning that another classification instrument, the International Statistical Classification of Diseases and Related Health Problems (ICD) developed by the World Health Organization (1993), introduced a diagnostic category that highly resembles the DSM's ASPD diagnosis, which is called 'dissocial personality disorder'. However, the DSM and ICD diagnosis for antisocial personality differ in that the ICD acknowledges the existence of a broader set of antisocial personality types (e.g., amoral, psychopathic, antisocial). While, the ICD may provide slightly more specification of antisocial personality types, it has not been a popular tool in research on antisocial behavior. And, it too suffers from the same drawbacks as the DSM in that it does not provide sufficient guidelines for how to differentiate between the clinical subtypes and also collapses them into a single category.

Interestingly, the DSM (and the ICD-10) diagnostic categories moved away from the early psychiatric distinctions between antisocial personality and other conditions that resembled psychopathy. While these classification systems may provide a broad and easily identifiable target for diagnosis, it ignores the evidence that antisocial behavior is heterogeneous and expressed in clinical diagnoses, like antisocial personality and psychopathy, in quite different ways. Next, we will discuss some of the most influential proposals that have been made on how to differentiate between antisocial personality and psychopathy.

2.2 Differentiating between psychopathic and non-psychopathic antisocial individuals

Well before the introduction of the DSM, Kraepelin (1913) developed the notion that there may be subtypes of antisocial individuals that differ significantly in the mental and personality determinants that lead them to engage in antisocial acts. Kraepelin

differentiated between seven subtypes of antisocial individuals. For example, he described individuals prone to acting antisocial due to impulsivity (“the impulsives”), others that were callous and lacked a sense of morality (“the born criminals”), and still others that were dramatic and emotionally unstable (“the excitable”). Although the seven subtypes proposed by Kraepelin are not currently used for research in antisocial populations, many of the core features he linked to antisocial personality and its subtypes still play a key role in modern conceptions of antisocial personality and psychopathy.

Lykken was another influential advocate of the existence of subtypes within the constructs of antisocial personality and psychopathy. He proposed a classification system in which ASPD was re-operationalized as a family of personality conditions (Lykken, 1995). In his view, there was a distinction between two general classes of antisocial disorders, which he labeled psychopaths and sociopaths, respectively, and each class contained subtypes that differed from each other in their etiology. He proposed that psychopathy is strongly linked to the presence of genetic idiosyncrasies that often cause difficult temperament. Behavioral and affective dysregulation combined with an inefficient parenting style ultimately leads to the development of psychopathy. The second, much larger, class consisted of individuals that became ‘sociopaths’ predominantly due to environmental factors such as poor parenting and neglect, perhaps combined with inherited temperamental problems. Importantly, Lykken believed that sociopaths may have become well-adjusted individuals in society had they grown up in a healthy environment.

Robert Hare also supported the notion that a distinction should be made between antisocial personality profiles (see Hare and Neumann, 2006), but differed with Lykken in that he did not distinguish between subtypes based on a biosocial perspective. Hare conducted some of the earliest experimental studies in antisocial offenders and his findings

consistently pointed out that there should at least be a division between psychopathic and non-psychopathic antisocial offenders (e.g., Hare, 1966, 1965a, 1965b).

Based on his early work, Hare questioned the appropriateness of the ASPD diagnosis, and also the suitability of other instruments available at the time for differentiating between subtypes of antisocial individuals, and went on to develop the Psychopathy Checklist (PCL)(Hare, 1980), and later the Psychopathy Checklist-Revised (PCL-R)(Hare et al., 1991; Hare, 2003). The PCL-R is a semi-structured interview that can be combined with clinical/criminal records to score individuals on 20 items reflecting personality and behavioral features that are typical of psychopathy (e.g., glibness, lack of empathy and superficial charm, lack of planning skills, sensation-seeking, and irresponsible behavior). Each item is assigned a score of 0 (absent), 1 (moderately present) or 2 (prominently present). The items measure interpersonal and affective functioning, antisocial tendencies and erratic lifestyle. Following scoring, a dimensional total score ranging between 0 and 40 is obtained. The total score is the gold-standard for differentiating between psychopathic and non-psychopathic individuals in forensic populations. An individual is considered psychopathic if the total score is at least 30 in the U.S. **However, analyses using item response theory in Scottish samples found that the cut-off score should be lower (26) in Europe (Cooke and Michie, 1999), and this score has been used in most European countries ever since.** This approach to differentiate between psychopathic and non-psychopathic individuals has been extremely influential and is still dominant in legal settings, clinical practice, and research in offender populations.

In sum, the notion that antisocial personality and psychopathy differ has a long history. Various suggestions have been made to clarify how these two personality constructs differ, but also to propose explanations in terms of differences in the etiological

mechanisms that may lead to the development of each of them. While there is consensus that antisocial personality and psychopathy differ, there is disagreement about how to characterize subtypes of antisocial personality, especially those within psychopathy.

2.3 Different approaches to typifying psychopathy

The term psychopathy has commonly been used to refer to a class of individuals, such as those scoring above a cut-off score on the PCL-R (Hare, 2003). The assumption made here is that the construct is unitary, without considering possible differences between individuals scoring high and low on particular characteristics (Skeem et al., 2003). However, many researchers now view psychopathy as being multidimensional (Neumann et al., 2015), and believe it includes multiple subtypes that differ substantially in personality characteristics and etiology (Skeem et al., 2003).

2.3.1. Psychopathy as a multifaceted disorder according to the PCL-R

The PCL-R has mainly been used to obtain a categorical distinction between psychopathy and non-psychopathy in offenders, but Hare also reported a dimensional two-factor model of psychopathy based on the checklist. In this model, Factor 1 represents the distinguishing interpersonal (charm, grandiosity, and deceitfulness) and affective (lack of remorse, empathy, and emotional depth) traits of psychopathy, which reflect low anxiety and deficient emotion processing (Neumann et al., 2013; Patrick, 2007). In contrast, Factor 2 describes the impulsive and chronic antisocial tendencies associated with psychopathy that are attributed to a deficit in behavioral inhibition and control (Hare and Neumann, 2010). The two-factor approach considers both interpersonal-affective deficiencies and impulsive-antisocial behaviors to be key components of psychopathy. However, it has

been challenged by researchers who claim that a three-factor solution that does not include the antisocial aspects offers a better description of the core dimensions of psychopathy (Cooke and Michie, 2001). These researchers have argued that the main characteristics of psychopathy are the presence of an arrogant and deceitful interpersonal style, blunted affect and impulsive-irresponsible behavior. Crucially, in the three-factor approach, antisocial behaviors are considered to play a secondary role in psychopathy. Hare and colleagues responded to the three-factor approach by developing a four-factor model of psychopathy (Hare, 2003). In this model, Factor 1 is decomposed into a facet capturing interpersonal style (Facet 1) and a facet concerning deficient affective functioning (Facet 2). Factor 2 is subdivided into a lifestyle (Facet 3) and a fourth facet representing antisocial tendencies (Facet 4). The belief is that the four-factor model may lead to a more specific understanding of psychopathic traits by identifying their unique correlates (for a more detailed overview see Brazil and Cima, 2016; Hare and Neumann, 2006).

Currently, the two-factor model of psychopathy is still very prominent in both research and clinical settings, but the four-factor solution is gaining popularity. PCL-R based psychopathy is seen as a mixture of these components, which are used as a basis for finding clinical subtypes. Importantly, however, the debate on how to best characterize different types of individuals with psychopathy is not limited to the theoretical model provided by the PCL-R. Others have proposed very different approaches in which clinical subtyping of psychopathy is considered in terms of its interactions with biological, cognitive-affective, and environmental factors.

2.3.2 Primary vs. secondary psychopathy

Karpman (1941) was probably the first researcher to differentiate between two subtypes of psychopathy, which he called the *idiopathic* (primary) and the *symptomatic* (secondary) subtypes (see also Blackburn, 1975). In his view, the two types share most of the typical traits such as lack of guilt and empathy, callousness, and antisociality, but they have different underlying etiologies. Primary psychopathy reflects a heritable affective deficit. It is generally characterized by the lack of anxiety and associated with affective and attention-related deficits. Conversely, secondary psychopathy is believed to stem from social disadvantage, excessive neurotic anxiety, and/or some other form of psychopathology (Cleckley, 1976; Lykken, 1995). Relative to primary psychopaths, secondary psychopaths exhibit greater levels of anxiety, but comparable levels of antisocial behavior (Skeem et al., 2007). Thus, hypotheses regarding primary and secondary psychopathy tend to distinguish between a syndrome with a genetically determined affective deficit (i.e., primary) and one that reflects the influence of a broader set of factors, including social environment (i.e., secondary).

One approach to uncovering differential causes of primary and secondary psychopathy was derived from Gray's reinforcement sensitivity theory (1970). He formulated a theory in which it was proposed that instrumental behavior is driven by two opposing motivational systems, which were termed the Behavioral Inhibition System (BIS) and a Behavioral Activation System (BAS). The BIS is heavily involved in inhibiting goal-directed behavior in response to the occurrence of aversive stimuli, such as punishment and non-reward, and controls the experience of anxiety. The BAS, on the other hand, serves to initiate and modulate behavior that is driven by factors such as reward or lack of punishment and is also linked to the experience of positive feelings. With respect to

psychopathy, Gray suggested that psychopathy is characterized by lower levels of BIS (low trait anxiety), while having normal levels of BAS, resulting in reward seeking behavior without being anxious of the possible negative consequences (e.g., punishment).

Since its conception, the BIS/BAS theory has played an influential role in the formulation of hypotheses about the subtyping of psychopathy, as others have used this framework to refine the distinction between primary and secondary psychopathy. Lykken (1995) and Fowles (1980) proposed that primary psychopathy arises mainly due to low levels of BIS (low anxiety), resulting in low avoidance of aversive events. In contrast, secondary psychopathy is the result of a hyperactive BAS, thereby increasing the risk of impulsive responding to rewarding events, including stressful situations. Thus, from this perspective, individuals with primary psychopathy are expected to present with low levels of trait anxiety, whereas secondary psychopathy should be associated with higher levels of anxiety.

The first empirical support for these claims was provided by a study reporting that primary psychopathy, defined as a high PCL–R score and low trait anxiety scores, was characterized by a weak BIS and a normal BAS (Newman et al., 2005). In contrast, offenders scoring high on psychopathy and high on trait anxiety had significantly elevated BAS scores relative to control participants, but the results regarding the role of the BIS in secondary psychopathy were unclear. Another study in offenders found support for an association between interpersonal-affective traits (Factor 1 of the PCL-R) and the BIS after controlling for the presence of impulsive-antisocial traits (Factor 2), and between Factor 2 and BAS after controlling for Factor 1 traits (Wallace et al., 2009). Newman and colleagues have suggested that anxiety would be a means for distinguishing between primary and secondary psychopathy (e.g., Schmitt and Newman, 1999; Wallace et al., 2009).

Thus, a distinction has been made between primary and secondary psychopathy and there is empirical support for the notion that differences in levels of trait anxiety is what differentiates between the two types of psychopathy. However, as we will discuss next, this has not been the only approach to finding subtypes of psychopathy.

2.3.3 Other approaches to subtyping psychopathy

Some studies have used the two-factor model to create subgroups of antisocial individuals by applying a median split to each dimension, thus creating quadrants of individuals based on their scores relative to the split (e.g., Baskin-Sommers et al., 2015; Patrick et al., 1993). The Factor and facet models of psychopathy also influenced studies that used cluster analysis of the PCL-R and/or scales from self-report measures to examine subtypes of psychopathy. For instance, Skeem et al. (2007) performed a cluster analysis on a sample of 123 Swedish violent male offenders with high PCL-R scores (score > 29). The data consisted of scores on all four PCL-R facets and a self-report measure of trait anxiety. Two clusters emerged, a “primary subtype” (60% of the sample), and a “secondary subtype” (40% of the sample). Compared to the secondary type, the primary subtype showed a higher mean PCL-R total score, higher mean scores on the Interpersonal, Affective, and Lifestyle facets, about the same score on the Antisocial facet, and a lower mean trait anxiety score. The authors viewed the identified subtypes to be consistent with Karpman’s (1941) conception of primary and secondary psychopathy, but their results are also consistent with the notion that there are “low-anxious” and “high-anxious” variants of psychopathy (Schmitt and Newman, 1999). The findings by Skeem et al. (2007) are in line with the model-based cluster analyses reported by Hicks et al. (2004) and Poythress et al. (2010), who also found two clusters. However, because of their lower stress reactivity, social dominance and lack of

close attachments, Hicks et al. (2004) labelled the cluster consistent with primary psychopathy as *emotionally stable psychopathy*. The second cluster, which was characterized by aggressive and impulsive behavior, was labelled as *aggressive psychopathy*.

Neumann, Hare, and Newman (2007) have suggested that psychopathy (according to the PCL-R) can be viewed as being multidimensional, but on top of the dimensions there is a superordinate factor representing psychopathy. Mokros et al. (2015) used the four facets of the PCL-R to conduct latent profile analyses, which is a technique that parses multivariate data to uncover latent homogeneous profiles (i.e., groups) that form meaningful subtypes of psychopathy. They found that a model with three profiles showed a better fit than a model with one or two profiles. They also showed that the model did not improve when the amount of profiles was increased to four. In agreement with their expectations, they found two different variants of (primary) psychopathy: one more emotionally stable, manipulative and complex, and the other more aggressive, predatory and simple. A third class had high scores on overall psychopathy, but scored very low on the affective component of the PCL-R. As affective disturbances are regarded as central to psychopathy, the researchers concluded that the third class was more similar to ASPD than primary psychopathy, and was therefore termed *sociopathy*.

Although the unitary construct and related Factors from the PCL-R is still the dominant conceptualization of psychopathy, others have developed alternative frameworks that assign a broader set of characteristics to describe psychopathy. Patrick, Fowles, and Krueger (2009) proposed the triarchic conceptualization of psychopathy based on the observation that previous literature reveals three important recurring facets within the construct of psychopathy: *disinhibition* (impulsivity and dysregulation of negative affect), *meanness* (cruelty, instrumental and aggressive behavior towards others) and *boldness*

(reduced emotionality, resilience to stress, and social dominance). Importantly, meanness is considered to represent maladaptive features, while boldness has been linked to adaptive traits. These three constructs are viewed as interrelated, yet (neurobiologically) distinct from one another, and can be measured and understood separately. **The assumption is that the three dimensions can be combined to create descriptions for different subtypes of psychopathy (e.g., high meanness and disinhibition, relatively low boldness, or vice versa).** This approach also claims to accommodate the adaptive features of psychopathy, which are not incorporated in the PCL-R, through boldness. Although the importance of boldness in the conceptualization of psychopathy is debated (e.g., Miller and Lynam, 2015), recent evidence suggests that boldness does have some relevance to psychopathy. For instance, Venables and others (2014) reported that boldness had incremental value in predicting psychopathy diagnosed with the PCL-R and suggested that boldness distinguishes between PCL-R diagnosed psychopathy and ASPD. The authors also argued that boldness parallels a constellation of traits that were incorporated in classic accounts of psychopathy, in which psychopathy was viewed as a condition entailing severe behavioral pathology masked by an outward appearance of psychological health (Cleckley, 1976; Lykken, 1995). However, it has been pointed out that the triarchic model does not truly capture the construct of psychopathy (Miller et al., 2015). Moreover, there have been no studies trying to identify subtypes of psychopathy within the triarchic conceptualization using sophisticated techniques, such as latent profile analyses, which could be a next step.

To summarize, there have been several studies attempting to identify subtypes of psychopathy using a variety of approaches. These approaches include creating subtypes based on the two-factor model of the PCL-R, conducting cluster analysis in offender populations, and latent profile analyses using the four facets of the PCL-R. In general, these

studies have identified two subtypes of offenders with psychopathy (as did the anxiety-based approaches), but differ in the characteristics assigned to the subtypes. An alternative model of psychopathy has proposed that psychopathy can be described best using a combination of three dimensions, but studies showing that this approach can dissociate subtypes in a data-driven way (e.g., with latent profile analyses) are still lacking.

2.4 Comorbidity

The presence of comorbid disorders forms an additional factor that can impact the characterization and treatment of antisocial personality and psychopathy (Widiger, 2006). A significant portion of prisoners with psychopathy will meet the criteria for ASPD. However, less than half of the inmates diagnosed with ASPD will meet the criteria for psychopathy (Hare, 2003). Psychopathy and ASPD differ (especially the affective and interpersonal features) with respect to personality pathology, behavior characteristics and etiology, despite a large overlap in observable behavioral tendencies. Besides ASPD, psychopathy also seems to be associated with higher prevalence of other personality disorders, such as narcissistic personality disorder and schizoid personality disorder (Coid and Ullrich, 2010). While narcissistic personality disorder correlates with the interpersonal characteristics of psychopathy, schizoid personality disorder is associated with the affective features of psychopathy (Coid et al., 2009)

Studies examining comorbidity in populations diagnosed with ASPD (often without differentiation of types) found elevated rates of co-occurrence with alcohol dependence (Sher and Trull, 1994) and drug dependence (Compton et al., 2005; Krueger et al., 1998; Taylor and Lang, 2006). There are also reports of increased prevalence of anxiety disorders (Goodwin and Hamilton, 2003; Verona et al., 2001) in combination with ASPD. However, the

latter does not seem to be the case for psychopathy and it has even been suggested that psychopathy 'protects' against the development of anxiety and mood disorders (Blair, 2012; but see Blackburn et al., 2003).

In sum, there seems to be an increased chance that antisocial individuals will present with certain types of comorbid disorders. Therefore, it is important to consider that interactions between antisocial personality or psychopathy and comorbid disorders may lead to personality types that do not fit in neatly in current theories and/or are typified by different cognitive profiles (see also Maes and Brazil, 2015).

2.5 Interim summary: diagnostic accounts of antisocial personality and psychopathy

This diversity in the classification of antisocial personality and psychopathy has led to a greater understanding of the need to differentiate between the two, but also to confusions and disagreements (especially after the introduction of the DSM). In general, antisocial personality has been associated with behaviors characterized by, e.g., impulsivity, excessive reward seeking, and hostility and reactive aggression. In contrast, psychopathy has often been linked to difficulties in establishing genuine relationships, shallow affect, in addition to chronic antisocial behavior. Antisocial personality and psychopathy also show different patterns of comorbid disorders. Although the distinction between antisocial personality and psychopathy is now accepted, there is still disagreement on how to best characterize these constructs and how to specify the different subtypes. Especially the subtyping of psychopathy has received a relatively large amount of attention, but there is still no consensus on this matter.

The evolution of the conceptualizations of antisocial personality and psychopathy has guided the development of assessment instruments and treatment. However, most

frameworks conceptualize antisocial personality and psychopathy based on behavioral tendencies or psychological constructs. As summarized above, though, individuals with antisocial personality or psychopathy often behave in similar manners, but it is their underlying characteristics and the causes of those characteristics that may differentially influence why they are engaging in those behaviors. Failing to consider the differences that exist across types of antisocial individuals has a major impact on treatment outcomes, as therapeutic interventions are more likely to succeed if they match the patient's needs (Andrews et al., 1990). Next, we will provide an overview of the main results of previous efforts to treat antisocial populations.

3. Treatment

Several attempts have been made to treat antisocial individuals using a variety of clinical approaches (for reviews see Gibbon et al., 2010; Harris and Rice, 2006; Messina et al., 2003; Salekin et al., 2010). Unfortunately, though, there are still no truly effective treatment programs available for these populations. Many clinicians and researchers have adopted the position that antisocial individuals, especially those with elevated levels of psychopathy, are so difficult to treat as to be next to untreatable (e.g., Harris and Rice, 2006; see also Salekin et al., 2010). In this section, we will briefly discuss different treatment approaches and their effects on antisocial individuals.

3.1. Psychological and behavioral treatment approaches

Many treatment studies in antisocial offender populations have employed cognitive behavioral therapy (CBT). The core of CBT is that maladaptive tendencies are tackled through treatment of unwanted behaviors and/or disturbed thought processes. Treatment

of psychopathology is approached from a unitary perspective in which emotions, cognitions and behaviors are interconnected. Through this combined focus, CBT has the potential to target multiple components of an experience and thus lends itself to incorporation into intensive experiential interventions for problems associated with antisocial behavior.

Hitchcock (1994) compared the effects of cognitive therapy in 20 psychopathic offenders and 20 non-psychopathic inmates and found that this form of treatment had little effect in either sample. Other studies using some form of group or individual CBT have reported that i) psychopathy correlated negatively with clinical improvements in forensic patients (Hughes et al., 1997), ii) offenders with elevated levels of psychopathy compared to low levels of psychopathy were more likely to reoffend despite showing improvements due to treatment (Olver et al., 2013; Seto and Barbaree, 1999), iii) sexual offenders with high levels of psychopathy compared to low levels of psychopathy were more likely to quit the program and to recidivate (Olver and Wong, 2009) and iv) PCL-R Factor 1, especially the affective facet, was a strong positive predictor of violent recidivism (Olver et al., 2013). Thus, the pattern of findings in studies using CBT in offender populations suggests no or very limited treatment efficacy, especially in individuals with high levels of psychopathy.

Integrative forms of the CBT approach have been incorporated into milieu therapy, which uses therapeutic communities to effect behavior change. Though there are differences across milieu therapy settings, this approach generally implements techniques that support self-examination, the development of accountability, and the enhancement of effective interpersonal engagement through CBT strategies. Messina et al. (1999) used this approach in individuals with substance abuse with and without ASPD to examine the likelihood of treatment completion, drug use, and recidivism after completion of the program. The results were similar for patients with and without ASPD, as both types of

patients had lower rates of recidivism, used less drugs, and were equally likely to complete the program. Thus, in the context of milieu therapy, ASPD was not related to lower treatment responsiveness.

In contrast, though, this milieu approach has not been effective in psychopathy. Rice et al. (1992) evaluated the efficacy of a therapeutic community program that targeted the development of empathy and responsibility, which was believed to be a good approach for treating psychopathy. A follow-up evaluation conducted approximately 10.5 years after treatment was terminated showed that participants with psychopathy had a higher rate of violent recidivism. In contrast, offenders without psychopathy that followed the treatment had a lower rate of re-offense. These findings led to the suggestion that the therapeutic community program promoted the further development of the disruptive interpersonal-affective features typically seen in offenders with psychopathy, while those without psychopathy were able to use the acquired skills to develop prosocial behavioral repertoires.

Another study conducted in 80 incarcerated offenders found that those with psychopathy tended to invest less time in the program and were less motivated to change their behavior, while those in the non-psychopathic and mixed (scoring medium-high on the PCL) groups did benefit from the treatment (Ogloff et al., 1990). Similar results reported by Hobson et al. (2000), found that especially PCL-Factor 1 traits were strongly associated with disruptive behaviors in the therapeutic community and on the ward. Thus, research indicates that therapeutic communities seem to be useful for treating antisocial personality in general, but not psychopathy. The evidence generated by this line of research has contributed to the pessimism regarding treatment of psychopathy that is still dominant in some settings.

One treatment method that seems to have positive effects in antisocial populations with comorbid substance use disorders is Contingency Management (CM). This method is based on the principles of instrumental learning and involves the use of negative and positive reinforcers to modify behavior. For example, Silverman et al. (1998) used the CM approach to reinforce cocaine abstinence in methadone abusers with and without a diagnosis of ASPD. Patients in the treatment groups received vouchers that could be exchanged for services or goods after handing in drug-free urine samples. The findings indicated that the use of vouchers as positive reinforcement increased the likelihood of abstinence in the treatment conditions. Another study employing CM in drug abusers with an ASPD diagnosis also provided encouraging results pointing out that the participants showed reduced intake of cocaine and heroin (although this was also the case in the comparison condition)(Brooner et al., 1998). However, these studies included relatively small samples and often suffered from flawed designs, precluding firm conclusions.

To address these issues, Messina et al. (2003) conducted a study in substance abusers with and without ASPD, in which they systematically compared the effects of CM, CBT and the combination of CM and CBT. The control condition consisted of a methadone maintenance program, which was followed by all patients in addition to CM and/or CBT. The intervention consisted of 16 weeks of treatment during which participants had to hand in three urine samples each week and follow-up measures were collected in weeks 17, 26, and 52. One intriguing result was that participants with ASPD were more likely to show a reduction in the use of cocaine, indicating that treatment responsivity was positively linked to ASPD. In fact, patients with ASPD were less likely to use cocaine during the entire follow-up period compared to those without ASPD. Also, treatment responsivity in the ASPD group was higher in the CM condition relative to the CBT and combined CM and CBT conditions,

but following treatment in general was related to less use of cocaine during follow-up compared to the control condition. The group without ASPD did not show reduced use of cocaine in this period. In sum, CM and CBT seem to have positive effects on individuals with co-occurring substance use disorder and ASPD (there are no studies focusing on CM in psychopathy).

Overall, there is mixed evidence that psychological and behavioral interventions are effective for antisocial individuals. Most consistently, individuals with ASPD seem resistant to some forms of CBT, but are more responsive to behavioral interventions that focus on reward and contingency learning. By contrast, psychopathic individuals seem to be unresponsive to individual, group, and community CBT. It is important to note that most studies that included a psychopathic sample were plagued by issues such as flawed designs, relatively small sample sizes, an inappropriate characterization of the target populations, and use of outcome measures that some have deemed inappropriate (D'Silva et al., 2004; Harris and Rice, 2006). In the light of these shortcomings, some have argued that it is premature to draw the general conclusion that treatment does not work in populations with high levels of psychopathy (D'Silva et al., 2004; Salekin et al., 2010). Still, it has become clear that different types of antisocial individuals can diverge greatly in the treatment approaches to which they respond best.

3.2 Medication

In addition to cognitive-behavioral interventions, there was once the expectation that medication would be able to target antisocial behavior, specifically in a class of medications labeled as “serenics” (or anti-aggressive agents). A good portion of the current literature on treatment of antisocial individuals consists of case reports. Hirose (2001) described the case

of a patient diagnosed with ASPD, who had a long history of aggressive and disruptive behavior. Risperidone, an antipsychotic, was administered to the patient at different time points and a reduction in aggressive behavior was observed in the periods that followed. Walker and colleagues (2003) described the cases of 4 individuals with psychopathy and a formal diagnosis of ASPD that were admitted to a maximum-security forensic psychiatric institute. These individuals were highly aggressive, impulsive and irritable and these symptoms were treated using antipsychotic medication (quetiapine). All of the patients showed a reduction in aggression, impulsivity, and irritability, which led to the conclusion that quetiapine seems effective in treating severe antisocial behavior. However, in these studies, the medications had to be administered in combination with other psychotropic medication before the behavior of the patients stabilized. Additionally, the suggestions made by Hirose (2001) and Walker et al. (2003) are not based on findings obtained with properly designed randomized control trials.

There are currently no reports of clinical trials specifically targeting groups of incarcerated individuals typified by antisocial personality or psychopathy. Instead, the handful of studies available were designed to target impulsive aggression in offender samples (Ripoll et al., 2011). Sheard and colleagues (1976) assessed the effect of lithium on impulsive aggression in incarcerated offenders using a double-blind, placebo-controlled study design and reported that lithium seems to have a positive impact on the reduction of violent behavior during detention. In another study, incarcerated offenders participated in a study in which 30 inmates were treated with phenytoin (an antiepileptic drug) while another 30 inmates from the control group were administered a placebo (Barratt et al., 1997). The results suggest that this anticonvulsant offers an effective way for treating aggressive outburst in incarcerated populations. Mattes (2012) has recently reviewed

previous pharmacological trials in both incarcerated and non-incarcerated populations and has argued that oxcarbazepine, a modern antiepileptic, should be suitable for treating aggression in offender populations. Finally, in adults with impulsive aggression, treatment with selective serotonin reuptake inhibitors has been found to increase glucose metabolism in the orbitofrontal cortex, suggesting a potential method for improving functioning in regions that have been identified as deficient in criminal populations (Glenn and Raine, 2014). While some research efforts persist in this field, notably targeting the serotonergic system, no pharmacologic intervention that specifically targets antisocial behavior or psychopathy currently exists (Olivier and van Oorschot, 2005).

Taken together, there is still no direct evidence that pharmacotherapy is a viable approach for treating antisocial individuals. However, there seems to be some level of optimism about the effectiveness of medication on targeting aggressive and impulsive behaviors, which are some behaviors present in individuals with antisocial personality or psychopathy. However, given the complex nature of antisocial personality and psychopathy, at the moment pharmacotherapy does not seem to be a strong treatment approach for these types of populations.

3.3 Interim summary: treatment of antisocial personality and psychopathy

Individuals with antisocial personality and psychopathy account for the majority of failed treatment efforts within the penal system. While some evidence exists that components of these disorders can be targeted with psychological and pharmacological treatment, there is no evidence that current treatments effectively address these disorders. The development of effective treatment programs may be affected by the heterogeneity of these disorders,

the inconsistency in the classification of these disorders, and/or the failure to incorporate knowledge about the underlying etiologies of these disorders into the development of more specific treatments. In the next section, we will discuss how modern approaches to understanding psychopathology that use biological and cognitive levels of explanation to inform clinical work may offer a (partial) solution to the lack of precision in the classification of antisocial individuals and promote the development of novel, personalized, treatment approaches.

4. A way forward: classification and treatment based on biology and cognition

Antisocial personality and psychopathy are complex, multifactorial concepts. As reviewed above, this complexity hinders the classification of these individuals and the effectiveness of treatment. In order for diagnosis and treatment to advance, a better understanding of the individual is essential. The challenge, then, is to develop methods that are able to identify those aspects of an individual that are relevant for explaining their pathological behavior and that allow us to address its causes. We advocate an approach where each individual is described as his/her own combination of traits on a multidimensional platform (see also Fair et al., 2012).

As noted above, most of the more traditional methods of describing antisocial behavior rely solely on **behavioral** observations (e.g., showing aggression, displaying impulsivity, engaging in criminal behavior). However, the same undesirable and antisocial behavior can have many different causes. For instance, a perpetrator can violently attack someone in an alley for monetary gains (e.g., during a robbery), but such an attack could also be driven by other motives such as retaliation. In both cases the same violent behavior can be observed (e.g., hitting and kicking the victim), but the motivation behind this

behavior will differ greatly. Despite this issue, the currently dominant clinical and research instruments still focus on scoring these behaviors to help make inferences about the overarching (hypothetical) personality constructs and do not take into account different motivations or etiologies. This then means that the challenge for psychiatry is to find novel ways of understanding the individual's behavior at the level of the underlying, not directly observable, causes.

Over the last several years there is an increasing interest in combining insights and methods from diverse research fields such as genetics and neuroscience with those from clinical psychology and psychiatry. The underlying premise of these approaches is that the symptoms observed in many mental and personality conditions are tightly linked to disturbances in the individual's biological and cognitive functioning (Montague et al., 2012). Thus, by understanding the 'biocognitive' markers of disease and psychopathology and how they combine in each unique individual, one can begin to understand how to approach each case. Based on this notion, we propose that antisocial personality and psychopathy should be redefined based on differences in biological and cognitive dimensions that can be combined to create subtype specific multidimensional biocognitive profiles, instead of relying on **classification based on scoring of observed behaviors, as is the case for currently available** personality and clinical assessment tools.

Our approach converges with the vision that has been spear-headed by the Research Domain Criteria (RDoC) framework developed by the National Institute of Mental Health (NIMH; Insel et al., 2010), which aims to understand mental illness as the interaction of factors at multiple levels of description. Of crucial importance is to stop linking a specific biological or cognitive factor to a specific, DSM-type, pathology. This has led to the development of multiple approaches that aim to discover new ways of describing

psychopathology. In the remainder of this section, we first discuss three prominent, but different, approaches that use latent variables to understand pathological behavior in general, and will provide examples of how each approach could be of significance for better understanding antisocial personality and psychopathy. Although each approach has the potential to provide major insights into the characteristics of these populations, we propose that an even more powerful approach would be to combine some of their core elements to obtain personalized biocognitive profiles for antisocial individuals. With this goal in mind, we will present a procedure describing how to combine the different strengths of the three approaches, and will explain how this integrative procedural framework may offer new possibilities for re-characterizing antisocial personality and psychopathy and inform the development of novel treatments.

4.1 Current approaches

4.1.1 Cognitive endophenotyping

There is a longstanding belief that many psychiatric conditions are causally related to genetic factors. In general, research on heritability has indicated reliably that there are large genetic components in antisocial personality and psychopathy. Across several studies, the estimated heritability of antisocial behavior varies between 40% and 80%, indicating that there is **a very strong** genetic basis for these behaviors (for reviews see Glenn and Raine, 2014; Viding and McCrory, 2012). Importantly, a recent meta-analysis indicated that there are no clear associations between single genes and antisocial aggressive behaviors across studies (Vassos et al., 2014), further highlighting that studying genetic factors in isolation may not be sufficient to explain pathological behaviors.

Given the limitations of genetic data, efforts have been made to use intermediate levels of description to study the neurobiological foundations of complex diseases and psychopathology (see Meyer-Lindenberg and Weinberger, 2006). Studying intermediate levels of description encompasses pinpointing and examining the neural mechanisms (or biological parameters) that bridge the gap between DNA sequence (i.e., the genotype) and behavior (i.e., the phenotype). Advocates of this approach argue that, because genes do not directly code for psychiatric symptoms, it is better to study those biological and cognitive correlates of the symptoms that seem to have a strong link with genetic factors. The assumption is that genetic factors promote the development of vulnerabilities in certain brain networks, and the resulting cognitive impairments can be measured and related to pathological behaviors in a systematic way. This is often referred to as ‘cognitive endophenotyping’ (Wiecki et al., 2015). Importantly, these cognitive endophenotypes are not limited to diagnostic categories, as they are held to represent fundamental ‘bridges’ that can vary in the degree of their expression. Therefore, cognitive endophenotypes can be used to study psychopathology across disorders (i.e., transdiagnostically; Robbins et al., 2012).

The cognitive endophenotype approach has already made an entrance in research on antisocial behavior, mostly to study externalizing. Externalizing is a broad transdiagnostic construct with a strong genetic basis that accounts for most of the disruptive behaviors seen in antisocial personality and other disorders such as substance abuse (Krueger et al., 2002). Psychophysiological measures have played an important role in the search for cognitive endophenotypes that correlate with externalizing behaviors, especially the use of electroencephalogram (EEG). This has led to the identification of a family of event-related potentials (ERPs) that show systematic negative correlations with externalizing in various

populations (Patrick et al., 2013). These ERPs belong to the P300-family and can be evoked using experimental paradigms that include the occurrence of unexpected events such as oddballs (target P3), novel stimuli (novelty P3) or bursts of noise (noise-probe P3). Perhaps the most reliable association between reduced P3 amplitude and externalizing comes from studies of at-risk individuals defined by their familial relationships (Iacono et al., 2002; Polich et al., 1994). Additionally, this reduction in P3 is not only associated with at-risk individuals, but a similar pattern has been reported with externalizing-related pathologies and behaviors, such as aggression, childhood conduct disorder, adult antisocial personality, and substance abuse (Bauer et al., 1994; Bauer and Hesselbrock, 1999; Brazil et al., 2012; Gao and Raine, 2009; Venables et al., 2011).

A recent addition to the cognitive endophenotype approach, namely the construct-network framework, advocates for a broader inclusion of indicators and specific statistical approaches for identifying an endophenotype (Patrick et al., 2013). In this framework, observable variables with indicators at different levels (e.g., self-reported clinical symptoms or physiological measures) are used to operationalize latent variables (called psychoneurometric variables) that capture the shared variance between the different types of measurements. Such latent variables can be created by conducting factor analyses in large samples. Thus, psychoneurometric variables can be seen as aggregated indices of the extent to which neurobiological constructs with a genetic basis are present in an individual. Patrick et al. (2013) have suggested that psychoneurometric variables can be useful for developing targeted treatment programs that take individual differences in cognitive processing into consideration. The interventions can be used to treat disordered populations, but could also be used in a preventative way for individuals at risk.

However, a recent review identified various issues with the endophenotyping approach, such as the need for very large samples and that the approach has failed in finding robust genetic associations for the cognitive endophenotypes (Iacono et al., in press). Another problem is that creating psychoneurometric variables using factor analyses (or one of its variants) is based on the assumption that all of the variables and domains of measurement included (self-report, psychophysiology, clinical data) are linearly related, which may not be the case. For example, Rodgers et al. (2000) collected self-report measures for alcohol use, depression and anxiety in 2725 individuals and found U-shaped relationships among these variables. Hence, although cognitive endophenotyping certainly offers many advantages (such as the use of latent multimodal variables) and is a step forward, there are still some practical and methodological considerations that require attention.

In sum, although there is evidence that antisocial personality and psychopathy have a substantial genetic basis, it has been difficult to pinpoint the isolated genes that cause antisocial behavior. This has caused the development of cognitive endophenotyping frameworks that aim to study intermediate levels of description, based on the notion that biological and cognitive measures are more closely related to the genotype and also correlate with behavior. This approach has provided a way of bridging the gap between genes and behavior, and has also highlighted the potential of using latent variables capturing the intersect between different levels of explanation to understand pathological behavior. While the cognitive endophenotype approach is promising, others have argued that the key to understanding pathological behavior lies in unraveling the exact cognitive operations that are impaired by using computational models, which will be discussed in the next section.

4.1.2 Computational psychiatry

Another approach that has been gaining an increasing following is computational psychiatry (Brazil et al., 2013a; Maia and Frank, 2011; Montague et al., 2012; Stephan and Mathys, 2014). The idea is to construct a mathematical model that performs a certain task in an analogous manner to our brain or cognitive system. By investigating the internal variables of the model, one can make some statement about aspects of cognition or brain function that are usually difficult to observe, which are latent variables for cognition (Mars et al., 2012). Novel insights into what is different in the patient can be gained by changing the internal workings of the model to mimic behavior in pathology. This approach assumes that dismantling cognitive mechanisms into its smaller, more fundamental, latent elements will offer the possibility of systematically studying how patient populations differ on these elements and how the differences relate to disturbances in the corresponding mechanisms. From this perspective, computational psychiatry advocates the use of these smaller cognitive units as transdiagnostic indicators of cognitive impairment. Ideally, this would lead to a re-characterization of patient populations based on variations along dimensions representing cognitive mechanisms (Stephan and Mathys, 2014).

Computational modeling has a rich tradition and, in combination with cognitive neuroscience, has led to numerous models of many aspects of cognition, such as visual attention (Itti and Koch, 2001), mentalizing (Hampton et al., 2008), and action selection (Frank, 2011). In psychiatry, one particularly promising avenue has been the study of the neurocognitive underpinnings of reinforcement learning and decision-making (Braver et al., 1999; Frank et al., 2004; Maia and Frank, 2011). This is not surprising, because many clinical

populations show problems in modulating maladaptive behavioral tendencies that are particularly well captured by such models (Montague et al., 2012; Wiecki et al., 2015).

Impaired reinforcement learning is also believed to play a key role in explaining poor decision-making in antisocial populations and many other disruptive characteristics observed in these individuals (Blair, 2005). For example, psychopathy has been linked to (context-modulated) impairments in reversal learning (Brazil et al., 2013b; Budhani et al., 2006; Gregory et al., 2015), disturbed use of negative feedback to adapt choice-behavior (von Borries et al., 2010), and problems in learning to avoid choices leading to unfavorable outcomes (e.g., Newman and Kosson, 1986). However, the exact cognitive operations underlying these impairments are still not fully understood (Brazil et al., 2013a; Hoppenbrouwers et al., 2016). A next step could be to employ computational models of learning and decision-making within these populations to significantly advance our understanding of the cognitive characteristics of these individuals. Ideally, this would occur by employing computational models that allow the estimation of several cognitive computations within a single theoretical framework to maximize comparability across studies. One example of such frameworks is the Hierarchical Gaussian Filter (HGF; Mathys et al., 2011, 2014). The HGF offers a framework in which many of the strengths of various prior computational models are incorporated into a unified theoretical framework of reinforcement learning and decision-making. The HGF postulates that choice-behavior is driven by a hierarchy of interacting latent cognitive processes, and unpacks learning into smaller 'cognitive units' that need to interact so that we can learn to make optimal choices. Some of these hidden computations represent an individual's expectations about the likelihood of an event occurring based on past experiences ('unit 1'), for example, how often choice A has led to a reward vs. choice B. This requires us to be sensitive to reward and

punishment information ('unit 2'). Importantly, contingencies are prone to change in the real world and a previously rewarded option can become punished and vice versa. To keep making optimal choices we need to learn how likely it is that these contingency changes may occur ('unit 3'), what is often called reversal learning (Brazil et al., 2013b), but also to how fast these changes may occur ('unit 4'; Iglesias et al., 2013).

An impairment in any of these smaller cognitive units subserving reinforcement learning (or a combination thereof) will be reflected on the behavioral level as poor decision-making across different types of antisocial populations. These individuals would all show a tendency to make impulsive and risky choices (Kuin et al., 2015), even though the underlying cognitive causes may differ between subtypes (Yechiam et al., 2008). The power of computational modeling is that it can solve the issue of equifinality (i.e., that antisocial behavior can be reached by many potential means) by quantifying each of the latent cognitive units involved in generating the observed behavior. One clear example concerns a study on reinforcement-based decision making in children with attention-deficit/hyperactivity disorder (ADHD) (Hauser et al., 2014). Similar to antisocial populations, the tendency to make poor choices seen in ADHD has often been (partly) attributed to a lack of impulse control (e.g., Winstanley et al., 2006). By employing a computational model, Hauser et al. (2014) discovered that that poor reinforcement-based decision making in ADHD may not be driven by dysregulated impulsive control per se, but rather by a tendency to explore other options more often than healthy controls when making choices. That is, these individuals will make incorrect choices more often because they are more prone to explore the potential gains of other options, rather than lacking the capacity to control their impulses when making choices.

In summary, computational psychiatry aims to decompose cognitive functions, such as learning, attention and action selection, into smaller cognitive operations. These smaller units are latent variables (or 'computational phenotypes', Montague et al., 2012) that can be studied across patient populations, with the goal of detecting and explaining psychopathology in terms of latent mechanistic impairments. Computational modelling has been almost completely absent in research on antisocial personality and psychopathy (Blair et al., 2004; Brazil et al., 2013a), but employing such an approach would allow us to zoom in on the exact sources of neurocognitive impairment and to determine how subtypes of antisocial personality and psychopathy differ on these various aspects. In turn, this creates the possibility of developing psychological interventions targeting impairments in specific cognitive mechanism. However, the challenges that come with this approach are that the interpretation of the results is not always straightforward (O'Reilly and Mars, 2011), and that various computational models are available that diverge in the mathematical formalization of the target cognitive mechanisms, which could reduce comparability across studies. Still, the application of computational modeling seems promising. It also can be combined with other approaches, such as neuroimaging (e.g., Behrens et al., 2008).

4.1.3 Neuroimaging

Mental disorders are increasingly understood to be disorders of brain function (Insel and Cuthbert, 2015). Accordingly, techniques to image the activity and structure of the brain in-vivo have seen a very rapid rise in the field of psychiatry. Functional neuroimaging techniques such as fMRI offer the potential to deconstruct the biological basis of mental operations and thus, it is hoped, identify the ultimate cause of abnormal behavior.

However, as was the case for endophenotyping, early successes in identifying differences in

brain activity during task performance in patients as compared to healthy controls have been followed by the realization that a full characterization of an individual requires a multimodal approach in which several types of neuroimaging measures are integrated. Rather than just focusing on brain activation, there is an increasing appreciation of measures of brain structure.

Neuroimaging is traditionally used to provide information about the structural architecture of the brain, such as the cortical thickness and surface area of specific parts of the cortex. More recently, various techniques have been developed to also quantify the connectivity between different parts of the brain. For example, diffusion-weighted MRI (dMRI) allows one to build up a picture of the major white matter pathways connecting regions of the brain (Johansen-Berg and Rushworth, 2009). Another technique, termed resting state functional MRI (rs-fMRI), quantifies the correlation in spontaneous activity between brain areas, allowing an assessment of the interaction between different nodes of the cortical network. These observed spontaneous interactions often mimic those seen during task performance (Smith et al., 2009), indicating that they identify relevant networks.

Importantly, all the different brain measures can be combined in a single framework, such that a researcher can investigate not only how each of the different measures relate to one another, but also how they contribute to distinct or the same environmental or behavioral variable(s) (Groves et al., 2011). The success of this multimodal neuroimaging approach was recently demonstrated in a study of aging (Douaud et al., 2014). These researchers were able to demonstrate different types of change in grey matter across the life-span, with grey matter showing a general monotonic decrease with age but on top of that a network of mostly association regions, such as lateral prefrontal cortex, intra-parietal sulcus, and posterior cingulate cortex, that show an inverted u-shape pattern. These regions

mature later in life but also show a strong decrease from age 40 onwards. Importantly, the spatial pattern of this network was similar to that of areas that show accelerated atrophy in Alzheimer's disease and an altered developmental trajectory in schizophrenia.

In the context of antisocial behavior, multimodal neuroimaging would allow the investigation of how variations in brain structure and function relate to dysfunctional behavior (Buckholtz and Meyer-Lindenberg, 2012; Calhoun and Sui, 2016). There is a growing number of imaging studies in antisocial individuals, focusing on identifying differences in brain structure and activation, especially psychopathy (for reviews see Koenigs et al., 2011; Yang and Raine, 2009). This has led to the suggestion that psychopathy is associated with several structural abnormalities in various brain regions, such as reduced amygdala volume, increased volume in the striatum, abnormal hippocampal shape and reduced frontal gray matter (see Koenigs et al., 2011). Diffusion MRI studies have also found that the connection between subcortical (e.g., the amygdala) and prefrontal cortical regions are impaired in relation to psychopathy (Craig et al., 2009; Hoppenbrouwers et al., 2013; Wolf et al., 2015). Most functional imaging studies in individuals with antisocial personality or psychopathy have employed experimental tasks to study brain activation. In general, psychopathy has been associated with reduced activations in several brain locations that fall within paralimbic and limbic brain areas. For example, there have been reports of reduced activation of the amygdala, the cingulate cortex, and the insula (see Anderson and Kiehl, 2012). Paradoxically, for some areas (**e.g., the amygdala**) both hypo- and hyper-activation have been shown in individuals with psychopathy. This is likely a consequence of differences between the tasks being used (Koenigs et al., 2011). **Alternatively, the inconsistencies could be attributed to the fact that groups were created in these studies using imprecise, man-**

made, personality-based cut-offs, an approach that allows for too much variation in the type of individuals included across studies.

Despite the large amount of imaging studies in antisocial individuals, there have been almost no studies employing a multimodal approach in which different types of neuroimaging measures are combined and linked to antisocial behavior (but see Aharoni et al., 2013; Steele et al., 2015). Studies linking brain measures to antisocial behavior have commonly employed correlational designs, and typically search for linear relationships between a specific brain measure and behavioral or personality dimensions (e.g., Wolf et al., 2015). However, not all relationships of this kind are linear (see e.g., Douaud et al., 2014) and one cannot expect a simple one-to-one mapping between any MRI change and a behavioral measure. Therefore, multimodal neuroimaging can be used as a more flexible and complete approach in which multiple latent dimensions can be created to capture the mutual dependencies between different brain measures and antisocial behavior. This would be a first step towards finding the multiple biological and cognitive dimensions that maximally distinguish between subtypes of antisocial individuals, thus improving classification.

In summary, neuroimaging has the potential to provide a wide range of indices of neural structure and functioning. The potential to combine these different brain measurements into a single framework that can subsequently be mined for relationships and used for the description of individual differences, make it a promising avenue to the biocognitive approach to typifying antisocial personality and psychopathy we advocate. Such an approach seems feasible given the large amount of imaging data obtained in antisocial populations that is currently available, and could provide a starting point for identifying biocognitive dimensions that differentiate between types of antisocial

populations. **However, multimodal neuroimaging is predominantly concerned with combining measures of brain structure and activation. To achieve a more complete description of the individual we will need to go beyond measures of the brain and also incorporate other levels of description, thus requiring a novel and broader integrative approach.**

4.2 An integrative approach to describing individual differences

From our perspective, the application of any of the approaches described above to study and redefine current views on antisocial personality and psychopathy has the potential to be fruitful. However, each approach has its disadvantages. For instance, multimodal neuroimaging does not necessarily offer the level of precision in identifying mechanistic cognitive impairments provided by computational psychiatry, or the insight into the cause of a disease that could be provided by cognitive endophenotyping. Therefore, we propose that a combination of the strengths of the three approaches will help advance our understanding of antisocial behavior. Our integrative approach will facilitate the development of profiles that describe the biocognitive dimensions on which subtypes of antisocial populations differ (Fig. 1).

In the remainder of this section, we discuss the proposed integrative approach that redefines the concepts of antisocial personality and psychopathy, and how this approach could ultimately lead to the development of targeted treatment programs. Specifically, we provide a procedural workflow in which we discuss the advantages of combining existing datasets to create large databases by means of large-scale consortia, how these data can be interrogated to develop the appropriate biological and cognition-informed profiles of antisocial individuals, and finally, how these results might be used to inform clinical

diagnostics and treatment. Each of these steps comes with significant challenges but, as we hope to demonstrate with examples from related fields, these challenges can be met.

4.2.1 Stage 1: Aggregation and integration of data

The combined approach advocated here obviously requires the availability of many different data types, such as genetic data, neuroimaging data, and behavioral measures, to the same researchers. However, because we are searching for potentially weak, multidimensional effects, the datasets will have to be much larger than can often be obtained by any one researcher or research group in isolation. It is thus imperative that researchers combine their efforts in large-scale consortia. This creates challenges in terms of collaboration, scientific credit, and costs, but also additional ones such as the need for infrastructure and computing power.

Although challenging, this is certainly not impossible and the feasibility and pay-offs of such endeavor are already becoming visible in other branches of psychiatry and in medical research. For example, scientists conducting research on the genetic causes of schizophrenia recognized that the sample sizes used in genome-wide association studies (GWAS) about a decade ago were not powerful enough to detect significant genetic effects.

Around that time, sample sizes in genetics studies in schizophrenia were about N=1,000 in both the patient and the control group (Sullivan, 2010). Their solution was to establish international consortia such as the International Schizophrenia Consortium, in which the participating research groups aggregated their datasets to facilitate large scale analyses (The International Schizophrenia Consortium, 2009). **Since then, sample sizes in GWAS studies have increased substantially due to the creation of aggregated datasets through various international research consortia.** Similarly, in the context of neuroimaging there are now a

number of publically available databases that provide high-quality data from a number of modalities, such as the Human Connectome Project (Van Essen et al., 2013) and the UK Biobank (Miller et al., 2016).

The ENIGMA consortium provides one example of a successful project in the context of such a consortium. ENIGMA is an international collaboration between more than 500 scientists that have combined their genetic, imaging and clinical data to study 12 target brain disorders (Thompson et al., in press). To date, their repository contains multimodal data of over 30,000 patients, thus allowing high-powered meta-analyses of the relationship between genetics, brain, and clinical variables. Recently, ENIGMA published the results of a study conducted in a combined sample of nearly 12,000 patients with schizophrenia in which they examined the relationship between genes and brain volume in 8 regions (Franke et al., 2016). Their findings suggest that the longstanding hypothesis that there is a causal link between genetics and abnormal brain morphology in schizophrenia seems less likely than commonly assumed. Although the statistical framework used does not allow the assessment of evidence in favor of the null hypothesis, the large sample size increases confidence in the validity of the claim that there may indeed be no relationship between genes and brain volume in these regions in schizophrenia. These endeavors in other branches of psychiatry further highlight the potential gains of creating large databases containing anonymized data in various measurement domains obtained in antisocial populations.

In sum, the creation of large databases is the first step towards obtaining biocognitive fingerprints for individuals with antisocial personality and psychopathy. Such databased should include many types of biological and cognitive measures obtained in

these populations. When a substantial amount of data has been aggregated, the next stage would be to reduce the amount of data.

4.2.3 Stage 2: Statistical learning and biocognitive fingerprinting

Once the required data are available at least three phases of data analysis are required, which can be performed together or separately (see Figure 2). First, we need to identify variance in the data that describes the differences between individuals in meaningful ways. Insel and Cuthbert (2015) described this as a ‘clustering’ stage in which the patients originally categorized across a range of disorders are re-assigned based on more homogenous clusters. Since this phase involves finding novel latent measures describing groups of individuals in a data-driven manner, we will refer to this as the ‘exploration’ phase. Second, once novel categories are defined based on the various types of data available, this high-dimensional space should ideally be condensed into a lower-level space in which individuals can be characterized based on a constellation of important dimensions. In other words, we want to identify ‘markers’ that have a maximal diagnostic power between the different categories. For instance, if the data mining approach illustrates that different types of antisocial individuals can be differentiated by specific genetic or neural patterns, we would like to be able to create a summary measure that identifies which critical tests are necessary to reliably identify which form of antisocial personality we are dealing with. As such, we can build a ‘fingerprint’ of the different types of antisocial and psychopathic individuals. Hence, we refer to this as the ‘fingerprinting’ phase. In the third phase, the fingerprints will need to be validated by examining their relationship with observed behavior. For example, if the fingerprint for a subtype of antisocial individuals includes a latent dimension representing hypersensitivity in the reward circuit of the brain,

these individuals should also show excessive reward-seeking behaviors. We will discuss each phase in the following sections.

4.2.3.1. Exploration

In the exploratory phase, we hope to learn from the data what types of individual variability exist between individuals and which biological or cognitive markers best describe them. In essence, this is a statistical learning approach (Bzdok, 2016) that searches for correlations between variables in high-dimensional datasets (Mullins et al., 2006). One of the advantages of statistical learning is that, when used appropriately, it can elucidate correlations between variables that were not previously observed. The algorithms can be used to analyze covariance between very large amounts of variables, or to probe for causal relationships, others are used to find clusters or as multivariate classifiers (Yoo et al., 2012). More recent algorithms are able to infer causal links between a large amount of variables in a data-driven way (e.g., Bayes-Constrained Causal Discovery; Claassen and Heskes, 2012). As a thorough discussion of these statistical learning algorithms and their application falls outside of the scope of this article (but see Bzdok, 2016; Yoo et al., 2012), we will draw examples from recent studies in healthy and antisocial individuals to illustrate the potential of these methods as useful tools for classifying subgroups of antisocial individuals based on their biocognitive characteristics.

A study linking resting state functional connectivity data to non-biological measures by Smith and colleagues (2015) offers one prominent example of the use of statistical learning for data exploration, outside antisocial individuals. They used data from 461 participants collected in the context of the Human Connectome Project and tried to relate the connectivity between 200 regions in each individual's brain to more than 100 measures

of behavior and demography, including performance on laboratory tasks, self-report questionnaires, and life history factors. Using a canonical correlation analysis that aims to investigate the underlying relationship between the two sets of variables, they discovered a 'positive-negative' axis linking lifestyle factors, demographic factors such as years of education, and psychometric factors such as fluid intelligence, with specific patterns of connectivity in the default mode network and areas of parietal-frontal attention networks.

Similar studies that explore the potential of applying machine learning algorithms to imaging data to classify adult antisocial individuals are slowly emerging in the literature. Sato et al. (2011) applied machine learning algorithms to grey matter data from healthy individuals and forensic inpatients with high levels of psychopathic features. The goal was to assess how well the groups could be classified based on structural brain data and to determine which brain regions had the highest discriminatory power. The best-performing algorithm was able to classify the groups with 80% accuracy and identified the superior temporal cortex as a brain area whose grey matter was particularly predictive in dissociating between healthy individuals and patients with psychopathic traits. Another example is provided by Tang and colleagues (2013), in which machine learning was applied to rs-fMRI data in 32 young adults with an ASPD diagnosis and 35 matched controls. They were able to classify individuals in their corresponding groups with an accuracy of approximately 87%, showing that precuneus, superior parietal cortex, and cerebellar connectivity had high predictability.

Thus, the use of statistical learning algorithms to explore dependencies between variables is the first step towards the creation of biocognitive fingerprints for different types of antisocial individuals. The few studies employing these algorithms to classify antisocial individuals have been good first steps in using statistical learning. However, the researchers

created groups a priori using scores on personality measures, such as the PCL, and tried to confirm group membership using data mining methods. This approach thus precludes the data-driven discovery of novel antisocial profiles based on biocognitive data that is being advocated here. In other words, these studies were conducted within the boundaries of current personality theories of antisocial personality and psychopathy and, therefore, are more confirmatory than exploratory and suffer from the drawback that they relied on subjective behavioral observations to create the groups. Ideally, one would not have to predefine the groups, since the goal is to move away from the current approach and to redefine antisocial groups in a data-driven way based on biocognitive fingerprints.

4.2.3.2 Fingerprinting

After the variables of interest have been identified through exploration during ‘data mining’, it is important to distill the results in such a way that they can easily be used to represent the most predictive information. In other words, to apply a data reduction step to distill the most informative features of the data. Within neuroimaging, such a ‘fingerprinting’ approach has been used in different contexts for some time and more of the techniques might find applications in the current endeavor. For instance, Mars and colleagues used the concept of ‘connectivity fingerprints’ (Passingham et al., 2002) to characterize the important connections within a brain area and used this to make quantitative statements about the similarity and differences between the brains of different species within a permutation testing framework (Mars et al., 2016). In principle, there is no reason a similar approach cannot be used to test for differences in brain architecture between individuals, as advocated by Buckholz and Meyer-Lindenberg (2012) and discussed above, for the case of connectivity differences indicative of mental illness.

Outside the context of brain connectivity, the profiling approach has also been used on a more cognitive level. Arnould and colleagues (2013) proposed a multidimensional framework to characterize apathy following traumatic brain injury. Their framework included cognitive, motivational, and affective factors, as well as aspects related to personal identity. This work opens a possible road to ‘fingerprinting’ of different types of apathy. Similarly, Njomboro and colleagues (2014) characterized differences in social functioning in relationship to apathy. These studies demonstrate how complex neurological and psychiatric phenomena can be better understood in terms of underlying, latent variables that can be identified, captured and used in combination.

We propose a similar approach to creating fingerprints that are capable of differentiating between subtypes of antisocial personality and psychopathy. Once the relevant dimensions have been identified at the population level during the exploration phase, the next step would be reducing the amount of dimensions to represent the relevant biocognitive characteristics of different antisocial and psychopathic individuals. These groups could differ in the constitution of the variables included in the corresponding fingerprints, as well as on their scores on dimensions for which the fingerprints show overlap (see Figure 2). It could also become evident that a subpopulation of antisocial individuals is typified by impairments in mechanism A (e.g., reward hyper-sensitivity), while another sup-group shows disturbances in mechanism B (e.g., insensitivity to punishment) instead of A, despite their similar behaviors.

Thus, we suggest biocognitive fingerprinting as an alternative approach that takes into account the full of cognitive and biological make-up of an individual. Importantly, the ultimate goal of this undertaking is to improve diagnosis and to try helping individuals modify dysfunctional behavior. Therefore, the next step is to take the biocognitive

fingerprints and relate them to different behaviors. As outlined above, this might lead to the finding that superficially similar behavior has widely different causes, and our approach might help identify a set of tasks that can be used to obtain standardized behavioral measures that have clear links with the underlying deficiency.

4.2.3.3 Linking biocognitive fingerprints to reliable behavioral indices

Once the latent biocognitive fingerprints have been identified, some dimensions could represent impairments in cognitive mechanisms. Each dimension should have clear relationships with behaviors that reflect impairments in the cognitive mechanisms it represents. Note that such validation will be more challenging for dimensions representing, for instance, rs-fMRI or cortical thickness, as the disturbances captured by these measures may not directly translate to abnormalities in specific behavioral measures. Consider the hypothetical scenario that four distinguishable biocognitive fingerprints have been identified in a group of antisocial individuals. If one subtype's biocognitive fingerprint includes very high scores on a dimension representing hyper-responsivity of the reward system in the brain, this should translate to behaviors reflecting excessive reward seeking behaviors, such as gambling or an inability to delay gratification. Conversely, if an individual's biocognitive fingerprint does not contain reward hyper-sensitivity as a dimension, this individual should not show pathological behaviors related to excessive reward-seeking. Importantly, for this type of validation to be successful, we will need to identify behavioral measures that can reliably be related to corresponding dimensions in the biocognitive fingerprints.

One attractive solution would be to use experimental tasks as standardized procedures for obtaining these behavioral indices. This step requires the use of tasks that

are reliable across studies. Unfortunately, as highlighted by the pattern of inconsistent findings obtained using task-based fMRI, the identification of reliable physiological and behavioral measures in antisocial populations, especially in psychopathy (Gao and Raine, 2009; Hoppenbrouwers et al., 2016; Koenigs et al., 2011; Maes and Brazil, 2013), is still needed. These inconsistencies are a clear indication that not all tasks are equally suitable for obtaining the level of precision required to generate robust claims about mechanistic impairments in heterogeneous populations. The need for better experimental paradigms is especially pressing for behavioral measures given their ambiguous nature. When interpreting behavioral indices, one complicating factor that is often overlooked is that experimental tasks are never 'process pure', thus requiring an intricate interplay between several domains. Thus, impaired task performance can be caused by disturbances in any of the cognitive-affective domains involved in generating the behavior (Brazil et al., 2013a; Daunizeau et al., 2010). Therefore, measures obtained with tasks that engage too many cognitive operations are not precise enough to be linked to the biocognitive fingerprints.

A clear illustration of the task impurity problem is provided by tasks assessing executive functioning, which are increasingly being used to typify cognitive dysfunctions in antisocial personality and psychopathy (Maes and Brazil, 2013). Executive functions (EF) may be generally described as a set of higher-order or top-down cognitive processes that enable control over more basic cognitive processes (Diamond, 2013). Traditionally, EF are believed to be subserved by prefrontal and parietal brain regions, but in fact there may not be a simple one-to-one relationship between EF and prefrontal activity. The Wisconsin Card Sorting Test is an example of a commonly used task to assess EF (Eling et al., 2008), and is also frequently used for examining EF in offender samples (for a review see De Brito and

Hodgins, 2009). The classical version of the task requires the participant to sort cards displaying geometrical figures that vary on three dimensions; color, shape, and number of items. Based on feedback, the participant first has to infer the currently relevant sorting dimension, after which this rule suddenly changes (usually unannounced). Such changes require a shift in attention from the previously relevant stimulus dimension to a previously irrelevant dimension. For this reason, this task is held to specifically tap cognitive shifting capacities. In the WCST, shifting capacity is mostly expressed in terms of number of trials on which the participant continues sorting on the basis of the previous, but now incorrect dimension, also called perseverative errors. Importantly, successful performance on this task does not solely depend on shifting ability. The task also demands the involvement of additional processes related to the deduction of the correct sorting principle, feedback processing, and maintenance of the current sorting rule in working memory. These additional processes are also reflected in the additional involvement of non-frontal brain regions (Nyhus and Barceló, 2009). To complicate things further, even within the shifting aspect, at least two fundamentally different processes may underlie perseverative errors. One is perseveration of responding to the former relevant dimension; the other is the tendency to continue ignoring the former irrelevant dimension that has now become relevant, also called learned irrelevance. The latter process seems to play a larger role in making errors than the former (Maes et al., 2004, 2006). In clinical populations, such as autism spectrum disorder, this task engages even more additional processes, which may all underlie bad task performance (Maes et al., 2011). Thus, finding better tasks that offer more precise outcome measures is a prerequisite for the validation of the biocognitive fingerprints, but would be beneficial for the field in general.

Given the importance of precision in computational psychiatry, Wiecki and colleagues (2015) have provided guidelines for task selection that will facilitate the development of tasks that reduce the impact of additionally engaged cognitive functions. They indicate that a task should i) be designed to disentangle the multiple cognitive operations involved, ii) engage as few cognitive functions as possible, and iii) include systematic variations that manipulate the engagement of only target cognitive functions. Such a task was employed by Diaconescu and colleagues (2014), and their study provides a clear example of how validation of latent cognitive variables can be achieved using behavioral measures in the context of computational modeling. In this study, healthy participants had to use social advice to learn which choices to make in a reinforcement-based decision making task. Importantly, the trustworthiness of the advisor was manipulated during the task. There were periods in which the advisor was more likely to provide correct advice, while he would work against the participants in others. Successful execution required participants to learn when to follow the advice in order to maximize their gains. A computational model (HGF) was used to estimate four latent cognitive variables quantifying i) learning about changes (e.g., when the advice shifted from trustworthy to untrustworthy), ii) learning about the rate at which these changes occur, iii) the extent to which these change-related operations are coupled, and iv) the weight given to the social advice, respectively. After estimation, the validity of each latent variable was established by examining their relationship with behavioral performance measures. In brief, they reported that the estimated latent variables that were expected to be involved in the generation of choice behavior (e.g., weighting of advice to make a choice) indeed predicted behavioral accuracy in the task. Moreover, three out of four latent variables predicted the strategy used by the advisor, indicating a) that the computational variables indeed reflected

different, but interacting, latent cognitive operations involved in social learning mechanisms, and b) that well-designed tasks make it possible to obtain a relatively precise mapping between behavior and the underlying specific elements of cognitive processing.

To summarize, once that different biocognitive fingerprints have been created to describe and discriminate between subtypes of antisocial personality and psychopathy, some of the dimensions within the fingerprints can be validated by using relatively ‘clean’ experimental tasks known to tap into a dimension included in a fingerprint. These tasks could be copied from studies employing computational models, or they could be developed according to the guidelines provided by Wiecki et al. (2015). These fingerprints will provide information about the relevant cognitive mechanisms that best explain the different etiologies of antisocial behavior, which will be useful targets for treatment.

This ‘precision medicine’ approach has been almost absent in treatment studies conducted in antisocial individuals. This is problematic, as a ‘one size fits all’ approach to treating antisocial populations has proven not to be effective (see section 3). Because of these expected differences in fingerprints between the antisocial subtypes, each group may require different treatment modules, specifically designed to target the latent biocognitive sources of the behavioral impairment (Stephan et al., 2015). **Next, we will discuss the final stage of our integrative framework in which we will focus on how the biocognitive fingerprints can be used to inform diagnosis and the development of treatment interventions. We will also provide an example to highlight the potential of personalized interventions.**

4.2.4 Stage 3: Development of personalized treatment

The fingerprints will make it possible to identify mechanisms that should be treated in each of the biocognitive subtypes of antisocial individuals. After validation, the next step will be to incorporate the use of the fingerprints into clinical practice to help guide diagnosis and subsequent treatment. One way of using the fingerprints to aid diagnosis would be to incorporate the collection of biological and cognitive data into the standard screening procedure, and use this information to construct the patient's biocognitive fingerprint using the group level fingerprints as references. Next, these measures can be used for classification of the individual into one of the biocognitive categories based on the best-matching fingerprint.

Once the individual has been classified, the dimensions in the fingerprint will provide a specific set of candidate target areas for treatment. For example, an individual typified by problems modulation of attention would benefit from training that is focused on improving this specific impairment. To date, there has been only one example of such a study matching treatment to target cognitive impairments in antisocial offenders. Baskin-Sommers et al. (2015b) employed cognitive remediation therapy (CRT) to develop group-specific treatment for psychopathy and non-psychopathic offenders, respectively. Cognitive remediation is a treatment strategy in which individuals are trained on improving cognitive skills that are known to be involved in psychopathological functioning. The use of this method forces researchers and clinicians to first carefully evaluate scientific evidence to determine the key cognitive impairments that should be trained to alleviate psychopathological symptoms. There is a large body of evidence suggesting that psychopathy is characterized by impairments in modulating attention to accommodate multiple streams of information (Newman and Baskin-Sommers, in press). However, these dysfunctions of attention do not seem to play a major role in driving antisocial behavior in

non-psychopathic offenders. Instead, some non-psychopathic offenders demonstrate exaggerated responses to affective information and various kinds of motivational cues, in combination with reduced regulatory capacity (Baskin-Sommers et al., 2014).

In their study, Baskin-Sommers et al. (2015) developed a program consisting of pre-training measurement of cognitive and psychophysiological functioning, a group-specific training using computerized cognitive tasks, and post-training measurements on the same task used before the training. Four groups were created from which one non-psychopathic and one psychopathic group followed a training program that matched their respective cognitive deficiencies, and the two other remaining groups received the training that was designed for the other pathology (e.g., a psychopathy group was trained using the program for the non-psychopathic group and vice versa). Each group followed the training for one hour a week for a period of six weeks. An attention to context training was designed for psychopathy, which consisted of three tasks requiring appropriate allocation of attention to contextual information for successful performance. The non-psychopathic offenders were matched with an affective control treatment that trained them in down-regulating their hyper-responsivity. The results were intriguing and indicated that only the groups that had followed a training program that matched their cognitive deficiencies exhibited improvements in task performance during the six weeks of training. Also, the performance on post-training measures also improved in these two groups, suggesting that the training of the targeted cognitive mechanisms generalized to other measures. **The advantage of the cognitive remediation approach is that it directly follows from the identification of biocognitive fingerprint. That is, the fingerprint can then be used to identify the target areas that may require treatment, which could consist of the administration of different**

cognitive remediation training modules that are each specifically designed to tackle specific impairments.

Though cognitive remediation is just one example of how to target specific domains for treatment, there is cautious optimism that candidate mechanisms, such as the modulation of attention (Brazil et al., 2012; Newman and Baskin-Sommers, in press), autonomic responses to threat (Hoppenbrouwers et al., 2016), and reinforcement learning (Blair, 2013; Budhani et al., 2006) can be used to specify fingerprints and targeted in treatments that differentiate between subgroups of antisocial individuals. Importantly, our fingerprinting approach allows for the discovery of new cognitive processes that also have discriminative power, as well as for monitoring of progression during treatment by periodically analyzing shifts in scores on specific dimensions included in the patient's fingerprint. Obviously, maximizing the clinical impact of our approach will be challenging and will require close collaboration between researchers and clinicians, but the current lack of effective treatment programs for antisocial individuals demands a significant shift away from established approaches.

5. General summary and conclusion

In this review, we have provided an overview of different historical conceptualizations of antisocial personality and psychopathy. These theories have been influential in shaping modern views on individuals with these types of personality, but have also caused a lot of confusion and imprecision in their characterization. A major cause of this imprecision has been the reliance on behavioral (self-report) measures to infer hypothetical psychological constructs, such as personality factors. This also seems to have had an impact on treatment of antisocial personality and psychopathy. While there has been some success in treating

certain types of antisocial individuals using methods such as Contingency Management, most therapeutic interventions have been ineffective for treating psychopathy. This is not surprising, as successful treatment requires interventions that match the needs of the patient and current treatment approaches are not suitable for achieving this goal (Andrews et al., 1990). Moreover, the lack of insight into the different biological and cognitive factors that can cause antisocial behavior has impeded the development of ‘personalized’ treatment programs that truly fit the needs of different types of antisocial individuals.

In response to these failures (in psychiatry in general), novel approaches have been developed that try to redefine psychopathology using multimodal latent variables. These approaches include the search for cognitive endophenotypes, computational psychiatry and multimodal neuroimaging, that each has the potential to offer major advances for understanding antisocial populations but also comes with limitations. We have proposed a procedural roadmap to combine different aspects of the three approaches, with the goal of re-characterizing antisocial personality and psychopathy using statistical regularities in biology and cognition as natural delineators between subtypes rather than less precise, man-made, psychological constructs (Cuthbert and Insel, 2013).

Our integrative approach is based on the premise that latent variables can be used to bridge different levels of explanations (e.g., physiology and genetics), similar to cognitive endophenotyping. We capitalized on the potential of multimodal neuroimaging to extend this notion to include multiple intersecting latent variables using different types of brain data, as well as the possibility to identify non-linear relationships between these latent variables and even with behavior. Finally, we included the strength of computational psychiatry in capturing latent cognitive variables capable of indicating impairments in

cognitive mechanisms with high precision, which could then be targeted through training with interventions such as cognitive remediation therapy.

Importantly, caution is always warranted. The goal of the approaches discussed here is to provide insight into the etiology of individual differences and into how pathological behaviors can be treated; it is not to stigmatize people or to argue for determinism. Still, establishing the fingerprints is of great importance, not only because they could improve the characterization of different subtypes of antisocial personality and psychopathy, but also because they provide information about which cognitive capacities could be targeted and be modified through treatment in each individual. This would be a major shift in how we currently conceptualize and treat antisocial behavior. Antisocial behavior produces suffering for the individual, for their family members, for their community, and for society at large. Importantly, the underlying mechanisms and associated fingerprints tell us *why* these individuals continue to engage in antisocial behavior, despite the persistence of suffering. Utilizing the approach of knowledge integration from basic science on these mechanisms to intervention research highlights the path for alleviating this suffering.

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Figure Captions

Figure 1. Schematic depiction of the bio-cognitive approach (after Insel and Cuthbert, 2015).

Currently, patients are often categorized based on behavioral symptoms. Using information from a variety of approaches, including genetics, structural and functional neuroimaging, cognitive measures, and computational psychiatry, latent categories that might be much better at grouping different patients and predicting therapy outcomes might be found.

Figure 2. Exploration and fingerprinting of multimodal data. Once the required data are available, various data mining approaches will be required to determine new categories and the measures that describe them. In the second step, the most diagnostic measures can be summarized in a ‘fingerprint’ or profile that can be used to describe each individual on a number of continuous latent dimensions.