The Neurobiology of Antisocial Personality Disorder and Psychopathy: Neurochemical Mechanisms, Empathic Processing, and Clinical Implications

A Continuing Education Reading Manual for Licensed Psychologists and Graduate-Level Clinicians

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Title Page

The Neurobiology of Antisocial Personality Disorder and Psychopathy: Neurochemical Mechanisms, Empathic Processing, and Clinical Implications

A Continuing Education Reading Manual Prepared for Licensed Psychologists, Forensic Clinicians, and Graduate-Level Mental Health Professionals

Based on the research of Tully, Pereira, Sethi, Griem, Cross, Williams, Blair, Murphy, and Blackwood (2023, 2024), and integrated findings from contemporary neuroimaging investigations of antisocial personality disorder and psychopathy.

Abstract

Antisocial personality disorder (ASPD), with or without co-occurring psychopathy (ASPD +/–P), represents one of the most consequential yet poorly understood conditions in clinical psychology and forensic mental health. Men meeting diagnostic criteria for ASPD are disproportionately responsible for violent crime, and the subset who also meet criteria for psychopathy exhibits an especially severe and treatment-resistant clinical profile. This manual synthesizes contemporary neuroimaging and neurochemical research into a coherent framework for understanding the pathophysiological underpinnings of these conditions. Drawing on magnetic resonance spectroscopy (MRS) findings demonstrating impaired striatal

glutamate/GABA regulation in violent offenders with ASPD +/–P (Tully et al., 2024), and functional magnetic resonance imaging (fMRI) findings documenting oxytocin-mediated normalization of empathic processing in psychopathy (Tully et al., 2023), the manual provides psychologists with an integrated conceptual model linking neurochemistry, neurocircuitry, decision-making abnormalities, and empathic processing deficits. It further examines the historical development of the diagnostic constructs, evaluates conceptual models of mechanism, considers methodological strengths and limitations of the current evidence base, and articulates clinical implications for assessment, formulation, and emerging pharmacological and psychosocial intervention strategies. The overarching aim of the manual is to provide psychologists with the conceptual depth and empirical grounding necessary to engage critically with an evolving translational science that is beginning to reshape our understanding of severe antisocial behavior.

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1. Introduction

Life-course-persistent antisocial behavior remains one of the most costly and destabilizing phenomena in contemporary society. A relatively small proportion of the population commits a disproportionately large share of violent crime, and this group is characterized clinically by a developmental trajectory that begins with conduct disorder (CD) in childhood and continues into antisocial personality disorder (ASPD) in adulthood (Falk et al., 2014; Moffitt, 2018; Piquero & Moffitt, 2014). The economic and social costs of this pattern of behavior have been documented extensively, encompassing not only direct costs to the criminal justice system but also indirect costs associated with victimization, loss of productivity, and intergenerational transmission of adverse outcomes (Heeks et al., 2018; Wickramasekera et al., 2015).

Within the broader ASPD population, a clinically distinct subgroup—approximately one-third—meets additional criteria for psychopathy (ASPD +P). These individuals typically display callous-unemotional traits during childhood (Lynam et al., 2007; Viding & McCrory, 2012), begin offending earlier in life, engage in a broader range and higher density of offending behaviors, and respond less favorably to established therapeutic approaches (Coid & Ullrich, 2010; Frick et al., 2014; Guy et al., 2005; Kosson et al., 2006). Clinical guidelines from national bodies have long emphasized that currently available pharmacological treatments have limited evidence supporting their use in ASPD or its associated behavioral

manifestations of aggression, anger, and impulsivity (National Collaborating Centre for Mental Health, 2010).

The development of effective interventions has been hindered by a limited understanding of the neurobiological underpinnings of these conditions. Over the past two decades, however, converging neuroimaging evidence has begun to identify the neural systems that appear dysfunctional in ASPD +/–P. Two lines of inquiry have proven particularly productive: research on decision-making and reinforcement learning, which has implicated the striatum and its cortical connections (Blair, 2015; De Brito et al., 2013; Glenn & Yang, 2012; Gregory et al., 2015; Hosking et al., 2017), and research on empathic processing—particularly implicit responses to distress cues in others—which has implicated the amygdala, insula, and cingulate cortex (Blair et al., 2004; Decety et al., 2013, 2014; Marsh et al., 2008). Recent work by Tully and colleagues (2023, 2024) has extended this literature in two crucial directions: first, by demonstrating that violent offenders with ASPD +/–P show impaired striatal glutamate/GABA regulation compared with healthy non-offenders, offering a novel neurochemical account of decision-making abnormalities; and second, by demonstrating that intranasal oxytocin abolishes group differences in the neural processing of fearful facial expressions between offenders with and without psychopathy, providing evidence of neurochemically modulable empathic dysfunction in psychopathy.

This manual provides an integrated synthesis of these findings. It is written for licensed psychologists and graduate-level clinicians who require a scholarly, in-depth understanding of the neurobiology of ASPD +/–P, and who must translate such knowledge into clinically meaningful formulations, ethical assessments, and evidence-informed treatment planning. The manual proceeds by first tracing the historical and theoretical foundations of ASPD and psychopathy, before turning to conceptual models of pathophysiology, empirical findings across neuroimaging modalities, psychological pathways implicated in the disorders, and their clinical and system-level implications. It concludes by identifying research gaps and future directions.

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2. Historical and Theoretical Foundations

2.1 The Emergence of Antisocial Personality Disorder as a Diagnostic Construct

The diagnostic categorization of persistent antisocial behavior has undergone substantial refinement over the past century. Contemporary classification systems, including the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), operationalize ASPD as a pattern of disregard for and violation of the rights of others, characterized by criteria including deceitfulness, impulsivity, aggressiveness, reckless disregard for safety, consistent irresponsibility, and lack of remorse. Importantly, DSM-5 criteria explicitly require evidence of conduct disorder onset before age 15, thereby anchoring the adult diagnosis in a developmental trajectory that begins in childhood or early adolescence (First et al., 2016).

The developmental continuity of antisocial behavior is not merely a diagnostic convention but reflects a robust empirical finding. Longitudinal work has consistently demonstrated that a subset of individuals shows persistent antisocial behavior beginning in early childhood and continuing across the lifespan, distinct from adolescence-limited patterns of offending (Moffitt, 2018; Piquero & Moffitt, 2014). This life-course-persistent pattern is associated with more severe outcomes, greater comorbidity, and greater resistance to change.

2.2 Psychopathy as a Distinct but Overlapping Construct

Psychopathy, though frequently discussed alongside ASPD, represents a partially distinct construct with its own theoretical and empirical history. As operationalized by the Psychopathy Checklist–Revised (PCL-R; Hare, 2003), psychopathy is characterized by four facets: interpersonal traits such as glibness and pathological lying; affective traits such as callousness and lack of empathy; lifestyle traits including impulsivity and irresponsibility; and antisocial behaviors including criminal versatility. Empirical studies confirm that ASPD and psychopathy exist on a continuum, with psychopathy representing a more severe and specific variant (Coid & Ullrich, 2010).

Cross-cultural research has revealed important methodological nuances in the application of PCL-R thresholds. Whereas North American samples typically employ a cutoff of 30 out of 40, European samples—including the United Kingdom population from which the work of Tully and colleagues (2023, 2024) drew—commonly employ a cutoff of 25, reflecting differences in the distribution of scores across cultural contexts (Cooke & Michie, 1999). This

methodological consideration is not merely technical but has substantive implications for the comparability of findings across studies conducted in different populations.

2.3 Callous-Unemotional Traits and Developmental Precursors

The developmental precursor to adult psychopathy is best captured by the construct of callous-unemotional (CU) traits in youth, which encompass reduced empathy, restricted affect, and a lack of concern for others' distress. Approximately one-third of youth with conduct disorder show elevated CU traits, and this subgroup demonstrates a more severe trajectory, greater treatment resistance, and distinct neurocognitive profiles (Frick et al., 2014; Lynam et al., 2007; Viding & McCrory, 2012). The developmental continuity between CU traits in childhood and psychopathy in adulthood is central to contemporary models of the etiology of these conditions.

2.4 Theoretical Frameworks for Understanding Antisocial Behavior

Several theoretical frameworks have shaped contemporary understanding of ASPD +/–P. Among the most influential is Blair's integrated emotion systems model, which posits that psychopathy specifically reflects a dysfunction in emotion-based learning systems, particularly those involved in processing distress cues from others (Blair, 2017). According to this framework, the ability to learn from others' distress serves a critical socialization function: it inhibits aggressive behavior by making the distress of a potential victim aversive to the aggressor. When this system is dysfunctional, as in psychopathy, individuals are less inhibited from engaging in instrumental aggression and are less responsive to the socializing feedback provided by others' emotional reactions.

A complementary framework draws on the Research Domain Criteria (RDoC) initiative, emphasizing the value of examining specific neurocognitive processes rather than diagnostic categories per se (Blair, 2015). From an RDoC perspective, psychopathy is understood as reflecting dysfunction in specific systems—particularly those involved in reinforcement learning, threat processing, and emotional responsiveness—that cut across traditional diagnostic boundaries. This transdiagnostic emphasis has proven particularly productive in guiding neuroimaging research.

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3. Conceptual Models and Mechanisms

3.1 The Striatum as a Central Substrate

The striatum, as the principal input structure of the basal ganglia, has emerged as a central substrate in contemporary models of ASPD +/–P (Tully et al., 2024). Anatomically, the striatum is subdivided into ventral (nucleus accumbens and olfactory tubercle) and dorsal (caudate and putamen) components, each with partially dissociable functions. The ventral striatum is thought to primarily process social reward and to underpin the reinforcement learning that predicts future outcomes (Rilling & Sanfey, 2011). The dorsal striatum, by contrast, predominantly mediates choice impulsivity and evaluates action-contingent outcomes to guide the selection of future goal-directed actions (Kim & Im, 2019).

Striatal function is orchestrated by a complex neurochemical architecture involving dopamine, glutamate, GABA, and acetylcholine, among other neurotransmitters and neuromodulators (Bolam et al., 2000; Kreitzer & Malenka, 2008). Dopamine, released in the striatum by long-range axons arising from the ventral tegmental area and substantia nigra pars compacta, is central to reinforcement learning through its role in encoding reward prediction error—the difference between experienced and expected reward (Schultz, 1998; Schultz et al., 1997). Reward prediction error signaling drives learning by regulating multiple aspects of neuronal and synaptic function (Fisher et al., 2017; Reynolds et al., 2001).

3.2 Excitatory/Inhibitory Balance and Its Regulation

Critically, dopaminergic function in the striatum operates within a broader context of excitatory/inhibitory (E/I) balance. This balance is set by the relative activity of glutamatergic excitatory inputs and GABAergic inhibitory circuits, and it determines the local level of striatal excitability. The regulation of dopaminergic function by glutamate-GABA-mediated E/I balance is thus likely a critical factor in controlling the capacity of striatal circuits to optimize their computational functions in reward learning and decision-making (Tully et al., 2024).

Preclinical evidence provides mechanistic insight into how these interactions unfold. Striatal cholinergic interneurons modulate reinforcement learning through characteristic pauses in firing in response to rewarding and punishing stimuli (Apicella et al., 2011). This cholinergic

signal is itself regulated by thalamo- and corticostriatal glutamatergic inputs (Chantranupong et al., 2023). Striatal dopamine release is inhibited by GABA-A or GABA-B receptor agonists and enhanced by combinations of GABA-A and GABA-B receptor antagonists (Lopes et al., 2019). The principal neurons in both ventral and dorsal striatum are medium-sized spiny GABAergic projection neurons that receive convergent glutamatergic and dopaminergic afferents, providing the anatomical substrate for these complex interactions (Mora et al., 2008).

3.3 A Neurochemical Model of Decision-Making Dysfunction in ASPD

Building on this framework, Tully et al. (2024) proposed that impaired valence-based modulation of dopaminergic prediction error signaling in the striatum may underpin the abnormalities of reinforcement-based decision making observed in ASPD +/–P. Specifically, if E/I regulation becomes dysfunctional—particularly through increased inhibitory tone—this could critically impair the striatum's capacity to generate appropriate output signals to cortical connections. Inhibitory GABAergic spiny projection neurons control striatal output through their relative excitatory state (Wickens et al., 2007a, 2007b); shifts in E/I balance therefore have consequences that propagate throughout the corticostriatal circuitry.

The functional implications of such dysregulation are substantial. If ventral striatal E/I balance is dysfunctional, neural reward prediction error signaling may be impaired, contributing to aberrant salience attribution (Boehme et al., 2015; Rothkirch et al., 2017). If dorsal striatal E/I balance is dysfunctional, the integration of information required for goal-directed action selection may be compromised (Balleine et al., 2007; Sharpe et al., 2019). Together, these impairments provide a neurochemical scaffolding for understanding the reinforcement-based decision-making deficits observed in ASPD +/–P.

3.4 The Neural Circuitry of Empathic Processing

A parallel conceptual model addresses the empathic processing deficits characteristic of psychopathy. Healthy empathic processing depends on partially separable neural systems, with prominent roles for the amygdala, insula, and anterior and mid-cingulate cortex in processing fearful expressions (Fusar-Poli et al., 2009; Tettamanti et al., 2012). The anterior insula plays a critical role in representing the salience of stimuli, generating an integrated awareness of one's cognitive, affective, and physical state that is re-represented in the

anterior cingulate cortex to facilitate homeostatic autonomic and behavioral responses (Uddin, 2015; Fullana et al., 2016).

The mid-cingulate cortex, in particular, occupies a central position in reactive fear circuitry, helping to inform rapid decisions of escape from predators signaled by the fearful expressions of conspecifics (Shackman et al., 2011). It coordinates emotional responses and motor actions according to learned values, particularly when a threat is proximal. Especially robust links have been demonstrated between activity in the anterior mid-cingulate cortex and the experience of intense negative affect, including fear (Tolomeo et al., 2016). The posterior mid-cingulate cortex may play a more specific role in threat appraisal and risk assessment through approach behaviors (Blanchard et al., 2015).

Dysfunction within this circuitry, particularly in the anterior insula and mid-cingulate cortex, could impair the recognition and integration of distress cues in others—a deficit central to Blair's (2017) model of psychopathy. Reduced responsiveness to others' distress would weaken the socializing feedback that normally inhibits aggressive behavior, thereby predisposing to instrumental aggression.

3.5 Oxytocin as a Neuromodulator of Social Cognition

The neuropeptide oxytocin has emerged as a key modulator of social behavior and empathic processing. Oxytocin receptors are densely expressed in social brain regions functionally implicated in ASPD, including the amygdala and cingulate cortex (Boccia et al., 2013). In healthy individuals, oxytocin enhances the explicit recognition of fearful faces (Shahrestani et al., 2013) and significantly modulates activity within fearful facial-processing regions (Tully et al., 2018). These properties position oxytocin as a candidate agent for pharmacologically modulating empathic processing deficits in ASPD +/–P.

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4. Empirical Findings Across Studies

4.1 Neurochemical Findings: Striatal Glutamate/GABA Dysregulation

The empirical demonstration of impaired striatal E/I regulation in ASPD +/–P represents a significant advance in the neurobiological characterization of these conditions. In a proton magnetic resonance spectroscopy (^{1}H-MRS) study using a 3 Tesla scanner with the MEGA-PRESS sequence, Tully et al. (2024) examined 51 men, comprising 16 offenders with ASPD –P, 14 offenders with ASPD +P, and 21 healthy non-offenders. Using a single voxel positioned to include the left striatum, they quantified GABA+ (GABA plus macromolecules) and glutamate, generating a glutamate:GABA ratio as an index of E/I balance.

The primary finding was a significant reduction in the striatal glutamate:GABA ratio in the combined ASPD group compared with healthy non-offenders (mean ratio of 2.847 vs. 3.164, respectively, with $p < 0.001$). Notably, this reduction was present across both ASPD subgroups; post-hoc comparison of ASPD-P and ASPD +P revealed no significant within-ASPD group difference ($p = 0.979$). The finding was robust to control for illicit drug use as a covariate, with the group difference remaining significant in ANCOVA ($\eta^2 = 0.223$, F■,■■ = 6.876, $p = 0.002$).

The direction of this effect—reduced glutamate:GABA ratio in ASPD—indicates relatively increased inhibitory tone within the striatum in violent offenders. This finding has important implications. First, it suggests that abnormal striatal E/I balance is a shared characteristic of offenders with ASPD, regardless of psychopathy status, and thus represents a potential cross-cutting mechanism that spans the ASPD +/–P continuum. Second, it provides a novel neurochemical account of the striatal dysfunction previously implicated in ASPD +/–P by fMRI studies of decision-making and reinforcement learning.

Correlation analyses did not reveal a significant relationship between PCL-R score and glutamate:GABA ratio within either the healthy non-offender group (Spearman's rho = –0.117, $p = 0.612$) or the ASPD group (Spearman's rho = –0.076, $p = 0.688$). The absence of a dimensional relationship, combined with the categorical difference between offenders and non-offenders, suggests that the E/I dysregulation may reflect a threshold effect associated with the antisocial phenotype rather than a linear function of psychopathic severity.

4.2 Neural Findings on Empathic Processing: fMRI Evidence

Complementing these neurochemical findings, fMRI research has documented specific abnormalities in the implicit processing of fearful facial expressions in ASPD +/–P. In a

placebo-controlled, randomized crossover design, Tully et al. (2023) examined 58 men—24 healthy non-offenders, 15 offenders with ASPD –P, and 19 offenders with ASPD +P—who completed a morphed faces task under both intranasal oxytocin (40 IU) and placebo conditions. The task presented facial expressions of fear at varying intensities (40%, 60%, 80%, and 100%), while participants engaged in a gender rating task that rendered emotion processing implicit.

Under placebo conditions, violent offenders with ASPD +P showed significantly reduced modulation of blood-oxygen-level-dependent (BOLD) responding by fearful expression intensity within the bilateral mid-cingulate cortex and right anterior insula compared with violent offenders with ASPD –P. The right anterior insula finding did not survive strict correction for multiple comparisons and thus requires replication, but the mid-cingulate finding was robust. This differentiation between ASPD +P and ASPD –P is theoretically important: it suggests that although the two groups share the striatal neurochemical abnormality documented by Tully et al. (2024), they diverge in the neural processing of empathy-relevant stimuli, with reduced responsiveness to others' distress being specific to the psychopathic subgroup.

Importantly, there were no significant main effects or between- or within-group findings in the amygdala in either the placebo or oxytocin condition. This null finding, contrary to earlier expectations based on studies in youth with CU traits (Marsh et al., 2008), suggests that in adults with ASPD +P, the empathic processing deficit may be more prominently expressed in cortical and insular regions than in the amygdala itself. Alternatively, this may reflect the well-documented challenges of achieving adequate statistical power in fMRI studies of clinical populations (Cremers et al., 2017; Marek et al., 2022; Turner et al., 2018).

4.3 The Effect of Oxytocin on Neural Processing

The most striking finding from the Tully et al. (2023) study concerns the effect of intranasal oxytocin. Violent offenders with ASPD +P showed significant increases in modulation by fearful expression intensity in the bilateral mid-cingulate cortex and left anterior insula under oxytocin compared with the placebo condition. Crucially, this pharmacological effect abolished the group differences between ASPD +P and ASPD –P observed under placebo, and this pattern was supported by a statistically significant group by condition interaction effect in the left mid-cingulate cortex.

The implications of this finding are considerable. It provides the first demonstration, to the authors' knowledge, that the neural processing abnormalities observed in a robustly classified group of men with ASPD +P can be modified by neurochemical intervention. The enhancement of fear-associated activity in the mid-cingulate cortex and anterior insula under oxytocin suggests that fearful faces are accorded increased salience in these regions, with the potential to alter downstream behavioral processes related to empathic responding and inhibition of aggression (Menon & Uddin, 2010; Newman et al., 2010).

4.4 Integration of Neurochemical and Neural Findings

Considered together, the findings of Tully et al. (2023, 2024) provide a complementary neurobiological account of ASPD +/–P. The striatal glutamate/GABA dysregulation appears to be a shared feature of violent offending across the ASPD spectrum, potentially underpinning the reinforcement-learning and decision-making deficits observed in both ASPD +P and ASPD –P. The cortical empathic processing deficits, by contrast, appear to differentiate psychopathic from non-psychopathic offenders and may be pharmacologically modifiable through oxytocin administration. Table 1 provides a synthetic overview of these findings.

Table 1

Synthesis of Neurobiological Findings in Violent Offenders with ASPD +/–P

Domain	ASPD –P	ASPD +P	Shared vs. Specific
Striatal glutamate:GABA ratio	Reduced vs. non-offenders	Reduced vs. non-offenders	Shared across ASPD
Mid-cingulate response to fearful faces	Preserved	Reduced	Specific to ASPD +P
Insular response to fearful faces	Preserved	Reduced (right)	Specific to ASPD +P
Amygdala response to fearful faces	No significant group difference	No significant group difference	Not differentiating
Response to oxytocin (mid-cingulate)	Not significant	Significant increase	Specific to ASPD +P

Domain	ASPD –P	ASPD +P	Shared vs. Specific
Behavioral aggression (RPQ)	Elevated vs. non-offenders	Further elevated vs. ASPD –P	Dimensional

Note. Findings are synthesized from Tully et al. (2023, 2024). RPQ = Reactive-Proactive Aggression Questionnaire.

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5. Psychological Pathways and Stress Responses

5.1 Reinforcement Learning and Its Disruption

The psychological pathways implicated in ASPD +/–P begin with reinforcement learning—the process by which organisms adjust behavior based on the consequences of their actions. Healthy reinforcement learning depends on the ability to encode reward prediction errors, integrate outcomes over time, and flexibly adjust behavior when contingencies change. Antisocial adults, both with and without psychopathy, show deficits across these domains. They demonstrate impaired reversal learning, in which they fail to update behavior when previously rewarded responses become punished; deficits in decision-making under risk; and impaired stimulus-reinforcement-based decision-making (De Brito et al., 2013). Both groups fail to learn from punishment cues, struggle to change behavior in the face of changing contingencies, and make poorer-quality decisions despite longer periods of deliberation.

At a neural level, these behavioral deficits map onto abnormalities in striatal and connected cortical regions. In childhood, youths with disruptive behavior disorders show decreased ventral striatal response during reward anticipation (Holz et al., 2017), reduced responsiveness to positive prediction errors and increased responsiveness to negative prediction errors within the dorsal striatum (White et al., 2013), and reduced dorsal striatal response to early stimulus-reinforcement exposure (Finger et al., 2011). Persistent disruptive behavior into late adolescence is associated with reduced ventral striatal responsivity during reward outcome processing (Cohn et al., 2015). In adulthood, psychopathy is associated with a complex profile: stronger subjective value-related activity within the ventral striatum during intertemporal choice (Hosking et al., 2017), reduced ventral striatal response to monetary loss

(Pujara et al., 2014), and increased responses to reward anticipation (Geurts et al., 2016; Hosking et al., 2017).

5.2 The Role of Aberrant Salience

The demonstration that striatal E/I regulation is impaired in ASPD +/–P provides a neurochemical account of how these functional abnormalities may arise. Aberrant salience attribution—the assignment of undue importance to stimuli that do not warrant it, or the failure to attribute salience to stimuli that do—has been linked to disrupted dopaminergic signaling and altered E/I balance (Boehme et al., 2015). In the context of ASPD +/–P, aberrant salience could manifest as increased reactivity to potential rewards (particularly those associated with immediate gratification) combined with reduced reactivity to negative outcomes and threat cues. This profile is consistent with the phenomenology of the disorder, characterized by impulsivity, sensation-seeking, and diminished responsiveness to punishment.

5.3 Empathic Processing as a Stress Response System

Empathic processing, particularly the automatic detection of distress in others, functions in part as a socially embedded stress response system. When another individual displays distress, healthy observers show rapid activation of neural systems involved in fear processing (amygdala, insula, cingulate cortex), leading to autonomic arousal and, in most cases, prosocial or inhibitory behavioral responses. The reduced neural responsiveness to fearful expressions observed in ASPD +P (Tully et al., 2023) suggests that this system operates atypically in individuals with psychopathy, with distress cues from others failing to elicit the salience and physiological response that would normally inhibit aggressive behavior.

Notably, this deficit appears to be relatively specific to the affective components of empathic processing rather than to face processing more generally. Studies of dynamic facial expressions have documented reduced activation in core face-processing regions and associated emotional and motivational areas in men with ASPD +P (Decety et al., 2014), while related work in a small pilot sample reported reduced activation in response to fearful facial expressions at low and prototypical intensities in men with psychopathy compared with healthy controls (Deeley et al., 2006).

5.4 The Interplay of Approach and Avoidance Systems

A conceptually important consideration is the interplay between approach-related systems (associated with reward pursuit and dopaminergic signaling) and avoidance-related systems (associated with threat processing and empathic responsiveness). In healthy functioning, these systems operate in dynamic balance, with the recognition of threat or distress in others tempering approach behavior directed toward goals that would produce such distress. In ASPD +P, both systems appear to be dysregulated: the striatal E/I abnormality may bias reinforcement learning and decision-making, while the cortical empathic processing deficits reduce the inhibitory influence of others' distress. The combination may produce a phenotype characterized by unmodulated pursuit of immediate rewards without adequate weighting of the costs to others.

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6. Mental Health Outcomes and Severity Spectrum

6.1 The Spectrum of Antisocial Presentations

The ASPD +/–P construct captures a spectrum of clinical presentations that vary in severity, chronicity, and comorbidity. At one end of this spectrum are individuals with mild antisocial features whose behavior may be primarily impulsive and reactive; at the other end are individuals with psychopathy whose antisocial behavior is more instrumental, callous, and pervasive across life domains. The samples described by Tully et al. (2023, 2024) represent the more severe end of this spectrum, comprising violent offenders with convictions for serious offenses including murder, rape, attempted murder, and grievous bodily harm.

Within these samples, aggression profiles differed significantly between subgroups. On the Reactive-Proactive Aggression Questionnaire (Raine et al., 2006), offenders with ASPD +P showed significantly higher reactive, proactive, and total aggression scores than offenders with ASPD –P, who in turn showed elevated scores compared with healthy non-offenders (Tully et al., 2023). This dimensional pattern of aggression severity is consistent with the broader literature indicating that psychopathy represents a more severe variant of the ASPD phenotype (Coid & Ullrich, 2010).

6.2 Comorbidity Patterns

Comorbidity is a defining feature of ASPD +/–P and complicates both assessment and treatment. In the samples reported by Tully and colleagues (2023, 2024), offenders showed significantly higher rates of comorbid Cluster A and Cluster B personality disorder diagnoses compared with healthy non-offenders. Furthermore, offenders with ASPD +P showed higher rates of these comorbidities than offenders with ASPD –P. Lifetime substance-use disorders were also more prevalent among offenders, though rates did not differ significantly between the ASPD subgroups.

The high rate of substance-use disorders is particularly clinically significant. Substances such as cocaine and opiates are known to impact both GABAergic and glutamatergic systems (Kalivas, 2004; Kupchik et al., 2014; Schmidt & Pierce, 2010; Ye & Ren, 2006), raising the possibility that some of the neurochemical abnormalities observed in ASPD populations may be secondary to substance use rather than primary features of the disorder. Tully et al. (2024) addressed this concern by including illicit substance use as a covariate in their analyses; the striatal glutamate:GABA differences remained significant, suggesting that the neurochemical abnormality is not simply an artifact of substance use. Nevertheless, the complex bidirectional relationships between substance use and ASPD neurobiology represent an important area for further investigation.

6.3 Cognitive and Educational Profiles

Beyond diagnostic comorbidity, offenders with ASPD show consistent differences in cognitive and educational profiles compared with healthy non-offenders. In the Tully et al. (2024) sample, offenders had significantly fewer years of education than non-offenders, and there was a non-significant trend toward lower IQ scores. These findings are consistent with the broader literature and likely reflect a combination of factors including early developmental adversity, disrupted educational trajectories, and possibly primary neurocognitive vulnerabilities.

6.4 Treatment Response and Prognosis

The prognosis for ASPD +/–P varies substantially with psychopathy status. Individuals with psychopathy generally respond less favorably to psychosocial treatment programs than those

without (Guy et al., 2005), and clinical guidelines emphasize the limited evidence base for pharmacological treatments (National Collaborating Centre for Mental Health, 2010). This treatment-resistance is one of the most clinically consequential features of the disorder, contributing to a pattern of persistent offending, high rates of recidivism, and substantial personal and societal costs.

The findings of Tully et al. (2023) offer preliminary but important evidence that neurochemical modulation of empathic processing may be possible, with intranasal oxytocin producing observable normalization of neural responses to fearful expressions in men with ASPD +P. Although this finding is preliminary and requires substantial further work before clinical application can be contemplated, it represents an important shift in the field toward the possibility that even the most severe and treatment-resistant forms of antisocial behavior may be amenable to neurobiologically informed intervention.

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7. System-Level and Contextual Psychological Effects

7.1 The Societal Burden of Antisocial Behavior

The psychological effects of ASPD +/–P extend well beyond the individuals meeting diagnostic criteria to encompass victims, families, communities, and broader social systems. As noted earlier, the small proportion of the population meeting criteria for these disorders is disproportionately responsible for violent crime (Falk et al., 2014), and the costs of this offending—both direct and indirect—are substantial (Heeks et al., 2018; Wickramasekera et al., 2015). Psychologists working with victims of violence, with families affected by intergenerational patterns of antisocial behavior, and with communities disproportionately impacted by crime must contend with the reverberating consequences of the neurobiological and psychological patterns described in this manual.

7.2 Intergenerational Transmission

Antisocial behavior shows substantial intergenerational transmission through both genetic and environmental pathways. Children of parents with ASPD are at elevated risk for developing

conduct problems themselves, and the presence of CU traits in these children—the developmental precursor to psychopathy—represents a particular concern for treatment resistance and severity (Viding & McCrory, 2012). Understanding the neurobiological substrates of these conditions is therefore not merely an academic exercise but has implications for early identification, prevention, and intervention across generations.

7.3 Forensic and Criminal Justice Contexts

Psychologists working in forensic and criminal justice contexts encounter individuals with ASPD +/−P with high frequency. Accurate assessment of these individuals—including differentiation of ASPD +P from ASPD −P—has significant implications for risk assessment, sentencing recommendations, and treatment planning. The findings synthesized in this manual underscore the importance of comprehensive assessment that goes beyond behavioral descriptions to incorporate an understanding of the neurocognitive and neurobiological features of the disorder.

7.4 Ethical Considerations in Neurobiological Research

The neurobiological characterization of ASPD +/−P raises important ethical considerations. Some critics have expressed concern that biological accounts of antisocial behavior may promote deterministic or reductionist thinking, potentially undermining moral agency or justifying discriminatory practices. Psychologists engaging with this literature must maintain critical awareness of these concerns while recognizing that neurobiological understanding is not inherently reductionist. On the contrary, evidence that neural systems can be modulated pharmacologically—as with the oxytocin findings of Tully et al. (2023)—may open avenues for compassionate intervention that reduce, rather than reinforce, the marginalization of individuals with these conditions.

7.5 The Ecosystem of Treatment Provision

At a system level, the treatment of ASPD +/−P requires coordination across multiple service providers, including mental health services, forensic services, probation, and correctional facilities. The evidence base for effective treatment remains limited, and the emergence of neurobiologically informed interventions—if validated through further research—would require

substantial changes in service structures, professional training, and interdisciplinary collaboration. Psychologists in leadership and consultative roles will play a critical part in translating emerging research into ethical, evidence-informed clinical practice.

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8. Clinical Implications for Psychologists

8.1 Assessment and Diagnostic Formulation

The findings synthesized in this manual have several implications for psychological assessment and diagnostic formulation. First, they underscore the importance of careful differentiation between ASPD +P and ASPD –P, as these subgroups show partially distinct neurobiological profiles and, potentially, distinct treatment implications. Standard use of the PCL-R (Hare, 2003), with attention to appropriate cultural cutoffs, remains central to this differentiation. Assessment should also incorporate structured diagnostic interviews such as the Structured Clinical Interview for DSM-5 Personality Disorders (First et al., 2016) and attention to comorbid conditions, particularly other personality disorders and substance-use disorders.

Second, psychological assessment should incorporate consideration of the specific neurocognitive domains implicated in these conditions. Assessment of decision-making, reinforcement learning, and empathic processing—through both standardized neuropsychological instruments and clinical observation—can provide a more complete picture of an individual's strengths and vulnerabilities than diagnosis alone. Such assessment is particularly valuable in forensic contexts where risk formulation depends on understanding the specific processes that drive behavior.

8.2 Case Formulation

Case formulation for individuals with ASPD +/–P should integrate an understanding of the neurobiological, cognitive, developmental, and social factors that contribute to the presentation. The framework provided by contemporary neuroimaging research suggests that formulations should attend to at least three domains: reinforcement learning and

decision-making processes, which may reflect striatal E/I dysregulation and be shared across ASPD subgroups; empathic processing, particularly the recognition and integration of distress cues in others, which may be specifically impaired in ASPD +P; and the developmental trajectory linking childhood conduct problems and CU traits to adult presentations.

8.3 Treatment Planning

Treatment planning for ASPD +/–P remains challenging, with limited evidence supporting either psychosocial or pharmacological interventions. However, the emerging neurobiological framework has several implications for treatment.

First, it emphasizes the potential value of targeting specific neurocognitive processes rather than the diagnostic category as a whole. Interventions that address decision-making, reinforcement learning, or empathic processing may prove more tractable than attempts to change the broader personality structure.

Second, the demonstration that intranasal oxytocin can normalize neural responses to fearful expressions in ASPD +P (Tully et al., 2023) provides preliminary evidence for the potential of pharmacological interventions targeting specific neurochemical systems. While this finding is far from clinical application, it opens a line of investigation that may eventually yield pharmacological tools with more specific effects than currently available agents.

Third, the neurochemical findings of Tully et al. (2024) point toward potential therapeutic targets for the E/I dysregulation observed in ASPD. Candidate approaches include agents targeting glutamate decarboxylase (GAD), which converts glutamate to GABA and has been implicated in aggression, autism, schizophrenia, addiction, and ADHD (Blatt & Fatemi, 2011; Bruxel et al., 2016; Fatemi et al., 2002; Grimes et al., 2003; Levran et al., 2016; Sandhu et al., 2014; Stork et al., 2000); agents such as N-acetylcysteine and ceftriaxone that normalize glutamatergic function through effects on the cystine-glutamate exchanger (Knackstedt et al., 2010; Zhou & Kalivas, 2008); and psychostimulant medications that have been shown to increase striatal glutamate in preclinical work (Furlong et al., 2018; Mark et al., 2004; White et al., 2018). Each of these approaches, however, requires substantial further investigation before clinical translation can be contemplated.

8.4 The Role of Psychological Interventions

Notwithstanding the emerging interest in pharmacological approaches, psychological interventions remain central to the clinical management of ASPD +/–P. The neurobiological findings synthesized in this manual do not diminish the importance of psychological intervention; rather, they may inform more targeted and effective approaches. For example, understanding that empathic processing deficits in ASPD +P reflect specific neural dysfunctions may support the development of interventions that explicitly target these processes, potentially in combination with pharmacological agents that enhance the salience of distress cues.

For offenders with ASPD –P, the shared striatal E/I dysregulation and relatively preserved empathic processing suggest that interventions targeting decision-making, impulse control, and reinforcement learning may be particularly relevant. For offenders with ASPD +P, additional attention to empathic processing may be warranted, with the recognition that this domain represents a specific vulnerability.

8.5 Working with Complex Comorbidities

The high rates of comorbidity in ASPD +/–P, particularly with other personality disorders and substance-use disorders, require careful clinical attention. Substance use, in particular, has bidirectional relationships with the neurobiological substrates of ASPD, potentially both contributing to and reflecting underlying dysfunctions in E/I regulation and empathic processing. Effective treatment planning must therefore address substance use in an integrated manner rather than treating it as separable from the primary presentation.

8.6 Ethical Practice and Professional Boundaries

Working with individuals meeting criteria for ASPD +/–P raises specific ethical challenges that psychologists must navigate carefully. These include the management of dual roles (particularly in forensic settings), the balancing of individual autonomy with public safety, the ethical use of risk assessment instruments, and the maintenance of therapeutic engagement in the context of manipulative or antagonistic interpersonal behavior. The emerging neurobiological understanding of these conditions should inform, but not replace, careful attention to these longstanding ethical considerations.

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9. Future Directions and Research Gaps

9.1 Methodological Considerations and Limitations

The research synthesized in this manual, while representing significant advances, is subject to important methodological limitations that must be acknowledged. Sample sizes in the studies of Tully and colleagues (2023, 2024) were modest, reflecting the well-documented challenges of recruiting forensic populations for detailed neurobiological investigation. Small samples reduce statistical power and may result in the failure to detect meaningful subgroup differences (Cremers et al., 2017; Marek et al., 2022; Turner et al., 2018). Future work will benefit from larger samples, ideally through collaborative multi-site studies.

Technical limitations of the MRS methodology also require attention. The MEGA-PRESS sequence used by Tully et al. (2024), while an acceptable means of estimating brain glutamate, was not specifically designed for this purpose, and the best means of estimating the excitatory component of the glutamatergic pool remains debated (Goryawala et al., 2016; Ramadan et al., 2013; van Veenendaal et al., 2018). The relatively large voxel size used in the study means that measurements may be confounded by signal from surrounding tissue, and no distinction can be made between functional subdivisions of the striatum (Bai et al., 2017; Blüml, 2013). Future work with ultrahigh field strengths (7T and above) may address some of these limitations (Finkelman et al., 2022).

Similarly, the fMRI findings of Tully et al. (2023) require replication, particularly the findings that did not survive strict correction for multiple comparisons and the null findings in the amygdala. The absence of significant differences between either antisocial group and healthy non-offenders on some measures, while differences between the two antisocial groups were significant, requires careful interpretation and further investigation.

9.2 The Need for Integrated Multimodal Investigation

A key priority for future research is the integration of neurochemical, structural, and functional neuroimaging with detailed behavioral and neuropsychological measurement. The current literature has proceeded largely in parallel streams, with MRS studies focused on neurochemistry, fMRI studies focused on task-related activation, and behavioral studies

focused on cognitive and emotional processes. Integrated designs that combine these modalities in the same participants would allow direct examination of relationships between neurochemistry, neural activation, and behavior—for example, the relationship between striatal glutamate:GABA ratios and neural correlates of reinforcement learning during task performance.

Emerging techniques such as combined MRS-fMRI, which can acquire simultaneous glutamate and BOLD signals (Ip et al., 2017), offer particular promise in this regard. Such approaches would allow investigators to move beyond correlational associations toward causal accounts of how neurochemical abnormalities give rise to functional impairments.

9.3 Stratification and Precision Approaches

The heterogeneity of ASPD +/–P, even within subgroups, suggests the value of stratification approaches that identify subgroups of individuals with particular neurobiological profiles who might respond to specific interventions. Tully et al. (2024) proposed that individuals with striatal glutamate:GABA ratios below a specified threshold might be selected for pharmacological interventions addressing E/I imbalance. However, the cost and complexity of MRS assessment limit its practicality as a routine stratification tool.

Alternative approaches include the use of proxy measures such as electroencephalography (EEG) and electroretinography (ERG). EEG has been used extensively in research on ASPD +/–P (Gao & Raine, 2009; Pasion et al., 2018; Schulreich, 2016) and has shown promise as a marker of E/I balance in other conditions such as autism (Snijders et al., 2013) and schizophrenia (Chen et al., 2014). Specific EEG signatures, such as activity in the gamma band, have been linked to GABAergic dendritic inhibition (Wendling et al., 2002). ERG, which measures electrophysiological activity in the retina, is emerging as a potential proxy marker of central nervous system function in psychiatric disorders (Schwitzer et al., 2017) and has been used to demonstrate abnormalities in major depressive disorder (Bubl et al., 2010, 2012) and ADHD (Bubl et al., 2015). Linking specific EEG or ERG measures to MRS-defined neurochemical abnormalities represents a promising direction for developing accessible stratification tools.

9.4 Longitudinal and Developmental Investigation

Much of the current neurobiological literature on ASPD +/–P is cross-sectional, providing snapshots of adult presentations without illuminating the developmental trajectories that give rise to them. Longitudinal studies that follow at-risk youth into adulthood, with repeated neurobiological assessment, would provide crucial information about the timing and nature of the neurobiological changes associated with the development of ASPD +/–P. Such work would also help clarify whether the observed neurobiological abnormalities are primary features of the disorder or secondary to environmental and behavioral factors accumulated across development.

9.5 Therapeutic Development

The most immediate translational priority arising from this literature is the development and testing of therapeutic interventions targeting the neural systems identified as dysfunctional. Pharmacoimaging studies examining the effects of candidate agents on E/I balance and empathic processing represent an important next step. A priori selection of participants with established neurochemical or functional abnormalities would enhance the sensitivity of such studies to detect meaningful effects.

Beyond pharmacological interventions, research on non-invasive brain stimulation techniques such as transcranial magnetic stimulation and transcranial direct current stimulation may offer additional avenues for modifying neural activity in specific circuits. Such approaches, if validated, could complement or substitute for pharmacological interventions in some contexts.

9.6 Neuroprediction of Behavioral Outcomes

An emerging area of research concerns the use of neuroimaging measures to predict future behavioral outcomes, including recidivism. Preliminary work has suggested that multimodal imaging measures can predict rearrest in criminal populations (Aharoni et al., 2013; Steele et al., 2015). This work, however, raises significant ethical and methodological concerns, including the risk of false positives, the ethical implications of using neuroimaging in decisions about sentencing or release, and the potential for reinforcing rather than mitigating disparities in criminal justice outcomes. Continued research in this area must proceed with careful attention to these concerns.

9.7 Investigating Women and Diverse Populations

A significant limitation of the current literature, including the work of Tully and colleagues (2023, 2024), is the near-exclusive focus on male samples. Women can and do meet criteria for ASPD and psychopathy, though at lower rates than men, and the neurobiological features of these conditions in women remain poorly characterized. Similarly, most neurobiological research has been conducted in relatively narrow demographic samples, limiting generalizability to more diverse populations. Extending this research to include women and more diverse samples represents an important priority.

9.8 Understanding the Interplay of Multiple Neurochemical Systems

The neurochemical accounts developed to date have focused primarily on individual systems (glutamate/GABA in the case of Tully et al., 2024; oxytocin in the case of Tully et al., 2023). However, brain function reflects the coordinated activity of multiple neurochemical systems, and future research will benefit from investigating the interactions among these systems. Dopaminergic, cholinergic, serotonergic, and endocannabinoid systems, among others, are all likely to be involved in the pathophysiology of ASPD +/–P, and understanding how these systems interact will be crucial for developing effective interventions.

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10. Conclusion

Antisocial personality disorder, with or without co-occurring psychopathy, represents one of the most clinically challenging and socially consequential conditions encountered in psychology and forensic mental health. For decades, the development of effective interventions has been hampered by a limited understanding of the neurobiological underpinnings of these conditions. The research synthesized in this manual—particularly the work of Tully and colleagues (2023, 2024)—represents an important advance in this understanding.

The demonstration that violent offenders with ASPD, both with and without psychopathy, show impaired striatal glutamate/GABA regulation compared with healthy non-offenders (Tully et al., 2024) provides a novel neurochemical account of the decision-making abnormalities

long observed in these individuals. The finding is significant not only for what it reveals about pathophysiology but also for what it suggests about potential therapeutic targets. Agents that modify glutamate/GABA balance, whether through direct effects on these systems or through modulation of related neurochemical systems, may offer new avenues for pharmacological intervention.

Complementing this neurochemical account, the demonstration that intranasal oxytocin normalizes the neural processing of fearful facial expressions in violent offenders with psychopathy (Tully et al., 2023) provides the first evidence that the empathic processing deficits characteristic of psychopathy may be pharmacologically modifiable. While clinical application remains distant, this finding represents a significant conceptual advance: it suggests that even the most severe and treatment-resistant features of psychopathy may not be immutable but may be amenable to intervention through targeted neurochemical modulation.

Considered together, these findings support a model in which ASPD +/–P reflects dysfunction across multiple neural systems, with some features shared across the ASPD spectrum (striatal E/I dysregulation, decision-making abnormalities) and others more specific to psychopathy (empathic processing deficits, reduced responsiveness to distress cues). This differentiated model has important implications for assessment, formulation, and treatment planning, and it opens avenues for more targeted and effective interventions than have previously been available.

Psychologists working with individuals affected by ASPD +/–P are increasingly called upon to engage with this rapidly evolving neurobiological literature. Doing so requires not only familiarity with specific findings but also critical awareness of methodological limitations, ethical considerations, and the complex relationships between neurobiological findings and clinical practice. This manual has aimed to provide the conceptual grounding for such engagement, situating specific empirical findings within broader theoretical frameworks and considering their implications for clinical practice.

Much work remains to be done. The current evidence base, while significant, is limited by modest sample sizes, technical limitations of neuroimaging methods, and the challenges of studying complex clinical populations. Larger, more diverse, and methodologically sophisticated studies are needed to consolidate and extend the findings reported to date. Longitudinal investigation will be essential for understanding the developmental origins of

these conditions. Translational research, connecting neurobiological findings to clinical intervention, remains in its early stages.

Yet the trajectory of the field is unmistakable. From a position of near-complete ignorance about the neurobiological basis of severe antisocial behavior, the field has moved toward the beginnings of an integrated model that connects neurochemistry, neural circuitry, cognition, and behavior. Psychologists have both the opportunity and the responsibility to engage with this emerging science, contribute to its development, and translate its insights into more effective, ethical, and compassionate care for individuals and communities affected by these deeply challenging conditions.

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