Jack and Heather, I apologize for the terrible formatting of this chapter. It is all I have been able to get the Editor to send at this point. Joe

Contributions of Prefrontal Lobe Subregions to Antisocial and Aggressive Behavior

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Theoretical conceptualizations of antisocial and aggressive behavior from a central nervous system (CNS) perspective have increasingly focused on the frontal lobes or foremost region of the brain. A growing body of research suggests that this brain region mediates key personality traits ranging from empathic understanding and emotion regulation to behavioral inhibition and self-monitoring. Consequently, the frontal lobes have been of great interest in neurobiological studies with aggressive and antisocial populations. Early indications of a link between the frontal lobes and aberrant behavior were sparked by case studies that detailed dramatic personality changes following selective brain damage. Perhaps the most famous case involved the unfortunate accident suffered by Phineas Gage. Despite providing compelling clinical evidence of a frontal lobe-disruptive behavior link, however, nearly a century passed before more rigorous attention was paid to the role the frontal lobes play in regulating social behavior.

In this chapter we review research on the frontal lobe-antisocial behavior link. We begin with a basic overview of the functional neuroanatomy of the frontal lobe, which is largely drawn from a prior summary (Ishikawa & Raine, in press). We then move into a review of the literature on neurobiological correlates of antisocial behavior, paying particular attention to studies that parcellate the frontal lobe into functionally distinct yet inter-related sectors. The studies center on the three frontal lobe subdivisions that have been most frequently linked to antisocial behavior problems: dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), and ventromedial frontal cortex (VMC).

Introduction to the subregions of the frontal lobe

When referring to location and directionality within the brain, standard nomenclature is used. The terms ôdorsalö and ôventralö represent location along a vertical axis, with dorsal referring to ôsuperior or toward the top of the headö and ventral referring to ôinferior or down toward the jawö. The terms ômedialö and ôlateralö represent location along a horizontal axis extending between the ears, with lateral referring to the sides or surface of the brain and medial referring to the middle portion deep within the brain. The terms ôrostralö and ôcaudalö are also located on a horizontal axis, although this axis extends from the front to the back of the head (i.e., rostral = front or towards the nose; caudal = towards the back of the head).

The frontal lobe consists of approximately one-third of the human brain and supports many complex cognitive functions. It is located in the anterior region of the brain rostral to the primary motor area (see Figure 1). Historically, the most common subdivisions of the prefrontal region of the frontal lobe are the dorsolateral prefrontal cortex, orbitofrontal cortex, and medial frontal cortex, with the former two having been the most studied in relation to antisocial behavior. A slightly different subdivision û the ventromedial frontal cortex û has been reported in more recent studies of antisocial behavior and also bears some mention. The ventromedial frontal cortex overlaps portions of both the orbitofrontal and medial frontal cortices, and specifically refers to the medial area of the orbitofrontal cortex and ventral area of the medial cortex.

The dorsolateral prefrontal cortex (DLPFC) is located in the superior, lateral portion of the prefrontal area just anterior to the supplementary motor area and includes the dorsal region of the frontal pole (see Figure 1). It is extensively interconnected with the orbitofrontal cortex and more posterior cortical association areas. It

has traditionally been associated with information processing skills such as working memory and executive functions (Cummings, 1995; Damasio & Anderson, 1993). With regard to specific working memory processes, functional brain imaging studies have found that the DLPFC appears to be necessary for the manipulation and encoding of information (DÆEsposito, Postle, & Rypma, 2000). The DLPFC is also important for the maintenance of information in the presence of distracting stimuli (DÆEsposito et al, 2000; Stern, Sherman, Kirchhoff, & Hasselmo, 2001), and is hypothesized to be involved in emotion processing (Davidson, Jackson, & Kalin, 2000). The medial frontal cortex (i.e., MFC) is made up of the ventromedial frontal cortex and the anterior cingulate (i.e., see Figure 1; Kaufer & Lewis, 1999; Stuss & Levine, 2002). The medial prefrontal cortex interconnects with the dorsolateral prefrontal cortex and posteriorly projects to the amygdala and hypothalamus. It subserves motivational processes and maintenance of activity (Cummings, 1995). Finally, the orbitofrontal cortex (OFC) is located just above the orbits or eye sockets and includes the ventrolateral cortex, ventromedial cortex, and posterior region of the frontal pole (see Figure 1). The orbitofrontal cortex significantly interconnects with the temporal pole and amygdala. It regulates autonomic reactivity, social and self-awareness, and regulation of affect (Damasio & Anderson, 1993; LaPierre, Braun, & Hodgins, 1995). In addition, the ventromedial frontal cortex, partially contained within the OFC, is implicated in risk-related and emotion-based decision-making (Bechara, Damasio, Damasio, & Lee, 1999). Although response inhibition has traditionally been ascribed to the orbitofrontal cortex, recent imaging research has found that this executive function is subserved by a wide frontal neural network in which the dorsal anterior cingulate regulates monitoring and decision formation while the dorso- and ventrolateral prefrontal cortices regulate actual response inhibition (Liddle, Kiehl, & Smith, 2001; Elliot, Rubinsztein, Sahakian, & Dolan, 2000).

Antisocial behavior and the dorsolateral prefrontal cortex

Some of the earliest work to link the DLPFC to aggressive behavior was with animal lesion studies. After a subset of stump-tailed macaques underwent surgical placement of bilateral DLPFC lesions, a significant increase in aggression was noted within the overall colony (Mass & Kling, 1975). Although the increased display of aggressiveness was not solely restricted to the lesioned subjects, the lesioned monkeys received the most severe injuries during aggressive interchanges and fell in dominance ranking. Similarly, eight male rhesus macaques that underwent bilateral lesions to the DLPFC and were housed within a larger colony of un-operated monkeys engaged in significantly more physical aggression and significantly fewer threatening gestures post-operatively (Miller, 1976). As in the Mass and Kling study, the aggressive behavior appeared to have the function of maintaining dominance hierarchy, as aggression was always directed at lower ranking monkeys and these monkeys always submitted to the more dominant monkey. What was also noted, however, was that lesioned monkeys often aggressed abruptly, without warning, and with an atypical ômask-likeö expression. In contrast, un-operated monkeys appeared to regulate aggressive behavior by making threatening gestures before escalating into an attack. Finally, another study found that, while under the influence of alcohol, female pigtail monkeys with selective bilateral DLPFC lesions showed a significant increase in aggressive behavior towards a familiar human observer, whereas monkeys with selective bilateral OFC lesions did not (Kamback, 1973). Although the two lesion groups in this study showed comparable levels of aggressive behavior in control

(i.e., non-alcohol) conditions, the DLPFC monkeys chose to drink alcohol more often than did OFC monkeys and normal controls. Thus, these DLPFC monkeys were selecting to engage in behavior that disinhibited their regulation of aggression.

In general, findings from these animal studies suggest that lesions to the DLPFC interfered with appropriate regulation of aggressive behavior. These disruptions resulted in falls in social dominance and increased injury rates, the latter of which was likely the result of the lesioned monkeys failing to engage in appropriate threat (or submission) cues or inappropriately targeting larger, more dominant monkeys (Higley et al, 1996). Lesions to the DLPFC did not affect the rate of affiliative behaviors (i.e., grooming), indicating that the findings for aggression were not due to an overall change in motor activity or general social interactions. Thus, it appears that the DLPFC regulated appropriate displays of aggressive behavior that correspond to dominance status, such that individuals without appropriate self-regulation were aggressed against and displaced from the group as a way to maintain social order. It was further hypothesized that the behavioral changes following DLPFC lesions were consistent with the behavioral disorganization stemming from executive dysfunction. Executive dysfunction refer to the disruption of higher-order cognitive processes involving initiation, planning, cognitive flexibility, abstraction, and decision-making that, together, allow the execution of contextually appropriate behavior (Spreen & Strauss, 1998; Ishikawa & Raine, in press). In the above animal studies, the executive dysfunctions exhibited by the monkeys included perseveration, disrupted attentional capacities, and failure to habituate.

Direct extension of these animal lesion studies to human lesion cases, however, may be somewhat limited. A 7- year-old human boy suffered lesions to the DLPFC, subjacent white matter, and small portions of premotor cortex and anterior insula (Eslinger, Biddle, Pennington, & Page, 1999). Four years later, he demonstrated significant cognitive and behavioral problems such as difficulty organizing tasks and activities, difficulty initiating and properly sequencing behaviors, poor attentional control, and impaired cognitive flexibility and visuo-spatial memory. However, he demonstrated no significant changes in personality or level of aggressive behavior and was described as ôhappyö and ôquick to smile.ö Thus, although his executive dysfunction was consistent with the behavioral disorganization described in the non-human primate research, the boyÆs impairment did not specifically result in increased aggression. His executive deficits were also described as somewhat less debilitating than those observed in adults with DLPFC injuries. The authors speculated that the developmental differences in neural plasticity and reorganization may have accounted for the age differences in severity of executive dysfunction following DLPFC injury (Eslinger et al, 1999).

Perhaps the largest body of research from which DLPFC involvement in antisocial behavior has been inferred is the neuropsychological study of executive functions. Some of the more commonly used neuropsychological tests used to measure executive functions in humans (e.g., WCST, verbal fluency, Stroop Interference) show a preferential activation of the dorsolateral prefrontal cortex (Stuss & Levine, 2002). It should be noted, however, that dysfunction as measured by these tasks may also reflect abnormality in the medial and/or ventral sectors of the frontal lobes, as well as one or more of the neural pathways interconnecting the frontal lobe subregions or the more posterior regions of the brain to the frontal lobes (Lezak, 1995).

Despite a strong theoretical base for postulating frontal dysfunction in antisocial individuals, a qualitative review of executive function deficits in antisocial children concluded that, while the possibility of an executive dysfunction-antisocial behavior link cannot be ruled out, findings across studies are inconsistent (Teicher & Golden, 2000). A recent meta-analysis of executive dysfunction and antisocial behavior found that the magnitude of effect sizes ranged considerably depending on the subtype of antisocial behavior (Morgan & Lilienfeld, 2000), thus suggesting the presence of moderating influences on the executive dysfunction-antisocial behavior link. Because findings for executive dysfunction appear to be more consistent when examined in relation to impulsive aggression in children or adults, it has been hypothesized that a critical moderating factor is impulsivity (Ishikawa & Raine, in press). In addition, the strongest findings for executive dysfunction are found in children with ADHD or ADHD/conduct disorder rather than in those with only conduct disorder (Speltz, DeKlyen, Calderon, Greenberg, & Fisher, 1999). Impulsively aggressive individualsÆ poor neuropsychological test performance typically implicates different aspects of impulse control: response disinhibition, an inability to organize behavior and/or integrate information on complex tasks, and failure to adapt to changing environmental contingencies (i.e., perseveration). Thus, the inconsistent association between executive dysfunction and antisocial behavior noted above may be accounted for by the fact that, from study to study, the neuropsychological tests of executive function and/or the measures of antisocial behavior are not directly assessing impulsivity. In support of this argument, the above meta-analysis found that, of all the executive function measures examined (WCST perseverative errors, verbal fluency, Stroop Interference, Category Test, Trail Making Test Part B, Porteus Maze Q score) the measure with the strongest relationship to antisocial behavior was the Porteus Maze Q Score (Morgan & Lilienfeld, 2000), which was also the most direct measure of impulsivity. Future neuropsychological research might therefore benefit by addressing whether disrupted executive functions are observed most frequently in antisocial subtypes characterized by cognitive and behavioral impulsivity. It is also recognized, however, that poor performance on selected neuropsychological tests alone cannot determine the presence of DLPFC deficits. Although certain tests such as the Wisconsin Card Sorting Test and verbal fluency appear to show a preferential activation of the DLPFC (Stuss & Levine, 2002 for summary), these measures are nevertheless subserved by multiple prefrontal and non-frontal brain regions that may be accounting for the poor neuropsychological test performance. In addition, while the Porteus Maze Q score does appear to provide a marker of frontal dysfunction in general (Morgan & Lilienfeld, 2000 for summary), it has not necessarily been shown to be specific to the DLPFC.

Overall, then, DLPFC contributions to aggression and antisocial behavior appear to be mediated by executive dysfunction characterized primarily by impulsivity, difficulty shifting attention, behavioral and cognitive disorganization, and perseveration. Given this pattern, it is not surprising that DLPFC dysfunction appears to be more frequently observed in aggressive or antisocial individuals who have co-morbid ADHD or impulse control problems than in those who do not. DLPFC deficits that result in poor attentional shifting, impaired self-regulation, and behavioral disorganization may interfere with an individualÆs ability to shift away from a hostile attribution bias and/or to appropriately regulate oneÆs behavior during a tense

interaction. In turn, these deficits may lower the threshold for aggressive altercations. In addition, perseveration on laboratory tasks may represent an experimental correlate for aggressive and/or criminal recidivism characteristic of chronically antisocial individuals (Raine, in press).

Antisocial behavior and the orbitofrontal-ventromedial cortex.

A significant amount of research has also been conducted on the link between the orbitofrontal-ventromedial frontal sectors and aggression, antisocial behavior, and substance abuse. It has been argued that the OFC and VMC regulate different aspects of social behavior. That is, the OFC is argued to be related more to non-aggressive disinhibition (Giancola, 1995), while the VMC is argued to be related more to impulsive, risky decision-making (Bechara, Damasio, Damasio, & Lee, 1999). However, most studies to date have either not clearly differentiated these brain regions or have implicated both within the same study. Thus, these regions û while not neuroanatomically identical û are discussed together.

As briefly mentioned in the introduction, initial clues that the frontal lobes played a role in social behavior and awareness were provided in case studies of brain lesion patients. The most famous case study of personality changes following brain damage is that of Phineas Gage. Following a construction accident in which a tamping iron exploded out of a rock and passed though his skill, Gage was transformed from a well-liked, respected, and responsible man to an impulsive, profane, untrustworthy individual (Damasio, Grabowski, Frank, Galaburda, & Damasio, 1994). Surprisingly, however, his movement, speech, memory, and new learning remained intact. Recent brain-imaging analysis of Phineas GageÆs preserved skull suggests that both DLPF cortices were spared and the physical damage was specific to the bilateral VMF (Damasio et al, 1994). A similar behavioral and personality change was noted in a young adult male who, shortly after leaving home to join the army, suffered a penetrating head injury that damaged the right and midline ventromedial frontal cortex (Dimitrov, Phipps, Zahn, & Grafman, 1999). Like Gage, this individual exhibited disinhibition, social ineptitude, poor social decision-making, and irresponsibility, but his general cognitive and abstraction skills were preserved. Unlike what was documented about Gage, however, this adult patient exhibited criminal behavior and sexual violence. Two young children who suffered lesions to the right or bilateral ventromedial cortex also showed problems with understanding and responding to complex social situations (Anderson, Bechara, Damasio, Tranel, & Damasio, 1999). Unlike the later adult-onset cases, the children exhibited significant levels of antisocial behavior and demonstrated an inability to factually identify appropriate moral or social behavior. Based on differences in behavioral outcomes observed across clinical case studies such as these, it has been speculated that while OFC-VMF lesions disrupt social awareness and decision-making regardless of age, whether the lesions also result in aggressive or antisocial behavior is related, in part, to age of lesion onset (Dimitrov et al, 1999). That is, problems with antisocial behavior, aggression, and lack of social knowledge seem to be restricted to younger patients but are not typically observed in individuals who suffer lesions in adulthood and whose pre-morbid functioning was socially appropriate and responsible (Dimitrov et al, 1999). Dimitrov and colleagues hypothesized that early injury to the OFC-VMF impairs oneÆs actual ability to learn and internalize norms for socially appropriate behavior, whereas later injury is restricted to an inability to recognize and utilize social

norms at an emotional or behavioral level even though factual knowledge of these norms is intact.

Extending beyond qualitative observations of single case studies, Antonio Damasio, Antoine Bechara and colleagues have published a compelling series of studies linking orbitofrontal-ventromedial dysfunction to antisocial behavior. In some of the first studies to examine frontal and autonomic nervous system functioning simultaneously during a gambling task, Bechara, Damasio, and colleagues tested individuals who had acquired psychopathy through frontal lesions (Bechara, Tranel, Damasio, & Damasio, 1996). As participants turned cards over one at time, they either received money from ôthe bankö (i.e., reward) or owed money to the bank (i.e., punishment). They could choose to turn a card from among four decks, with two fixed as low-risk (i.e., average payment to bank was $100) and two as high-risk (i.e., single payment to bank could reach as high as $1250). Although the number of card turns remained constant, the players were not told how many turns they would make before ending the game. Compared to controls and patients with non-frontal lesions, the VMF patients failed to develop a conditioned skin conductance response when reaching for (or contemplating use of) the risky decks, and showed the worst gambling performance (i.e., they accrued substantial debt; Bechara et al, 1996). Interestingly, the researchers also found that the VMF patients continued to make risky decisions even after being able to articulate the correct strategy (Bechara, Damasio, Tranel, & Damasio, 1997). Thus, VMF patientsÆ poor performance was not the result of their failure to learn the punishment-reward contingencies.

In order to determine whether the VMF patientsÆ failure to shift away from the risky decks was due to hypersensitivity to reward or insensitivity to punishment, the researchers created variations of the original gambling task in which the immediacy or magnitude of the punishment and rewards were altered (Bechara, Tranel, & Damasio, 2000). They found that VMF lesion patients continued to fail to shift away from the disadvantageous decks despite the alterations in the reward and punishment schedules. They also noted that the VMF lesion patients exhibited skin conductance responses to reward and punishment that were comparable to normal controls. Bechara and colleagues interpreted the pattern of findings to indicate that lesion patientsÆ failure to learn to avoid the risky decks resulted from an insensitivity to future consequences (i.e., increasing punishment, decreasing reward) and not from reward hypersensitivity or punishment insensitivity.

Research with bilateral amygdala lesion patients and bilateral ventromedial frontal cortex lesion patients provides additional information on the role of the VMF in risky decision-making (Bechara, Dolan, Denburg, Hindes, Anderson, & Nathan, 2001). More specifically, Bechara and colleagues found that, relative to normal controls, selective amygdala and selective VMF patients both showed deficits in gambling performance and failed to develop anticipatory skin conductance responses. The two lesion groups were comparable to each other on these measures, however. They also found that VMF patients remained autonomically responsive to actual reward or punishment and demonstrated classical conditioning to an aversive stimulus. The amygdala patients, on the other hand, failed to demonstrate these autonomic responses. The authors concluded that the amygdala mediates decision-making through impairment in fear conditioning, whereas the VMF lesions disrupts the ability to integrate effectively the somatic state information generated from somatosensory limbic structures. Interestingly, in terms of real-life decision-making, the authors noted

that both VMF and amygdala lesion patients made decisions that had negative long-term consequences in terms of finances, employment, and social relationships, but only amygdala patients demonstrated problems with aggression and physical harm to self or others. Thus, while the amygdala patientsÆ disruptive behavior and poor decision-making was related to a fundamental and general deficit in fear conditioning and avoidance learning, the VMF patients poor decision-making emerged when the somatic input was experienced as more positive than negative (Bechara et al, 1999). In other words, the VMF patients performed poorly on the decision-making task because they were unable to delay instant gratification of a high reward despite the risk of great future loss. Yet they were able to successfully avoid aggressive altercations because these interactions were experienced as immediately punishing.
Blair & Ciplotti (2000) published a case study of a 56-year-old man with bilateral OFC and left amygdala abnormalities that extended the above work on the amygdala and VMF cortex. Although this manÆs premorbid behavior was described as quiet, withdrawn and non-aggressive, his post-lesion behavior was characterized as bizarre, uncooperative, and unpredictably, impulsively aggressive. Unlike the patients from the Bechara and Damasio studies, however, this patient performed appropriately on the Bechara gambling task, had intact cognitive reversal learning (i.e., the ability û following a mid-task rule change û to respond correctly to a stimulus that had originally been the punished response), and intact theory of mind skills (i.e., the ability to create representations of othersÆ mental states). Instead he showed a dramatic inability to recognize facial expressions (particularly anger and disgust), exhibit emotional responses to affective stimuli, or recognize descriptions of moral and social transgressions. Based on this manÆs symptom and injury pattern, Blair and Ciplotti argued that different aspects of social cognition are mediated by different prefrontal sectors. More specifically, they cited evidence that theory of mind is subserved by the medial PFC, whereas anger is subserved by the OFC. If one accepts the notion that impulsive aggression is strongly connected to angry affect, then a study of ventromedial patients by Grafman and colleagues provides some additional support for this argument. This study found that VMF patients exhibited significantly greater aggressive, violent, and/or antisocial behavior than did non-frontal brain lesion patients and non-lesion controls (Grafman, Schwab, Warden, Pridgen, Brown, & Salazar, 1996). Moreover, among the ventromedial patients, those with focal medial frontal lesions (i.e., intact OFC) were generally aware of and able to self-report the increase in their aggressive behavior, whereas those with focal orbitofrontal lesions were unaware of the increased aggression reported by a family member.
In addition to lesion studies, there has been growing interest in examining whether BecharaÆs decision-making task differentiates developmentally antisocial individuals (i.e., individuals in whom antisocial behavior did not occur following a frontal brain lesion but was observed as a part of their development) from various control groups. For example, boys with psychopathic tendencies were more likely than boys without such tendencies to make risky choices and perform poorly on the gambling task (Blair, Colledge, & Mitchell, 2001). The boys did not differ on cognitive response reversal. As with VMF lesion patients, avoidance learning in these boys also only occurred when the punishment for the undesired response was immediate and frequent. In contrast, however, a study with adult males incarcerated in a minimum security prison did not find the gambling

task to differentiate psychopaths from non-psychopaths (Schmitt, Brinkley, & Newman, 1999). However, when examining the effects of anxiety (regardless of psychopathy, high anxious individuals made significantly fewer risky choices than did low anxious individuals). One methodological issue should be highlighted, however. The participants in the Schmitt et al study played for real money with a maximum reward of $5.00, whereas the participants in the Bechara studies played for pretend money with a maximum reward/loss of approximately $2000.00. It is possible, then, that other factors moderate the relationship between developmental psychopathy and risky decision-making. For example, trait anxiety may be particularly important in understanding risk-related behavior in the face of low overall monetary risk and gain, whereas psychopathic traits may be more important in understanding risk-taking behavior when the overall stakes are much greater.

In contrast to the above study with incarcerated individuals, poor performance on the gambling task did generalize to antisocial individuals recruited from the community. Individuals diagnosed with APD, regardless of whether they were also diagnosed with early-onset alcoholism, demonstrated poorer decision-making on the Bechara gambling task compared to non-APD early-onset alcoholics and to normal controls (Mazas, Finn, & Steinmetz, 2000). However another study looking at gambling task performance in substance dependent groups found somewhat conflicting results (Bechara, Dolan, Denburg, Hindes, Anderson, & Nathan, 2001). While Mazas and colleagues failed to find an effect for non-APD alcoholics, Bechara and colleagues observed that individuals diagnosed with substance dependence (as well as patients with VMF lesion patients) showed a risky decision-making preference. Moreover, the substance dependent groupÆs poor performance was comparable to that of the VMF lesion group. It is unclear to what extent antisocial personality traits may have accounted for the findings in the Bechara et al study, however, as APD was not specifically assessed despite its frequent co-morbidity with substance dependence. On the other hand, Mazas et alÆs failure to find an effect in early-onset alcoholics without APD may represent an unusual and intriguing finding. It is possible, for example, that individuals who fail to exhibit additional impulsive and irresponsible behaviors that would lead to diagnosis of APD û despite the presence of early-onset alcoholism û may be somehow protected from generalized decision-making deficits.

At this point the relationship of poor decision-making to substance dependence versus antisocial behavior has yet to be better understood. A review of brain imaging studies on the role of the OFC in drug addiction, however, suggests that substance dependence is likely to be associated with OFC-VMF dysfunction (London, Ernst, Grant, Bonson, & Weinstein, 2000). According to the review on currently available studies, drug abusers showed decision-making impairment on tests akin to BecharaÆs gambling task but did not show deficits on general neuropsychological tests primarily mediated by the DLPFC. Moreover, while anticipating a drug reward, craving a drug, and making judgments on abstinence versus drug use, drug abusers show atypical brain activation patterns in the OFC and amygdala, two of the key neuroanatomical sites implicated in the poor decision-making of brain lesion patients. Similar to the explanation for the behavior of the aforementioned lesion patients, it was hypothesized that the VMF contributes to substance dependence by affecting an individualÆs ability to delay instant gratification (i.e., drug-seeking) despite the risk of future negative outcomes (i.e., loss of job, damage to

reputation, etc.; Bechara et al, 2001; London et al 2000).
Further support for a relationship between alcoholism and the VFC was also demonstrated in a structural imaging study. Compared to normal controls, repetitively violent forensic patients with a diagnosis of Type II alcoholism (e.g., comorbid APD and alcoholism) had volume reductions specifically in orbitofrontal and medial frontal gray matter (Laakso, Gunning-Dixon, Vaurio, Repo-Tiihonen, Soininen, & Tiihonen, 2002). After controlling for the effects of alcoholism on orbitofrontal gray volume and education on medial frontal gray volume, Laakso and colleagues found that antisocial behavior no longer correlated with the respective frontal gray volume measures (Laakso et al, 2002). It is possible that the elimination of the antisocial behavior-OFC relationship after controlling for alcoholism represented a true effect, with the dissimilarity between Laakso et alÆs findings and the above studiesÆ results arising from the dissociation of neuroanatomical structure and function. It is also possible, however, that controlling for alcoholism was the statistical equivalent of controlling for group classification, given the fact that all controls had zero duration of alcoholism and all Type II alcoholics had some duration of alcoholism. Clearly, future research needs to take into account the structure and function of the frontal lobe sectors and amygdala. It also needs to address whether these different neurobiological substrates are differentially related to aggression, substance dependence, and non-aggressive antisocial behavior.
Support for an OFC-aggressive behavior link can also be found in the animal literature, with studies suggesting that removal of the OFC disrupts modulation of arousal mechanisms that relate to social functioning (Butter, Snyder, & McDonald, 1970). Rats that were selectively lesioned in the OFC demonstrated a significant increase in aggression and locomotor activity following surgery, whereas control rats that had undergone sham surgery did not (De Bruin, Van Oyen, & Van De Poll, 1983). In a study of stump-tail macaques, decreases in threat, aggression, and grooming of others were observed in monkeys that underwent bilateral OFC resection but not in monkeys that underwent superior temporal cortex resection or those serving as un-operated controls (Miller & Levine, 1977). Although the OFC monkeys did show increases in joining and self-grooming, the behaviors were disconnected from the other monkeys and failed to facilitate social interactions. Another study found similar types of disruptions to arousal and social behaviors following OFC lesion placement. Rhesus monkeys that underwent bilateral OFC resection û compared to those that underwent partial temporal lobe resection û initially demonstrated a persisting, decrease in aggression and hyporesponsivity to environmental stimuli and then exhibited an increase in aversive (i.e., avoidance) responses to a novel stimulus (Butter, Snyder, & McDonald, 1970).
As a whole, then, human lesion, neuropsychological, and neuroimaging studies suggest that disruption to the OFC-VFC is related to various subtypes of antisocial behavior. Disruptions to these particular frontal brain regions appear to be strongest for substance dependence (although the influence of other concomitant antisocial behavior is currently unknown) and repeated impulsive aggression. OFC-VMF damage appears to be related to these antisocial behavior subtypes by impairing impulse control and the ability to delay instant gratification. Experimental work with animals further suggests that disordered impulsivity and inability to delay gratification stem from basic disruption to arousal and attention mechanisms that subserve

complex emotional and social behavior. The influence of the OFC-VMF cortices on antisocial and psychopathic subgroups not primarily characterized by their impulsivity, on the other hand, may need to be better understood within the context of other personality traits such as anxiety, as well as situational factors such as magnitude of the risk.

Conclusion

An earlier review on frontal lobe correlates of antisocial behavior posited that the dorsolateral prefrontal cortex subserved aggressive antisocial behavior, and the orbitofrontal cortex underpinned non-aggressive antisocial behavior (Giancola, 1995). The current review suggests that refinement of this model is in order. On a general level, both the dorsolateral prefrontal cortex and the orbitofrontal cortex (as well as the amygdala) mediate aggressive antisocial behavior. The nature of the disrupted processes that give rise to aggressive displays, however, are somewhat different depending on which frontal sector is involved, and are discussed in more detail below.

The ventromedial frontal cortex, which is partially located within the orbitofrontal cortex, appears to contribute to antisocial behavior by impairing decision-making in risky situations. Damasio (1994) theorized that these bad decisions resulted from disruption to the autonomic arousal mechanisms regulated by the VMF, thus resulting in an inability to emotionally appreciate the delayed negative consequences of high-risk decisions. The importance of the VMF in antisocial behavior was first noted in those who acquired psychopathic behavior through lesions to the ventromedial frontal cortex. It has since been extended to include individuals with diagnoses of substance dependence. However, VMF dysfunction and risky decision-making have been inconsistently related to developmental psychopathy, perhaps because of the influence of factors such as trait anxiety or the magnitude of perceived risk.

In addition, neuroimaging research suggests that the orbitofrontal cortex is preferentially involved in the regulation and expression of anger (Pietrini, Guazzelli, Basso, Jaffe, & Grafman, 2000). Interestingly, however, case studies indicate that no patient with selective VMF lesions had problems with anger or aggression regulation. Thus, whether OFC dysfunction or damage results in impulsive aggression may depend on whether, or to what extent, the functional disturbance falls outside of the VMF cortex. The OFCÆs role in the disregulation of anger and aggression appears to be directly related to a breakdown in efficient processing of emotional material, as well as the acquisition of social norms and their successful application to decisions and behavior.

Dorsolateral prefrontal dysfunction, on the other hand, appears to be related to antisocial behavior via executive functions such as disrupted arousal mechanisms, poor attentional shifting, perseveration, and behavioral disorganization. These deficits may work in concert to contribute directly to chronic impulsive behavior, one possible outcome of which is recidivistic antisocial acts. These executive dysfunctions may also indirectly lower the threshold for initiating or escalating aggressive altercations by keeping an individual ôstuckö on a hostile attribution bias or by interfering with the generation of adaptive, non-aggressive options. Given the nature of the behavioral disruption expected from DLPFC dysfunction, DLPFC abnormalities may be most frequently observed in antisocial individuals who have co-morbid ADHD or other significant impulse control or attention regulation disorders. In addition, another possible pathway for DLPFC dysfunction to result in antisocial behavior is through impaired aversive conditioning.

Although not discussed above, it warrants brief mention that the dorsolateral prefrontal cortex is an important component of the neural circuitry involved in aversive conditioning (Schneider, Habel, Kessler, Posse, Grodd, Muller-Gartner, 2000), and a number of psychophysiological experiments find that antisocial groups exhibit deficient fear conditioning or avoidance learning of punishment (Ishikawa & Raine, 2002). Such deficiency, in turn, is thought to result in poor conscience development (Fowles & Kochanska, 2000), which could predispose susceptible individuals to antisocial behavior. Practically speaking, however, multiple frontal subregions are likely involved in the development and maintenance of different antisocial behavior subtypes and, in fact, several studies have found just this pattern. At a structural level, individuals with antisocial personality disorder exhibited an 11% reduction in gray matter in the prefrontal area anterior to the genu of the corpus callosum (a general measure which included sections of orbitofrontal, dorsolateral, medial, and anterior cingulate cortex) compared to control, substance abuse, and psychiatric control groups (Raine et al. 2000). During a continuous performance task, murderers exhibited significantly lower activation in the orbitofrontal, ventromedial, and dorsolateral regions of the frontal cortex compared to normal controls (Raine, Buchsbaum, Stanley, Lottenberg, Abel, & Stoddard, 1994). Violent psychiatric patients, compared to normal controls, showed reduced activation in bilateral polar and lateral frontal areas and medial temporal regions (Volkow, Tancredi, Grant, Gillespie, Valentine, Mullani, Wang, & Hollister, 1995). In addition, reduced activation in the left dorsal and medial frontal regions and the left temporal lobe were observed when violent psychiatric patients were compared to non-violent psychiatric controls (Amen, Stubblefield, Carmichael, & Thisted, 1996). The extensive interconnections between the DLPFC and OFC may explain, in part at least, the functional involvement of multiple neuroanatomical sites, even if physical damage is present only in one subregion. Damasio (1994) hypothesized that ventromedial deficits interfere with the functions of the dorsolateral prefrontal cortex by failing to discard risky options and thereby overtaxing oneÆs working memory and attentional capacities. As a result, a person would be more inclined to choose immediate gratification because evaluation of negative, future outcomes could not be held on-line long enough for proper consideration.

Clearly, the past several years have provided us with interesting insights regarding the role that different regions of the frontal lobe have on developing and maintaining certain subtypes of antisocial behavior. It should be kept in mind, however, that our current understanding is still quite rudimentary. A case study recently reported how extensive bilateral lesions throughout the frontal lobe rather surprisingly did not result in antisocial and/or aggressive behavioral changes (Mataro, Jurado, Garcia-Sanchez, Barraquer, Costa-Jussa, Junque, 2001). Future research on the frontal lobe and antisocial behavior will therefore require a greater degree of specificity in neuroanatomical structure and function in order to determine when brain damage is likely to have specific negative social outcomes. In addition, these models will need to incorporate cortical and subcortical regions (i.e., cingulate, hypothalamus, motor cortex, dorsal pons, midbrain, insula, cerebellum) that provide important somatosensory and emotional input to the frontal sectors (Davidson, Putnam, & Larson, 2000; Damasio et al, 2000).

It is also clear that attention needs to be paid to antisocial

subtypes. Mechanisms underlying various forms of impulsive antisocial behavior (e.g., impulsive aggression, substance dependence) are beginning to be delineated, and hopefully consideration of premeditated antisocial behavior subtypes will soon follow. Finally, although not addressed in the current chapter, social and environmental influences play an important role in shaping development from both a biological and behavioral perspective. This is especially true with regard to antisocial behavior, and such considerations should be incorporated into future research (Ishikawa & Raine, in press). Although issues such as these are complex and involved, careful, thoughtful research like this will not only further our understanding of antisocial behavior in particular, but also our appreciation of social-emotional development in general.

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