CHAPTER 4

Biological Vulnerabilities to the Development of Psychopathology

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The history of psychopathology is replete with a fascination with biological explanations for various disorders. From the trepanations of early cave dwellers, in which holes were gouged in the skull; to the humoral theories of Hippocrates, circa 400 BCE; the custodial, animal-like treatment of the mentally ill of the Renaissance; the enlightened humanists period; the time of influential theorists such as Kraeplin, Freud, and Jung; and on to the present, the belief in biological mechanisms underlying pathology has existed. Nevertheless, today is not yesterday. Generally lacking even just 30 years ago was credible scientific evidence to support this specific and persistent belief. In fact, a sort of antibiological movement grew through the 1950s–1960s, and remnants of this view, which persist today, view mental illnesses as socially learned disorders treatable solely by behavioral interventions. Today, of course, the well-known vulnerability-stress model predominates as an explanation for the etiology of most disorders, representing an obvious interaction of these two historical views.

The relatively recent resurgence of biological explanations, however, has not been predicated on historical influence but rather has exploded from a cascading body of evidence driven by growth in the neurosciences. This growth, in turn, has benefited directly from powerful new scientific methodologies able to delineate the vulnerability component of the vulnerability-stress model. Discriminating biological vulnerabilities is the focus of this chapter.

NEW TECHNOLOGIES

The essence of biological studies of mental disorders is that there is an ascertainable relationship between a particular disorder and brain functioning. Measuring brain functioning is then basic. This, however, is not a simple task, and for centuries only nonfunctional measures, from the bizarre (phrenology) to the imprecise (X-rays) existed. Advances in pharmacology, neuropsychology, electrophysiology, and brain imaging are at the forefront of technologies that are prime contributors to

new investigations of biological variables. Pharmacology has been the traditional route for developing biological explanations for psychopathology. Unfortunately, "miracle drugs," which implicated specific chemical systems in various disorders, seemed over time to lose their luster, as did the implicated theory as well. Recently, the manipulation of neurotransmitters in both experimental and clinical subjects by regulating amino acid precursors has resulted in the ability, for example, to dramatically decrease brain serotonin (Young, Smith, Pihl, & Ervin, 1985). Similar procedures exist for dopamine, although like many pharmacological manipulations, which are improving, specificity is an issue. Parallel developments in new drugs that are more targeted in their effects on specific aspects of a neurotransmitter system have lent support to biochemical theories, as have drugs currently in pharmaceutical company pipelines that will affect the action of genes or target a single aspect of a neurosystem's function. Neuropsychology has benefited greatly from advances in neuroimaging, because many tests have been refined to assess specific abilities—be they cognitive, motor, or perceptual—and then validated by concomitant activity in particular brain areas. Neuropsychology has been at the forefront in determining behavioral deficits in frontal lobe functioning, which is implicated in many disorders. This evolutionary "new brain" seems to have a key role in working memory, learning, response inhibition, and coordinating sensory input with responding. Further, perhaps as Luria (1980) suggested, it is this part of the brain that projects the integration of the past, present, and future so basic to controlled responding. Many neuropsychological findings have been validated by imaging technology, which in combination can determine the endophenotypes that underlie and are the precursors to various clinical disorders.

Relatively recently, there has been a dramatic growth in noninvasive methods to monitor the brain and its functioning, all of which are dependent upon the rapid processing of complex information, an impossible task before the development of microprocessors. This includes measuring the brain's electrophysiology and advanced brain imaging technologies that can show structural aspects of the brain and the level and site of activity when the individual is presented with various stimuli. Electrophysiology, involving the measurement of brain oscillations, particularly in response to prescribed tasks, has determined differential patterns of action for various pathologies. More specifically, these patterns have been shown to represent localized activity and to be heritable and linked to a range of behaviors. Nuclear magnetic resonance imaging (MRI) is a noninvasive technique that involves measuring atoms in order to obtain a detailed structural picture of the brain and specific areas. A blood oxygenation signal measured by a functional MRI (fMRI) allows the assessment of neural activity without requiring the use of radioactive substances, which are needed with positron emission tomography (PET), also a valuable, but a more invasive, procedure for measuring activity to specific brain areas. More powerful technologies are rapidly coming online. Diffusion tension imaging, for example, is an MRI procedure uniquely suited to study white matter.

Burgeoning findings in other areas also direct one to the level of biology. One example is the increasing recognition that numerous psychopathological disorders run in families; this implies the existence of genetic vulnerabilities and biological mechanisms. Questions regarding which genes or genetic material affect which biochemical processes have drawn our attention first (see Lemery & Doelger, Chapter 7 in this volume, for details on genetic vulnerabilities). Subsequent concerns about brain development and functioning and the interactions of these biological factors with stressful environmental events represent the next critical step.

NORMAL FUNCTIONING OF BRAIN AREAS AND PATHWAYS

Decades of neuropsychological research, especially with the recent technological advances, have elucidated the normal function and purpose of various brain areas and the pathways that integrate these functions together. Here, we briefly review central brain areas, pathways, and the normal psychological functions that modern neuroscience believes they serve. Understanding how these brain areas and pathways normally function and what thoughts, behaviors, and emotions they are associated with is critically important for elucidating how deficits and dysfunctions in these brain areas may create biological vulnerabilities for the development of different psychopathologies.

The frontal lobes have been broadly associated with executive cognitive functioning, which is generally understood to refer to the "ability to plan, initiate, and maintain or alter goal-directed behaviours" (Pihl, Vant, & Assaad, 2003, p. 173). This ability is dependent upon specific cognitive functions, such as attention and working memory. The prefrontal cortex area is believed to subserve the representation of goals and the means to achieve them (Miller & Cohen, 2001). More specifically, through its connections with other brain areas, the prefrontal cortex is part of an important circuitry that underlies the emergence of appropriate responses and the simultaneous inhibition of inappropriate actions (Miller & Cohen). Connections to the basal ganglia, an agglomeration of nuclei within the forebrain believed to be important in motor control, contribute to the organism's ability to show appropriate motor response and inhibition (Carlson, 2001). Simultaneous connections to temporal limbic structures ensure the affective appropriateness of the response. Davidson and colleagues (Davidson, Pizzagalli, Nitschke, & Putnam, 2002) describe this process as "affect-guided planning and anticipation" (p. 548), whereby actions expected to provide "rewards" will be pursued, and actions known to lead to "punishment" will be inhibited. Davidson et al. (2002) proposed that the left prefrontal cortex may be particularly important for the anticipation of positive outcomes and approach behaviors, whereas the right prefrontal cortex may be crucial for appropriate inhibition and withdrawal. They report that imaging studies have found the left orbital and ventral regions to be sensitive to rewards, whereas the same areas in the right hemisphere were found to be particularly sensitive to cues of punishment (Davidson et al., 2002).

As mentioned above, the frontal lobes show strong connections with temporal limbic areas such as the amygdala and the hippocampus, which are believed to be crucial for emotional responses (Carlson, 2001). The amygdala has been shown to be important for promoting vigilance and attention to novel or affectively salient stimuli, both positive and negative (Davidson et al., 2002). The amygdala is intrinsically connected to the hippocampus, which has been found to subserve memory, contextual conditioning, and stress response (Davidson et al., 2002). Upon stress, the hypothalamus, a group of nuclei located at the base of the brain (Carlson, 2001), secretes corticotropin releasing factor (CRF), which in turn triggers synthesis and release of adrenocorticotropin (ACTH) by the pituitary. ACTH then stimulates synthesis and release of glucocorticoids by the adrenal cortex (Nestler et al., 2002). The hypothalamic-pituitary-adrenal (HPA) axis has reciprocal feedback connections with the hippocampus and the amygdala (Nestler et al.), so that glucocorticoids release triggers inhibition of the HPA axis by the hippocampus. High, chronic levels of glucocorticoids have been suggested to lead to hippocampal damage in the form of reduced dendritic branching and glutamatergic dendritic spines, as well as reduced genesis of

granule cell neurons (Nestler et al.). A vicious cycle may thus operate, as decreased HPA axis inhibition due to hippocampal damage would lead to increasing glucocorticoid levels, which in turn may lead to further hippocampal damage (Nestler et al.).

The prefrontal cortex, basal ganglia, and limbic structures, together with other brain areas, thus constitute an intrinsic system underlying our ability to appropriately respond to our environment. As will be described in sections of this chapter pertaining to specific disorders, functional or anatomical anomalies of these regions and their interconnections may contribute to difficulties in different spheres of functioning, such as impairments in regulating responses (e.g., motor, affective) to the environment.

CAVEATS

Unfortunately, the road to clarity of understanding is neither straight nor paved. The powerful methodologies briefly mentioned above cannot override definitional and philosophical issues seemingly fundamental to the study of mental disorders. Psychopathologies are laden with noise, replete with debate, and lacking in specificity. This issue is exemplified by Andreasen (1999), who in proposing a model for schizophrenia wrote,

> At present the most important problem in schizophrenia research is not finding the gene or localizing it in the brain and understanding its neural circuits. Our most important problem is identifying the correct target at which to aim our powerful new scientific weapons. Our most pressing problem is at the clinical level: defining what schizophrenia is. (p. 781)

Similar statements can and should be repeatedly made about most if not all definitions of mental disorders (see chapters in Part III of this volume for discussion of definitions and classifications of disorders). It is axiomatic in this area that names are bestowed, not discovered, and names have been growing at a prodigious rate. The number of disorders in the different versions of the American Psychiatric Association's (APA) *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) has grown from around 100 in 1952 to more than 360 in today's *DSM-IV-TR* (APA, 2000). That is a threefold increase, which clearly points to rampant inflation in mental disorders. Of course, an increase in definitions is expected as knowledge is gained and specificities refined. However, the fundamental question is, "Just how many disorders are there?" It is almost certain that there are not exactly 360 psychological disorders in nature. A factor analysis of 10 common mental disorders from the large, representative National Comorbidity Survey (NCS; Krueger, 1999) resulted in a three-factor fit, respectively labeled Anxious-Misery, Fear, and Externalizing. Similar results were obtained in a large, representative sample of children and adolescents (Lahey, Applegate, Waldman, Hankin, & Rick, 2004). Further, who gets hospitalized, both voluntarily and involuntarily, is less a function of diagnostic label than of the display of aggression, be it self- or other-directed (Pihl, 1995). Finally, there is the issue of comorbidity. In the two broad surveys of mental illness, more than one disorder was present in an individual 60% of the time in the National Institutes of Mental Health study (Robins & Regier, 1991) and 56% of the time in the NCS study (Kessler et al., 1994). Comorbidity is the rule with mental disorders, not the exception. This fact raises the possibility that, instead of many disorders existing, there may be a relatively small number of underlying biological processes that, through environmental interactions, result in many diverse behavioral forms.

A conundrum thus remains. In the *DSM-IV-TR,* and presumably in the *DSM-V* when it arrives, mental disorders are defined on a behavioral level, whereas disorders in general are seen in the definition of mental disorders as residing within the individual (APA, 2000). Thus, the necessary recrafting of current definitions of mental disorders must include biological factors if the unacceptable variability in current definitions is to be reduced and terminology become more meaningful. It is also axiomatic that nosology necessarily precedes etiology. Thus, it is necessary to determine which biological variables, as well as those vulnerabilities from other levels of analyses (see other chapters in Part II of this volume), are relevant to the definition of a disorder.

Studying individuals likely to develop a disorder, which should be the basis of risk research in psychopathology, provides a contemporaneous recording of events. This design thus controls for a major error in studies of psychopathologies in which findings with patients often reflect having a disorder rather than a causative factor. Put bluntly, by studying already diagnosed and treated individuals, we may learn more about the explosion than the triggering mechanisms. Studying vulnerable individuals also allows for the study of "escape" from risk processes, which can illustrate the importance of interacting variables, and heterogeneity of outcomes, where for example similar underlying biological conditions may have varying trajectories to divergent disorders depending upon interacting factors. This research also allows for the discrimination of the significance of age of onset, which is of critical importance, because most disorders are age sensitive. Finally, by assessing the development of disorders through the study of vulnerabilities, we are provided with the opportunity to elucidate feedback mechanisms, circular processes, and chain effects typically important in causation.

There are also caveats of import regarding the "new" methodologies. In the case of neuroimaging, these range from the general issue of inference to specific concerns regarding how a region of interest is selected. Regarding inference, mental and physical states are seldom measured simultaneously, because a label is hardly a mental state, and thus any connections to a disorder represent speculation. Even when testing for specific cognitive states, converging evidence of that state is required; these states are often altered with experience and context. Even specific paradigms, such as an attentional go-stop procedure, have multiple neural functioning explanations (Schall, 2004). Another problem is that the brain is active in general, and PET and fMRI results simply point to one or more areas being relatively more active than other areas. The area highlighted is labeled the region of interest. Because there is widespread activation in the brain, strong preexperiment rationale is required for selection of a specific area versus contrasting areas. Further, because the typical design in psychopathology involves group comparisons between psychiatric patients and controls, resolution is further distorted because of imperfect registration, because individual brains differ both in anatomy and function. Finally, it is important to remember that the brain is dynamic and ever-changing. The deterioration of neuroanatomy with age is well known, and more recently the negative ramifications of emotional states, pain, and drugs have been documented. In the case of stress, the release of emotion-correlated glucocorticoid hydrocortisone has been shown to be related to significant hippocampal atrophy in patients with depression (Sheline, Wang, Gado, Csernansky, & Vannier, 1996) and with posttraumatic stress disorder (Bremner et al., 1995). It thus seems likely that there are other neuropathological consequences of stress, and perhaps other emotional states. Longitudinal neuroimaging

studies, for example, show progressive deterioration in brains of some schizophrenics over time, yet debate rages as to whether or not this is a primary feature of the disorder (Mathalon, Rapoport, Davis, & Krystal, 2003). From one perspective, these changes may reflect the basis of the chronicity of the disorder, whereas for others it represents concomitants such as medication histories, comorbid drug use, incidental head injury, and so forth.

The good news is that new technology is begetting newer technology at an exponential rate. MRI studies, for example, must continually be reevaluated in light of the development of increasingly more powerful scans. For example, in the future, temporal and spatial resolution will be at the level of individual neurons. Thus, the following representative reviews of biological vulnerabilities for attention deficit/hyperactivity disorder (ADHD), conduct disorder, depression, and substance abuse should be seen as current state-of-the art knowledge and theory, yet likely ephemeral and open to change with new developments. What the reviews do underscore, however, is that currently, "the brain is the game," and there exist substantial biological vulnerabilities to psychopathologies.

ATTENTION DEFICIT/ HYPERACTIVITY DISORDER

ADHD is the most prevalent of the childhood-onset psychiatric disorders. Estimated to affect between 3% and 7% of school-age children, with affected boys outnumbering affected girls by a ratio of approximately three to one (APA, 2000), it represents 50% of all referrals to child health professionals (Hale, Hariri, & McCracken, 2000; Wicks-Nelson & Israel, 2000). ADHD is a heterogeneous syndrome, with the current psychiatric nomenclature recognizing three subtypes: inattentive, hyperactive/impulsive, and combined. Comorbidity with other psychiatric disorders has been well established, with at least 50% of ADHD children receiving an additional diagnosis of oppositional defiant disorder, conduct disorder (CD), depression, anxiety, or learning disability (APA, 2000). Once considered a childhood-limited condition, ADHD is increasingly perceived as chronic, with symptoms persisting in as many as 75% of affected individuals through adulthood (Wilens, Biederman, & Spencer, 2002).

British pediatrician George Still (1902) first described ADHD symptomatology using the label of "defective moral control," which he believed was caused by subtle anomalies in the structure and activity of neurons resulting from physical illness or heredity, with minimal environmental contribution. Since then, although inattention, hyperactivity, and impulsivity have been the object of numerous categorizations and conceptualizations (Baumeister & Hawkins, 2001), brain anomalies have remained at the core of etiological models of the disorder. Researchers have sought to confirm the biological roots of ADHD using a variety of methods, such as behavioral and molecular genetics, neuropsychology, drug challenges, and investigation of environmental factors likely to affect brain structure and functioning. Although numerous neurobiological theories of ADHD have been put forward, most have focused on dysfunctions of the frontal lobes, as well as the basal ganglia and the cerebellum. This emphasis logically follows from the well-established association between frontal lobe lesions or deficits with impulsivity and executive function deficits (i.e., problems regulating responses because of impairments in attention, working memory, self-monitoring, and planning) as well as the known importance of the basal ganglia for the regulation of motor activity (Anderson, Polcari, Lowen, Renshaw, & Teicher, 2002). These impairments are congruent with the impulsivity, difficulty in planning and concentrating, and context-inappropriate hyperactive behaviors displayed by individuals described as having

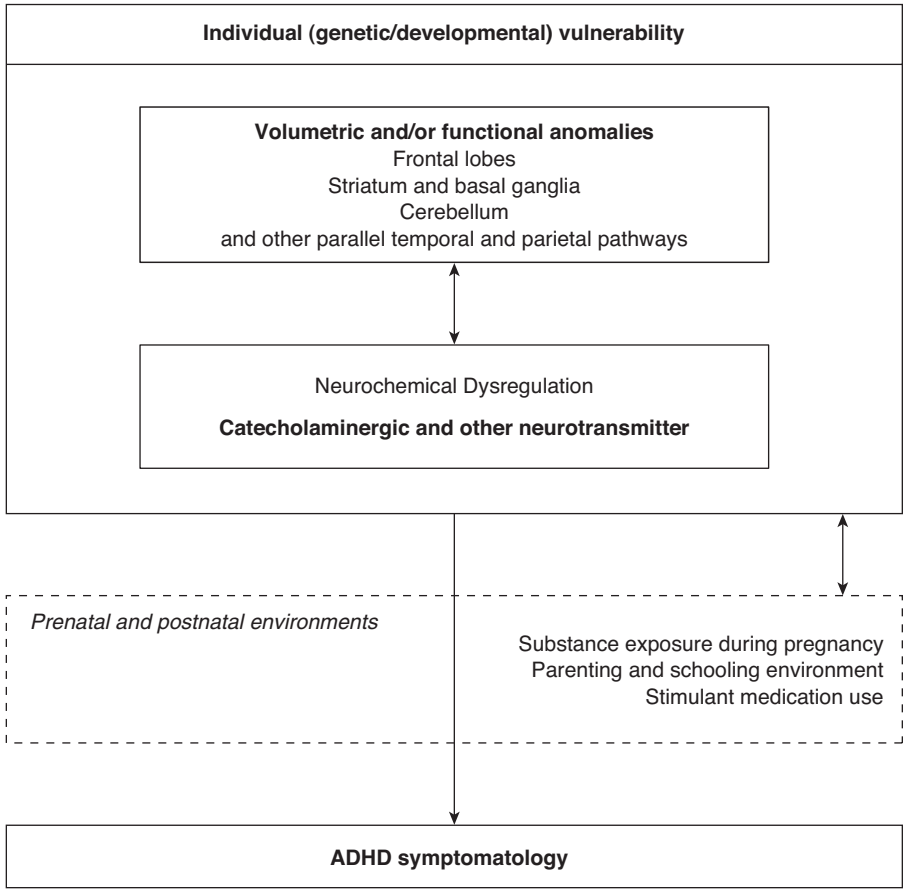

Figure 4.1 Attention Deficit/Hyperactivity Disorder

ADHD. Together with the cerebellum, the frontal lobes and the basal ganglia form a pathway that is subserved by the mesolimbic and mesocortical dopaminergic systems, neurotransmitter systems directly affected by stimulant medication (Anderson et al., 2002). Figure 4.1 summarizes the interactions between the fronto-striatal-cerebellar pathway, the dopaminergic system, and pre/postnatal moderating influences in leading to ADHD symptomatology. However, it is only within the last two decades that the available neuroimaging technologies have enabled researchers to directly investigate the specific nature of the brain anomalies putatively responsible for the disorder.

Brain Structural and Functional Abnormalities Associated With ADHD

In the largest structural imaging study of ADHD patients to date, Castellanos and colleagues (2002) investigated brain volumetric changes over time, with repetitive MRI scans at 2- to 3-year intervals, in 152 both medicated and unmedicated patients and 139 matched controls. Results indicated that at initial scan, patients exhibited smaller whole-brain volumes (see also Hill et al., 2003; Mostofsky, Cooper, Kates, Denckla, & Kaufmann, 2002, for other supportive evidence, but Filipek et al., 1997; Lyoo et al., 1996, for negative findings).

This difference was most significant for unmedicated patients. Unmedicated patients were found to have smaller total white matter volumes than medicated patients and controls. They also exhibited smaller cerebellar, temporal gray matter, and total cerebral volumes than controls. Medicated patients and controls were not significantly different on white matter volumes, but they differed for all measured gray matter regions, with ADHD patients exhibiting smaller volumes. At follow-up, differences in total and regional volumes between the groups were found to persist over time, except for the caudate nucleus, which was originally smaller in patients but did not differ in size by adolescence. Except for the caudate nucleus, growth curves were found to be lower in patients but to follow the same shape as in controls. No significant differences were found between males and females.

The study by Castellanos and colleagues (2002) is very important because it attempts to provide answers to important questions left lingering by previous research. First, the vast majority of studies on ADHD have used samples of male participants, so less information has been available on the possible sex differences in the biological underpinnings of the disorder (e.g., Baving, Laucht, & Schmidt, 1999; Ernst et al., 1994). Results by Castellanos et al. (2002) suggest that patterns of brain volumetric abnormalities in ADHD patients are similar in boys and in girls. Second, because the vast majority of patients participating in imaging studies have been exposed to stimulant medication, it becomes difficult to disentangle which brain anomaly may be attributed to the disorder and which may be attributed to medication use. Castellanos et al. (2002) suggest that stimulant medication use is not responsible for the reduced total and regional brain volumes observed in ADHD children. It may be that medication contributes to a normalization of brain volumes in ADHD children. Such findings are consistent with a growing literature suggesting that stimulant medication may help normalize metabolic activity in frontostriatal regions of ADHD patients (Hale et al., 2000). Last, there has been debate as to whether ADHD constitutes a form of developmental delay whose severity may lessen over time, or whether the disorder should be characterized as involving a stable biological vulnerability. Castellanos et al. (2002) showed, using a longitudinal design, that brain volumetric anomalies found in ADHD children are present early on and are stable over time, which is consistent with a vulnerability perspective and the increasing evidence that significant symptoms may persist through adulthood for a great number of individuals.

The structural and functional imaging literature provides support for the presence of frontal-striatal-cerebellar anomalies in ADHD patients. The majority of functional imaging studies have found evidence for frontal hypofunction in ADHD patients (Baving et al., 1999; Durston et al., 2003; Lou, Henriksen, & Bruhn, 1984; Sieg, Gaffney, Preston, & Hellings, 1995; Silberstein et al., 1998; Zametkin et al., 1990). Most investigations of the basal ganglia have focused on the caudate nucleus. Abnormalities of caudate volumes have been reported, with ADHD patients exhibiting reduced volumes (Castellanos et al., 1996; Filipek et al., 1997; Hynd et al., 1993; Mataro, Garcia-Sanchez, Junque, Estevez-Gonzalez, & Pujol, 1997). PET and fMRI studies have shown striatal activity to be reduced in ADHD patients (Durston et al.; Lou, Henriksen, Bruhn, Borner, & Nielsen, 1989; Lou, Henriksen, & Bruhn, 1990; Vaidya et al., 1998). Volumetric abnormalities of the cerebellum have been found in ADHD patients, but there are inconsistencies concerning the specific localization of these abnormalities (Berquin et al., 1998; Castellanos et al., 1996; Hill et al., 2003). In addition to the evidence showing that

ADHD stems from a dysfunction of the fronto-striatal-cerebellar pathway, ADHD is also influenced by other parallel circuits involving association areas (e.g., temporal, parietal, and occipital lobes) important to the integration of information (Sowell et al., 2003).

Neurochemistry of ADHD

In light of evidence from neuroimaging studies of frontal-striatal-cerebellar anatomic and functional anomalies in ADHD patients, as well as the neuropharmacology of stimulant medications (Kirley et al., 2002), great attention has been given to the contribution of dopaminergic functioning to the presentation of ADHD. A number of studies using single-photon emission computed tomography technology found evidence of increased striatal dopamine transporter density in ADHD patients (Dougherty et al., 1999; Krause, Dressel, Krause, Lung, & Tatsch, 2000). The evidence, however, has been somewhat mixed, with some studies finding no differences (van Dyck et al., 2002). PET studies labeling catecholamine terminals have found reduced uptake in the left medial prefrontal cortex in adults with ADHD but have also found increased uptake in the right midbrain of ADHD adolescents (Ernst, Zametkin, Matochik, Jons, & Cohen, 1998; Ernst et al., 1999). Animal studies have found that both hypo- and hyperdopaminergic states are positively linked with hyperactive behaviors (Castellanos & Tannock, 2002; Denckla, 2003). The pattern of findings thus suggests that dysregulation of the catecholaminergic system is involved in ADHD, although the nature of the dysregulation is not well defined. It is also possible that other neurotransmitter systems are involved in the etiology of the disorder. Stimulant medications, as a group, increase synaptic levels of all catecholamines. Methylphenidate, for one, inhibits reuptake of dopamine and noradrenaline (Denckla). As well, the noradrenergic system has been shown to be essential to executive functions and may be especially important for inattention symptoms (Denckla). Serotonin also may be implicated, especially for comorbid aggression. It has also been shown to play a role in executive functioning (Denckla). However, medications that affect catecholaminergic functioning are generally found to be effective, whereas those that affect primarily the serotonergic system have not (Wilens et al., 2002). In a meta-analysis of 20 genes for dopaminergic, serotonergic, and noradrenergic metabolism by Comings and colleagues (2000), noradrenergic genes were found to account for a greater proportion of the variance in the ADHD phenotype than dopamine and serotonin genes combined. It has been suggested that an anomalous balance between levels of different neurotransmitters, rather than anomalies in one neurotransmitter system per se, may contribute to the etiology of ADHD (Oades, 2002).

Conduct Disorder

One of the most common comorbid conditions observed in children with a diagnosis of ADHD is CD (see Hankin, Abela, Auerbach, McWhinnie, & Skitch, Chapter 14 of this volume, for greater discussion and description), which is defined as a persistent and recurrent disregard for social rules and the basic rights of others. In contrast to ADHD, CD, as a diagnosis, has not received as much attention from the field of brain neuroimaging. Instead, research has focused on the neuroimaging correlates of the most disruptive symptoms of CD, aggression and violence, in both normative adult samples and in individuals who show the most extreme forms of antisocial behaviors, namely murderers and psychopaths. Special attention has also been given to the contribution of serotonergic functioning, testosterone, cortisol, and sympathetic arousal to

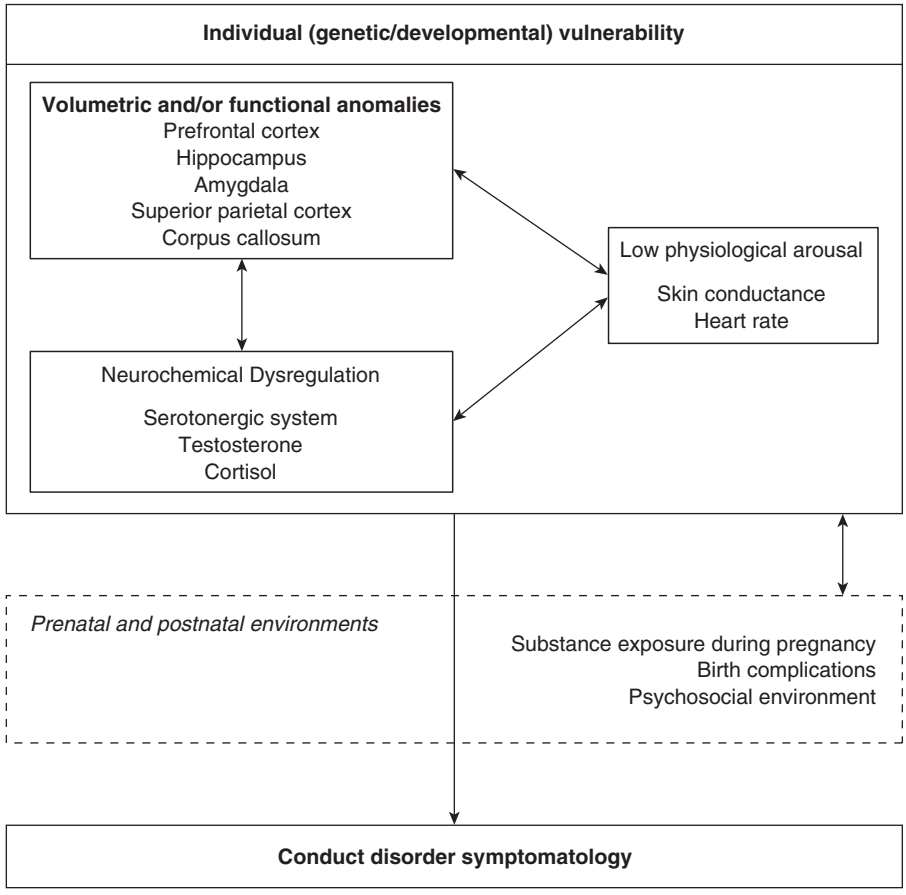

Figure 4.2 Conduct Disorder

aggression, as well as the potential role of abnormal prenatal brain development. Current conceptualizations of antisocial behavior point to dysfunctions in areas and neurochemical systems important to the regulation of impulsivity and aggression (e.g., prefrontal cortex, serotonin), as well as affect-guided anticipation (e.g., amygdala, hippocampus). Davidson, Putnam, and Larson (2000), for example, suggest that impulsive aggression results from anomalies in the threshold for activating negative affective states and the anticipation of negative consequences of aggression. Figure 4.2 illustrates how these dysfunctions interact with pre- and postnatal moderating factors in leading to symptoms of CD.

THE BRAIN AND AGGRESSION

Lesion studies have provided evidence for a link between damage to specific brain regions and behavioral symptoms similar to conduct disorders and associated antisocial behaviors. One of the earliest cases—and perhaps the most famous case—is that of Phineas Gage, who, upon an explosion at his work site, had an iron rod blown through his inferior frontal cortex, more specifically the ventromedial region. Previously a conservative and friendly young man, Gage became highly irritable and impulsive, showing little consideration for the consequences of his actions (Stuss, Gow, & Hetherington, 1992). This pattern of impulsivity, antisocial

behaviors, and inability to inhibit responses resulting from damage to the inferior frontal temporal lobes has been labeled by some as "acquired sociopathy" (Damasio, Tranel, & Damasio, 1990). Damage to the amygdala, in turn, has been found to lead to symptoms reminiscent of psychopathy, such as reduced emotionality and understanding of emotions, as well as disturbed fear processing (Hoptman, 2003).

In his recent review of the neuroimaging literature of antisocial and violent behaviors, Hoptman (2003) notes that anger induction in healthy adults has been linked with increased blood flow to the left orbitofrontal cortex, the right ventral anterior cingulate cortex, and bilaterally to the anterior temporal poles, as well as to the thalamus. In violent patients and offenders, aggression levels are associated with reduced metabolism of the anterior, inferior, and medial frontal and temporal lobes, as well as of the thalamus (Hoptman). In a series of studies by Raine and colleagues (Raine et al., 1994; Raine et al., 1998; Raine, Buchsbaum, & LaCasse, 1997), accused murderers were found to have reduced metabolism of the prefrontal and superior parietal cortex, as well as the angular gyrus and corpus callosum. Abnormal functional asymmetry of the amygdala, thalamus, and medial temporal lobe were also observed. Reductions of prefrontal activity were more pronounced in individuals whose crime could be described as impulsive (Raine et al., 1998). It has been suggested that hypometabolism may be most pronounced in criminals with a positive psychosocial background (e.g., from relatively affluent socioeconomic conditions, intact homes, with absence of deprivation or abuse) (Combalbert, Bret-Dibat, & Favard, 2002; Raine, 2002). More recently, Soderstrom et al. (2002) observed a negative correlation between right frontal and temporal blood flow and scores on the personality dimension of a psychopathy interview (Factor 1 of the Psychopathy Checklist-Revised) in violent offenders. Raine and colleagues (2003) observed increased interhemispheric connectivity in a study of the corpus callosum in psychopathic, antisocial individuals. The functional anomalies observed in violent, antisocial individuals appear to be accompanied by structural anomalies. Raine, Lencz, Bihrle, LaCasse, and Colletti (2000) found that individuals with antisocial personality disorder exhibited an 11% reduction of prefrontal gray matter volumes. As well, hippocampal volumetric reductions have been negatively associated with psychopathy levels (Laakso et al., 2001). In a recent study of successful and unsuccessful psychopaths, Raine and colleagues (2004) noted that unsuccessful psychopaths exhibit a greater asymmetry of the hippocampus than successful psychopaths and controls. This greater asymmetry was caused by decreased left hippocampal and increased right hippocampal volumes.

Lesion and imaging studies have thus pointed to a number of brain anomalies as potentially underlying violent and antisocial behavior. Studies investigating the relationship between perinatal complications, prenatal exposure to toxins, and aggression suggest that these brain anomalies may in part be caused by disrupted prenatal brain development due to very early exposure to stressors. Alcohol and nicotine exposure during pregnancy have been shown to increase the risk of later conduct disorders (Raine, 2002). Birth complications also increase the risk of CD; delinquency; and impulsive, violent offending, through causing brain damage to the frontal lobes and other regions, such as the hippocampus, which have been found to be abnormal in certain types of offenders (Combalbert et al., 2002; Raine). Exposures to toxins and birth complications interact in predicting conduct outcomes (Combalbert et al.; Raine). Consistent with a vulnerability-stress perspective, Brennan, Grekin, and Mednick (1999) found that whereas children whose mothers smoked 20 cigarettes per day during pregnancy had a twofold increase in violent offending as

adults, children who were exposed to both nicotine and delivery complications exhibited a fivefold increase in violent offending as adults. Thus, it appears that exposure to toxins and obstetric complications interact with the postnatal psychosocial environment in predicting later aggression and violence in children (Raine).

Aggression and Arousal

Low resting heart rate has been shown to be characteristic of antisocial individuals, especially those who come from privileged social backgrounds (Raine, 2002). A similar pattern is generally found for skin conductance (Raine). Both indices of reactivity appear to have some predictive value, because lower heart rate and skin conductance at age 3 have been shown to predict violence levels at age 11 (Combalbert et al., 2002). In turn, higher physiological arousal may serve a protective function, because individuals who desist from adolescent antisocial behavior have been shown to have increased electrodermal and cardiovascular activity (Raine). Increased heart rate and skin conductance have also been observed in individuals with criminal fathers who do not themselves commit crimes (Combalbert et al.). Although the specific mechanism through which low physiological arousal may lead to conduct problems is still unclear, it has been hypothesized that lowered physiological arousal may result from prefrontal damage and may predispose individuals to low levels of fear, high levels of stimulation seeking, or both, which may in turn cause them to act out (Raine).

The Neurochemistry of Aggression

The contribution of serotonergic functioning to aggression has been studied in rodents, nonhuman primates, and humans using a variety of methods, such as lesions, measurement of serotonin metabolites in CSF and plasma, tryptophan depletion and supplementation, platelet serotonin uptake, and prolactin response to serotonergic agonists (Krakowski, 2003). In rodents, increased levels of aggression have been observed following serotonin depletion or neuronal destruction. In nonhuman primates, low serotonin levels have been associated with severe, unrestrained, dysfunctional aggression, whereas no relationship with more positive, assertive types of aggression has been observed (Krakowski). More specifically, low serotonin early in life has been linked with later violence and death, and experimental manipulations of serotonin levels have confirmed this inverse relationship between aggression and serotonin (Krakowski). In human studies, negative correlations have been found between lifetime aggression in individuals with personality disorders and serotonin levels, and low serotonin levels are associated with impulsive violence and recidivism in offenders (Krakowski). Experimental studies have shown reduction of irritability and aggression in patients with personality disorders upon treatment with selective serotonin reuptake inhibitors (SSRIs) (e.g., Cherek, Lane, Pietras, & Steinberg, 2002). Furthermore, tryptophan depletion and supplementation have been shown to yield changes in aggression levels in the expected directions, although these changes may occur only in individuals who have a preexisting vulnerability (e.g., family history of alcoholism, high hostility) (Krakowski). In a recent meta-analysis (Moore, Scarpa, & Raine, 2002), reduced 5-HIAA levels in antisocial individuals were found compared with nonantisocial individuals. However, age was found to be a significant moderator: Individuals younger than 30 years of age exhibited significantly lower 5-HIAA levels. The attenuation with age of decreased serotonergic levels may contribute to the observed age-related decline in crime (Moore et al.).

Age differences have also been found with regard to the relationship between testosterone and aggression. High testosterone levels have been associated with increased levels of aggression in adults. Patterns are less clear in children and adolescents, for whom the relationship between testosterone and aggression has sometimes been found to be reversed or absent (Raine, 2002). Raine has suggested that inverse relationships between testosterone and aggression in younger and older individuals may be attributed to the differing social experiences of these age groups. Aggressive children and adolescents usually exhibit poor academic and social functioning, and it may be these aversive experiences that decrease their testosterone levels. However, as they get older and are perhaps able to use their aggression to obtain dominance and success, their testosterone levels rise to their naturally high levels (Raine). Activity of the HPA axis has also been proposed as influencing aggression and conduct problems. Individuals with a diagnosis of CD who show significant levels of anxiety have greater levels of cortisol, show less aggression, and have fewer police contacts (Pihl et al., 2003). It is likely that testosterone and cortisol interact together in contributing to aggression and conduct disorders. Finally, it is also most likely that neurochemical functioning interacts with psychosocial experiences in predicting the presence or absence of antisocial behaviors. Caspi and colleagues (2002), for example, found that polymorphism of the *MAOA* gene, located on the X chromosome, interacts with childhood maltreatment in predicting adult criminal behaviors. The *MAOA* gene encodes an enzyme that metabolizes a number of neurotransmitters, including serotonin. Although low activity of the *MAOA* gene was not found to predict adult criminal behavior by itself, its combination with childhood maltreatment was significantly related to the presence of antisocial behaviors during adulthood (Caspi et al.).

DEPRESSION

The *DSM-IV-TR* (APA, 2000) defines major depressive episode as being characterized by affective (e.g., depressed mood, anhedonia), cognitive (e.g., worthlessness or guilt, diminished concentration), and vegetative symptoms (e.g., changes in sleeping or eating) (see Hankin & Abela, Chapter 10 in this volume, for greater description and discussion about depression). Faced with the increasing prevalence of depression and its progressively earlier onset, researchers are focusing more and more on the factors that render individuals vulnerable to depression. This endeavor, however, is not novel, because proposals regarding the etiological role of both innate and environmental factors have been present since the first descriptions of the disorder more than 2,000 years ago (Nestler et al., 2002). However, it is only with the use of increasingly sophisticated imaging technology that researchers have been able to begin describing the specific brain anomalies potentially associated with the disorder. Davidson and colleagues (2002) proposed a model whereby hypoactivation of the left prefrontal cortex and anterior cingulate cortex and hyperactivation of the right prefrontal cortex would lead to decreased approach behaviors and increased withdrawal and anxiety, which are often seen in depressed patients. Decreased activity of the left prefrontal cortex could in turn lead to a decreased inhibition of the amygdala and thus persistent negative affective states. Abnormalities of the hippocampus were also suggested to contribute to an absence of appropriate contextual modulation of emotions (Davidson et al., 2002). Figure 4.3 summarizes brain areas and neurochemical systems found to be involved in depressive affective states and their interactions with various psychosocial moderating factors.

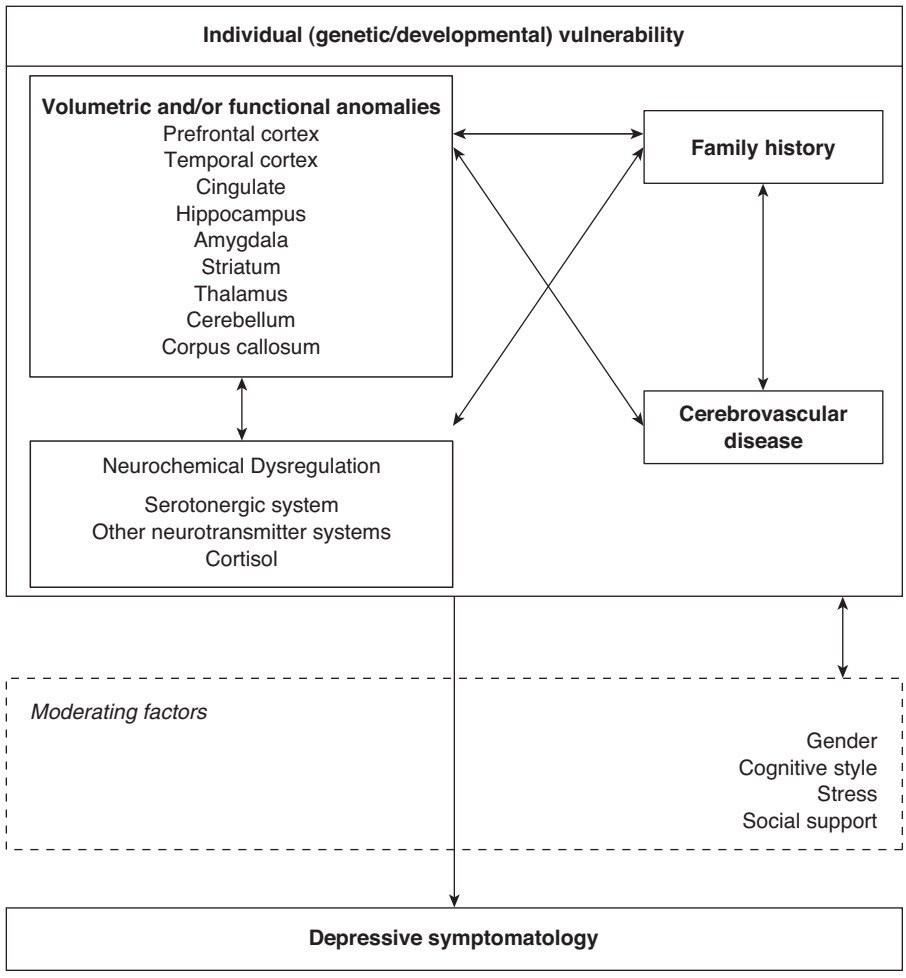

Figure 4.3 Depression

Functional and Structural Anomalies

Little evidence has been provided for differences in overall whole-brain volumes in depressed patients when compared with healthy controls (Strakowski, Adler, & DelBello, 2002). However, consistent with the model proposed by Davidson et al. (2002), differences in metabolism and volumes have been reported for a number of subregions, such as the prefrontal and cingulate cortex, the hippocampus, and the amygdala (Nestler et al., 2002). Total frontal lobe volumes have been found to be reduced by approximately 7% in depressed patients. The subgenual prefrontal cortex appears to be particularly reduced, with studies finding reductions of approximately 48% (Drevets et al., 1997). As well, reduction of the right-greater-than-left asymmetry of the frontal lobes usually found in controls has also been observed. The extent of total frontal lobe volumetric reduction and decreased asymmetry has been associated with severity of symptoms (Beyer & Krishnan, 2002; Strakowski et al., 2002). Imaging and postmortem studies have provided support for the presence of

volumetric anomalies in the orbital region, more specifically bilateral volume reductions and decreased cortical thickness, as well as decreased neuronal size and density (Lai, Payne, Byrum, Steffens, & Krishnan, 2000; Rajkowska et al., 1999). It is important to note, however, that a number of studies have not found evidence for significant volumetric differences in these brain regions between depressed patients and healthy controls (Nestler et al.).

Decreased bilateral or left prefrontal cortex activation is one of the most often reported functional anomalies in the imaging literature on depression (Davidson et al., 2002). Resting state imaging studies have shown hypometabolism of the frontal lobes, more specifically of the dorsolateral and dorsomedial prefrontal cortex (Davidson et al., 2002; Drevets, 2000; Liotti & Mayberg, 2001). Specificity of reduced activity to the left hemisphere has been replicated numerous times by electroencephalogram (EEG) studies, although negative evidence has also been found (Davidson et al., 2002). Partial support has been provided for an increase in dorsolateral and dorsomedial activity with antidepressant use, more specifically to the left hemisphere (Davidson et al., 2002; Drevets). However, although the dorsolateral and dorsomedial prefrontal regions have been found to be hypoactive in some studies, evidence for hyperactivity of other prefrontal regions in depression has also been provided. Increased activity in the subgenual prefrontal cortex, as well as bilateral posterior orbital cortex, left ventrolateral prefrontal cortex, and anterior insula has been found, together with a body of findings suggesting that antidepressant treatment may lead to a reduction of activity in these regions (Drevets).

Evidence for volumetric anomalies of the temporal lobes and limbic structures has been somewhat mixed (Beyer & Krishnan, 2002). Patients suffering from major depression have been found to have decreased temporal cortical volumes when compared with healthy controls in some studies, although a number of investigations have reported null findings (Strakowski et al., 2002). Structural imaging studies have reported reductions of hippocampal volumes in patients with major depression, a finding also reported in patients with bipolar disorder, posttraumatic stress disorder, and borderline personality disorder (Davidson et al., 2002; Strakowski et al.). Hippocampal volumetric reductions for patients with major depression have been estimated to range from 8% to 19% (Davidson et al., 2002). Decreased hippocampal activity has also been reported using PET technology (Davidson et al., 2002). Findings for volumetric anomalies of the amygdala have been inconsistent, with different studies reporting increased, decreased, or no differences in volumes in depressed patients compared with controls (Davidson et al., 2002). Studies have also reported a left-greater-than-right asymmetry of the amygdala found in patients but not in controls (Davidson et al., 2002). Functional studies have reported increased activity of the amygdala in depressed patients, an increase evaluated by some to be of a magnitude of 44% (Davidson et al., 2002). As well, although remission of major depressive symptoms is associated with a reduction of activity levels of the amygdala, relapse is associated with increased amygdala activation (Davidson et al., 2002). It is interesting to note that increased amygdala activity has also been associated with bipolar disorder and anxiety disorders (Davidson et al., 2002). Bilateral reductions in anterior cingulate activity have also been noted and have been found to correlate with the extent of gray matter reduction, which is consistent with the finding that antidepressant treatment does not generally lead to a normalization of activity in this region (Davidson et al., 2002; Drevets, 2000).

Reduced volumes of the basal ganglia have been noted in depressed patients, most specifically of the caudate nucleus and the putamen, in the context, however, of numerous

null findings (Beyer & Krishnan, 2002; Strakowski et al., 2002). Limited research has been done on the presence of cerebellar and corpus callosum structural anomalies in depression (Beyer & Krishnan). A number of studies have found decreased volumes of the cerebellum (Strakowski et al.), whereas some evidence has been provided for increased volumes of some subregions of the corpus callosum in depressed patients (Beyer & Krishnan). Research on thalamic structural anomalies has been limited and inconsistent. Volume reductions have been observed in some studies, but it has been suggested that thalamic volumetric reductions may be more common in bipolar disorder (Strakowski et al.). Increased, decreased, and no change of thalamic activity in depressed patients have all been reported (Liotti & Mayberg, 2001).

The imaging literature on the brain structural and functional correlates of depression has thus produced a number of heterogeneous findings, with partial empirical support provided for an involvement of the frontal and temporal lobes, the amygdala, the hippocampus, the basal ganglia and thalamus, and the cerebellum and corpus callosum. The equivocal nature of evidence for volumetric and functional anomalies in depression has been attributed by some to the heterogeneity of the disorder. More specifically, it has been suggested that some brain anomalies may characterize specific subtypes of patients (Davidson et al., 2002). For example, patients with a family history of major depression have been shown to be more likely to have increased activity of the amygdala, orbital cortex, and medial thalamus and decreased activity in specific subregions of the prefrontal cortex, as well as volumetric anomalies of the basal ganglia (Drevets, 2000). As well, patients with a family history of major depression do not exhibit the reduced amygdala activity usually associated with remission of symptoms, suggesting that amygdala hyperactivity may constitute a marker of a depressive trait rather than a depressive state in this subpopulation (Davidson et al., 2002). Patients with a late onset of the disorder have also been shown to exhibit a specific pattern of anomalies (Drevets, 2000). They exhibit sulcal and ventricular enlargement, as well as reduced volumes of the frontal lobes and the basal ganglia. Infarction to the frontal lobes or striatum has been associated with increased risk of depression, and there has been suggestion that late-onset depression may develop as a result of cerebrovascular disease (Strakowski et al., 2002). Some brain functional and structural anomalies may thus be specific to familial or late-onset depression cases (Strakowski et al.). Overlap in some of the observed regional anomalies may confer a common vulnerability to both subtypes, although different causal mechanisms are at play (Drevets).

Neurochemical Anomalies

Evidence for a serotonergic contribution to the physiology and treatment of depression comes from several lines of evidence. All pharmacological treatments of depression to date have focused on the monoamines, and the latest generation of antidepressants, the SSRIs, has been shown to be effective in reducing symptoms (Stockmeier, 2003). As well, depletion of tryptophan, a serotonergic precursor, has been shown to cause recurrence of symptoms in unmedicated patients in remission (Young & Leyton, 2002). Reduced levels of serotonergic metabolites in the cerebrospinal fluids of depressed patients with a history of suicide attempts have also been found, as well as decreased neuroendocrine response to serotonin stimuli (Stockmeier). In his recent review, Stockmeier reported a number of anomalies in serotonergic receptor binding sites associated with depression. Serotonin-1A receptor binding was found to be reduced in a number of regions, such as the medial temporal cortex,

the temporal pole, the orbitofrontal cortex, the anterior cingulate cortex, the insula, and the dorsolateral prefrontal cortex. Alternatively, serotonin-2A receptor binding was found to be increased in the prefrontal cortex (Stockmeier). However, it is most likely that serotonin is not acting alone in the neurochemistry of depression. Norepinephrine receptor and transporter anomalies have been noted in depressed patients (Stockmeier). As well, depressed patients have been shown to have cortical levels of the inhibitory neurotransmitter GABA that are half that of healthy controls, levels that are restored by antidepressant medications (Stockmeier). Antagonists of substance P, a peptide neurotransmitter, have been shown by some researchers to be as effective as SSRIs in alleviating symptoms of major depression and anxiety (Stockmeier). In certain brain regions, nearly half of serotonergic neurons are colocalized with substance P neurons, and substance P antagonists have been shown to increase firing activity of serotonergic neurons in certain brain areas (Stockmeier). Interactions of a number of neurochemical systems are thus most likely involved in the etiology and treatment of depression.

Neurochemical explanations of depression have also focused on possible hyperactivity of the HPA axis. Research has shown that abnormally elevated HPA activity may be present in approximately 50% of depressed patients, most importantly those with a family history of major depression, and that these anomalies may be corrected with antidepressant administration (Nestler et al., 2002). Thus, hyperactivity of the HPA axis may contribute to depression through hippocampal damage, which is consistent with reduced hippocampal volumes sometimes found in depressed patients (Nestler et al.). As well, hippocampal volume reductions have been positively associated with duration of illness, which concurs with exposure to chronically elevated glucocorticoid levels (Davidson et al., 2002). Furthermore, centrally administered CRF has been shown to trigger symptoms found in depression such as anxiety and neurovegetative symptoms. This suggests that the contribution of the HPA axis hyperactivity to depression may not be limited to the hippocampus, but may also extend to other brain regions such as the hypothalamus (Nestler et al.).

The vast majority of studies on the biological bases of depression have focused on adult depression, using cross-sectional designs. This has made difficult a clear understanding of the role biology plays in the emergence of the disorder and how biological contributions to depression evolve over time. Research with children and adolescents has pointed to possible anomalies of the frontal lobes. Steingard and colleagues (2002), for example, have noted smaller white matter volume but greater gray matter volumes in depressed adolescents. Nolan and colleagues (2002) found that although depressed children and adolescents with no family history of major depression (MD) had larger left prefrontal volumes than depressed individuals with a family MD and normal controls, depressed children and adolescents with a family history of MD and controls did not significantly differ in terms of prefrontal volumes. Furthermore, a study focusing on depressed preschoolers has pointed to a possible contribution of the stress system to childhood-onset depression (Luby et al., 2003). Depressed preschoolers exhibited increased cortisol levels in response to both situations of separation and frustration. Nondepressed preschoolers, however, showed decreased cortical levels in separation situations and increased cortisol levels when frustrated. A longitudinal study by Goodyer, Herbert, and Tamplin (2003) has suggested that anomalies in steroid levels may precede the onset of the disorder. Adolescents who developed persistent depressive symptoms within 2 years initially showed a higher morning cortisol/dehydroepiandrosterone ratio. More longitudinal studies focusing on individuals at

risk of developing depression are required in order to disentangle the biological roots of the emergence and development of the disorder.

SUBSTANCE ABUSE AND DEPENDENCE

Of the many "fat" words in psychopathology, perhaps the most obese is substance abuse/dependence (see Kassel, Weinstein, Mermelstein, Skitch, & Veilleux, Chapter 13 in this volume, for greater description and discussion). The size (the large number of differential drug diagnoses) and obtuseness (the myriad of paths to the end point) of the diagnosis make this diagnosis highly prevalent but often meaningless. Nevertheless, depending on the survey, substance abuse remains the most prevalent form of mental disorder, with alcohol abuse and dependence accounting for a majority of diagnoses (Pihl, 1999). Until recently, there has been a dearth of knowledge concerning etiology.

It is now clear that some individuals, for varying reasons, are more likely than others to develop problems with drugs. To understand reasons for abuse, it is no longer necessary to look at each drug individually; instead, the focus is on what a drug or group of drugs does for a specific individual. By adopting this perspective, one can get a glimpse of how genetic, biochemical, physiological, neuropsychological, and experiential facts interact. Two major drug groupings are the stimulant drugs and the depressant drugs, although there are obvious additional groupings (e.g., pain relief, hallucinogenics). Further, this dual, broad classification also suffers from the fact that some drugs have, for example, both stimulant and depressive effects. The most notable substance displaying this characteristic is alcohol, because for most individuals, on the rising limb of the blood alcohol curve, approximately 30 minutes postingestion of the drug, one reacts as if stimulated, whereas later on the blood alcohol curve, depressant brain effects are normative.

Stimulant Drugs

Research with rats and monkeys had clearly demonstrated in the 1960s and 1970s that certain parts of the brain, when stimulated electrically or chemically, produced reinforcing effects. That is, animals would work to receive this stimulation and would learn new responses based on pairing some behavior with the stimulation of the mesolimbic brain area, particularly the ventral tegmental area and specifically the nucleus accumbens. Dopamine has been implicated in this response in that these effects are directly related to the density of dopamine neurons. Further, drugs that blocked these neurons reduced these effects (Fibiger & Phillips, 1988). Stimulant drugs such as cocaine and amphetamines have been shown not only to directly release dopamine as well as other neurotransmitters but also to block the reuptake process, thus prolonging dopamine's effects (Koob & Blume, 1988). Some other drugs that increase dopamine flow into the nucleus accumbens are alcohol, marijuana, and opiates. At issue is whether these various drugs have a direct or indirect effect, but it is clear that the dopaminergic system, which is related to psychostimulation, is affected. Recently, Boileau and colleagues (2003) used PET technology to show increased dopamine release in the nucleus accumbens in humans after consuming an alcohol challenge. In addition, the study provided clues to the critical issue of why some individuals develop drug problems, whereas a large percentage of individuals who try various legal and illegal stimulant drugs do not develop abuse or dependency problems (i.e., a vulnerability to substances). Specifically, individuals who had previously demonstrated an accelerated heart rate response to alcohol were significantly more likely to show this dopamine release than individuals who did not previously show an accelerated heart rate response to alcohol. Although many situations, physical and psychological,

affect heart rate, this intoxicated heart rate response has been shown to distinguish individuals who self-report positive subjective feelings to alcohol (Conrod, Peterson, & Pihl, 2001) and those for whom alcohol is positively reinforcing on a memory task (Bruce, Shestowksy, Mayerovitch, & Pihl, 1999). Thus, some individuals at risk for developing problems with alcohol are characterized by this elevated heart rate response on the rising limb of the blood alcohol curve, which has also been shown to be characteristic of individuals who reflect externalizing behaviors such as CD (Pihl et al., 2003) and pathological gambling (Brunelle, Assaad, Pihl, Tremblay, & Vitaro, 2003). The fact that these groups seem to respond with this response as well as having a propensity to develop stimulant substance abuse problems suggests particularities in baseline biological functioning. In rats selectively bred to prefer alcohol, increased functioning of the dopamine system has been demonstrated (McBride, Murphy, Lumeng, & Li, 1990). In these particular strains, alcohol facilitates stimulant-like behaviors, such as increased motor activity. In addition, rats selectively bred to self-administer opiates and cocaine demonstrate heightened place learning when administered these drugs, reminiscent of the early electrical stimulation studies (Guitart, Beitnes-Johnson, & Nestler, 1992). These findings suggest some preexisting genetic vulnerability. Indeed, there is a large literature showing that children of alcoholics, particularly sons—who are at four to nine times increased risk to develop the disorder—have discernible neuropsychological, electrophysiological, and behavioral responses to alcohol characteristics (Pihl, Peterson, & Finn, 1990). Further, sensitization (i.e., the fact that the use of one drug makes other similar drugs more reinforcing) has been shown to be potentiated by environmental stimuli such as stress (Deminiere, Piazza, Le Moal, & Simon, 1989). However, these effects are not only the result of biologically determined vulnerability but also are affected by using certain drugs. Some drugs per se do produce long-term potentiation of dopamine-releasing cells in the ventral tegmental area of the brain. Further, cross-sensitization with stress means that stress can reinstate drug taking, perhaps accounting for the difficulties in treatment and the high probability of relapse. This pattern is called neural adaptation and occurs by raising the excitatory neurotransmitter glutamate, which stimulates specific receptors on dopamine cells (Saal, Dong, Bonci, & Malenka, 2003). Similar effects are likely to occur with other stimulant drugs, such as nicotine, where withdrawal has been associated with a significant decrease in dopamine levels. Recent research shows that treating smokers with a drug designed to increase dopamine levels is more effective than typical nicotine replacement therapy (George & O'Malley, 2004).

The precise nature of the reward when dopamine is released in this particular brain area is also open to some debate. It appears not to be reinforcement in the classical sense, because the behavior affected does not satiate. Consequently, we have referred to this system as the "cue for reward system" (Pihl & Peterson, 1995) in that it stimulates locomotor activity and feelings of pleasure as if something is about to happen or is happening. Thus, commonalities are found in behavior among individuals who are sensation seekers, conduct disordered, and generally externalizing, and the abuse of stimulant drugs (Pihl & Peterson). These characteristics are particularly reminiscent of individuals at risk for type 2 alcoholism, which involves high heritability, early onset, and associated antisocial behavior (Pihl et al., 1990). Further, it has been recently demonstrated that the risk for ADHD and CD is 3.8 and 6.6 times greater, respectively, among children whose parents were alcohol dependent compared with controls. Twin studies have shown that shared genetic factors are largely responsible for this comorbidity

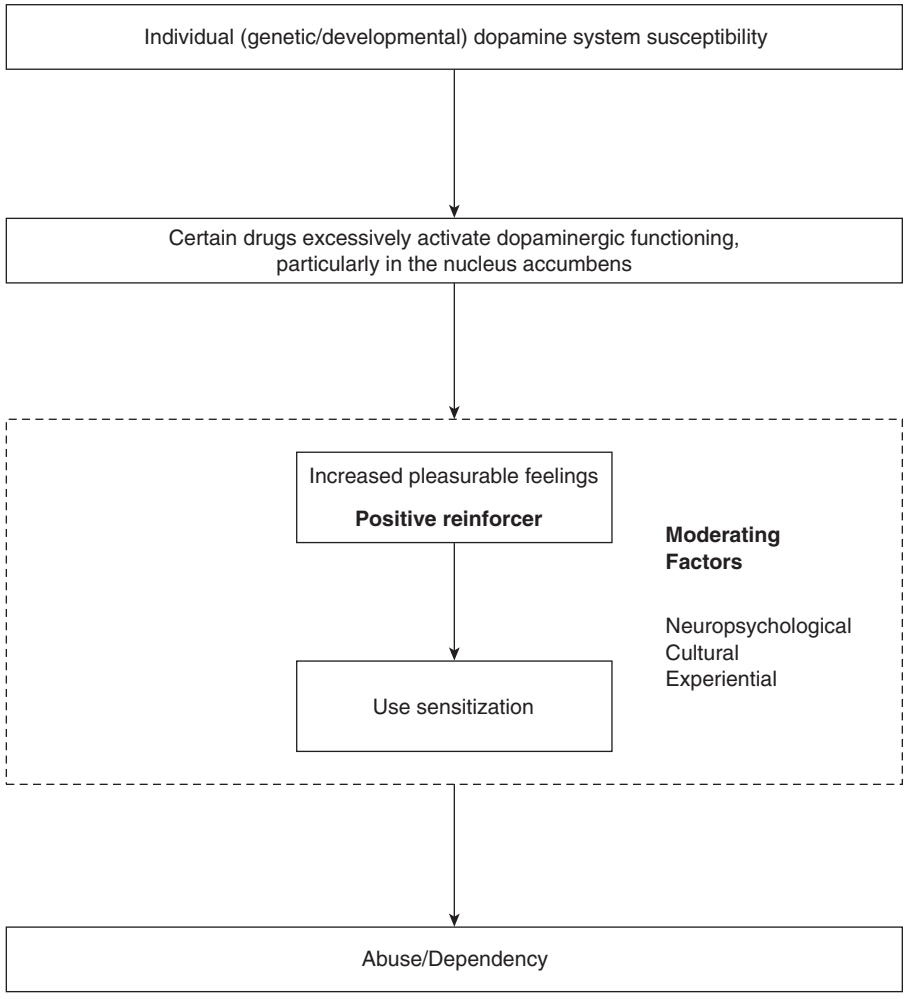

Figure 4.4 Substance Abuse

(Kendler, Prescott, Myers, & Neale, 2003). Commonalities between these groups in neuropsychological and electrophysiological findings have also been reported. In particular, cognitive deficits associated with the functioning of the prefrontal cortex, specifically involving problems in attention, planning, and foresight, have been well documented in both populations, as have particular EEG and event-related potential responses. Further, it has been shown that this particular response pattern, as well as the neuropsychological deficit, precedes onset of heavy drinking and dependence (Harden & Pihl, 1995). More recent electrophysiological work in individuals at risk for alcoholism has also shown a genetic linkage, which has focused on the neurotransmitter GABA, and specifically on the *GABA2* gene, which is thought to modulate the level of neural excitation (Edenberg et al., 2004). This *GABA-A* receptor gene on chromosome 4 has further been shown to be related to P300, N100, N400, and beta frequency EEG abnormalities in individuals at risk for alcoholism (Porjesz et al., 2002).

Depressant Drugs

Negative reinforcement (i.e., when an aversive situation is reduced) is another reward response that can also explain drug abuse. Drugs that reduce anxiety, fear, and dysphoric pain are frequently abused. Individuals with phobias, for example, are 2.5 times more likely to abuse alcohol and individuals with panic disorder four times more likely (Weissman, 1988). "Stress response dampening" is a phrase used to characterize the effect of some drugs on these and otherwise vulnerable individuals. The implied mechanism for abuse is thus seen as a form of self-medication that reduces the intensity of an aversive state. Although some experimental results in this area have been contradictory to this explanation (e.g., Steele & Josephs, 1990), like most studies in psychopathology the choice of subjects is critical. Vulnerable subjects are required, and one particularly vulnerable group is anxiety-sensitive individuals. In the paradigmatic study, these individuals are first shown stimuli when sober, which results in heightened physiological reactivity, which then is greatly diminished when they are alcohol intoxicated (Stewart & Pihl, 1994). Alcohol in this case is acting as an antianxiolytic, putatively by potentiating the action of the inhibitory neurotransmitter GABA. These drugs and other sedatives operate on selective GABA-A and benzodiazepine receptor sites. There are actually three subunits of the GABA-A receptors and 14 variants of the subunits. What is notable is that alcohol and benzodiazepines act on one specific subunit (Suzdak et al., 1986). It is also known that when measured in plasma, baseline levels of GABA are heritable and that individuals at risk for developing alcoholism, like alcoholics, have lower levels (Song et al., 2003). PET studies with offspring of alcoholics have also shown a reduced GABA response to a drug challenge, supporting the notion of reduced gabanergic activity. This conclusion is reinforced by numerous animal studies on selectively bred alcohol-preferring rats; these studies have shown that such rats have dense gabanergic innervation in the nucleus accumbens, that GABA chronically inhibits this system, that alcohol inhibits the action of the gabanergic inhibitory system, and that this inhibitory action accounts for the reward these rats receive from alcohol (McBride et al., 1990). Thus, it is suggested that at high doses needed to produce intoxication (Stewart, Finn, & Pihl, 1995), alcohol might directly potentiate inhibition of certain neurons.

Similar autonomic reactivity and dampening in children of alcoholics, particularly sons, have been reported, perhaps as a result of the same mechanisms just described, but not from fear or anxiety. This response, however, likely results from an overreactivity to novelty, the latter likely resulting from the aforementioned frontal neuropsychological deficits (Pihl & Peterson, 1995). Consequently, both highly anxious and externalizing individuals can display dampening and negative reinforcement, albeit for divergent reasons: those high on anxiety to self-medicate and those with externalizing problems possibly to improve focus.

CONCLUSION

Studies of the biological bases of psychopathology have pointed to subtle anatomical, functional, and neurochemical anomalies being associated with disorders such as attention deficit/hyperactivity disorder, conduct disorder, major depressive disorder, and substance abuse. Generally, results to date for most disorders have been inconsistent and of small magnitude, with a great overlap in distributions observed between patients and controls. As well, few biological findings have been found to be specific to a single disorder. Therefore, our understanding of biological vulnerabilities

must be refined before we can use such vulnerabilities as markers or diagnostic tools for psychiatry and psychopathology. However, current psychiatry and diagnostic systems are the problem. The use of broad, heterogeneous, behavioral definitions as classification measures is undoubtedly the major contributor to the observed lack of consistency. The assumption that diagnostic categories are distinct, when in fact psychiatric disorders show very high comorbidity with each other, is simply spurious. It must be recognized that psychiatric nomenclatures represent the ways in which mental health researchers and professionals have carved out the edges of psychopathology in a way that is meaningful to them and that supposedly allows communication between them, but these are not the true frontiers of psychopathology. It may be that many disorders that we think of as distinct in fact share similar biological etiological mechanisms and that the same phenotype may result from a number of etiological mechanisms, with multiple pathways.

In keeping with the need to consider the multicausal nature of psychopathology, biological vulnerability must be considered in the context of the environment in which the human organism evolves. The environment provides the context in which psychosocial risk and protective factors interact with biological vulnerability in determining whether psychopathology will emerge or not, as well as the prognosis for each individual. The scientific literature is replete with examples of how biology interacts with events in the environment in creating or preventing psychopathology, as well as in determining its outcome. Research on antisocial behaviors, for example, has shown that adolescent boys whose fathers have been convicted of various crimes, but who do not commit crimes themselves, show higher sympathetic arousal, pointing perhaps to a protective effect of biology (Raine, 2002). Furthermore, low sympathetic arousal is often more characteristic of criminals from advantaged than disadvantaged psychosocial backgrounds, suggesting that biological vulnerability may add little to the risk associated with an upbringing in low socioeconomic circumstances. In contrast, minor physical anomalies have been found to predict violence only in individuals growing up in unstable and stressful family environments (Raine). Additionally, the provision of firm structure, combined with warmth by parents or teachers, has been found to be particularly important for behavioral management of children with a diagnosis of ADHD (Denckla, 2003; Wicks-Nelson & Israel, 2000). Not all individuals exposed to psychosocial stress or biological vulnerability will go on to develop signs of psychopathology, and biological or environmental risks are often not sufficient in themselves to trigger onset of psychiatric disorders or to determine their course. It is the interaction of both types of contributors that determines psychopathology. Biological and psychosocial research must thus take into account contributors from each field in order to create a more complete etiological picture of each psychopathology.

However, it may be in many ways impossible to attempt to distinguish the separate contributions of biological and psychosocial factors to psychopathology, because both types of factors are in constant interaction, and the boundaries between them are at best blurry. For example, smoking during pregnancy could be considered as a stressor that confers risk, through biological processes, for the development of later psychopathology through disruption of early brain development (potentially a biological vulnerability). However, women who smoke during pregnancy may be likely to create a postnatal environment for their child that is very different from that created by women who refrain from smoking (i.e., a more stressful environment). This postnatal environment

may then contribute to the emergence of different psychopathological symptoms, such as disruptive behaviors observed in children with ADHD or CD. Parents with a history of antisocial behaviors are more likely to have children who will grow up displaying some forms of antisocial behaviors as well. The extent to which this familial aggregation of socially inappropriate behaviors is due to genetic or biological transmission, the creation of a disruptive environment during upbringing, both, or some interactive combination is, however, unclear. Divisions between different vulnerabilities, especially biological, are thus artificial ones, because all behaviors, thoughts, and emotions ultimately have biological substrates. A multicausal approach to psychopathology, such as embodied in this volume, is the approach that will provide the most complete understanding of psychiatric disorders and their etiology.

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