CHAPTER 2

Pediatric Versus Adult Psychopathology: Differences in Neurological and Clinical Presentations

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Psychological and psychiatric disorders in children and adults have historically been viewed as similar without considering developmental issues that are present both psychologically and neurologically (Semrud-Clikeman, Fine, & Butcher, 2007). Previously, most attention was paid to adult disorders, with child disorders viewed as the same disorder but in a smaller body. Research and clinical practice have now established that psychopathology in children and adults differs and is related to differences in neurological development as well as in expression of psychopathology.

Psychopathology has been related to brain dysfunction for several types of disorders in children and adults, but the contribution of direct and indirect effects of brain dysfunction have not been examined empirically (Tramontana & Hooper, 1989). Direct effects are those that are related to specific behaviors like disinhibition, attention deficits, memory deficits, and the like. Indirect effects are those that produce an emotional or behavioral disturbance as the person attempts to deal with difficulties, such as frustration and failure, as a result of the specific behaviors. At times, the

caretakers in the child's life may view him or her as unmotivated, difficult, slow, or many other negative attributions, thus serving to exacerbate the problems at hand (Semrud-Clikeman & Ellison, 2009).

In many cases, there is an overlap in disorders such that symptoms that may indicate an attention deficit hyperactivity disorder (ADHD) may also be common to anxiety or depression or a metabolic disorder. An approach to evaluation that has been helpful and applicable for neuropsychologists is the use of hypothesis testing. When using this approach, a good history of the disorder is paramount, particularly to determine possible alternative diagnoses. The use of a hypothesis testing approach requires a familiarity with diagnostic nomenclature and disorders that are frequently comorbid or overlapping. This approach provides an opportunity to intertwine information from several sources, including medical personnel, school personnel, and family data. A well-trained clinical psychologist or neuropsychologist can combine medical, academic, and family data to determine appropriate interventions (Hartlage & Long, 1997).

The following sections of this chapter are designed to explore the developmental and neurological differences that may be present in children and adults with externalizing or internalizing disorders. We are limiting our chapter to these disorders as they are the most common presentations seen across the life span. Externalizing disorders include ADHD and intermittent explosive disorder in adults and children as well as oppositional defiant disorder (ODD)/conduct disorder (CD) in children and antisocial personality disorder (APD) in adults. For the purposes of this chapter, internalizing disorders include depression, anxiety, and bipolar disorder.

EXTERNALIZING DISORDERS

Externalizing disorders generally involve difficulties in controlling behaviors due to impulsive responding and acting out. Such disorders may also be classified as disruptive behavior disorders as seen in the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision* (*DSM-IV-TR*; American Psychiatric Association [APA], 2000). Many of the externalizing disorders co-occur at rates that are at greater-than-chance levels. For example, ADHD has been found to co-occur with ODD and

conduct disorder (CD) between 29% and 71% of the time in large epidemiological studies as well as in clinical studies (Burt, Krueger, McGue, & Iacono, 2001).

ADHD

ADHD is a highly prevalent neurodevelopmental disorder that appears in early childhood and for many patients continues throughout adulthood. There are two main subtypes of ADHD: combined (ADHD-C) and inattentive (ADHD-PI). Children and adults with ADHD-C have significant difficulties with inattention, hyperactivity, and impulsivity, whereas those with ADHD-PI experience difficulties mainly with inattention. The expression of ADHD also changes with age. In childhood, the primary symptoms may be reflected in hyperactivity and impulsivity, whereas for adults, inattentive symptoms become more paramount (Semrud-Clikeman & Fine, 2010). Adults with ADHD-C report feelings of restlessness and a need to move, whereas those with ADHD-PI report significant problems with inattention. For children, ADHD-C is frequently found to be comorbid with ODD and CD, as discussed earlier. In adulthood, however, personality disorders such as borderline personality disorder, APD, and histrionic disorders have been found to frequently co-occur with a more severe form of the disorder (Miller, Nigg, & Faraone, 2007). In contrast, ADHD-PI has been found to be comorbid with dysthymia, substance abuse, and learning disabilities for both children and adults (Millstein, Wilens, Biederman, & Spencer, 1997).

Differences are also present in gender incidences. In childhood, the ratio of males to females is approximately 2:1 to 9:1, with the majority being diagnosed with ADHD-C (Biederman, Faraone, Keenan, Knee, & Tsuang, 1990). In contrast, for adults a more balanced ratio has been found with more women diagnosed with ADHD-PI than ADHD-C (Biederman et al., 2002). Additional studies find that men with ADHD are more likely to have a comorbid diagnosis of APD or substance abuse with equal incidence of bipolar disorder, social phobia, and anxiety disorders (Biederman et al., 2002). Women were also found to be diagnosed much later than men and were more likely to be diagnosed with ADHD in adulthood.

Neuropsychological differences are not as pronounced between adults and children. Whereas symptoms of hyperactivity decrease with age, signs of motoric disinhibition continue to be present into adulthood as do problems with inattention. Verbal memory difficulties continue from childhood, particularly when tasks become more complex and intricate. Cognitive flexibility difficulties also continue into adulthood and likely cause additional problems occupationally as requirements increase with responsibility. Executive functioning continues to be problematic for adults and has been found to negatively influence occupational functioning (Barkley & Murphy, 2010).

Neuroimaging findings are consistent across adults and children. Smaller volumes in the prefrontal cortex as well as in the anterior cingulate have been found in adults and children with ADHD (Castellanos et al., 1996; Hesslinger et al., 2002; Nakris et al., 2007; Semrud-Clikeman et al., 2000). Less brain activation has also been found in adults with ADHD, particularly in the right frontal regions of the brain (Valera, Faraone, Biederman, Poldrack, & Seidman, 2005) as well as for children (Pliszka, Liotti, & Woldorff, 2000) and for children in the dorsolateral regions of the frontal lobe (Pliszka et al., 2006).

Psychopathy

Our knowledge of psychopathy in childhood is less well-studied that than for adults. The rubric of psychopathy may include CD or Antisocial Personality Disorder (APD). A diagnosis of ODD or CD involves heterogeneous symptoms that generally involve inappropriate social behavior that is either physically or verbally aggressive. Most of the research has been conducted with adolescents, and if patients with a comorbid diagnosis of ADHD are excluded, very little is known about the neurological underpinnings of the disorder (Tramontana & Hooper, 1997). It has been strongly suggested that antisocial behavior can arise from many different causes and appear differently over development (Hinshaw & Lee, 2003).

ODD has been characterized by a persistent and age-inappropriate display of angry, noncompliant, and oppositional behavior, whereas CD

involves aggressive and antisocial actions that hurt animals and/or other people as well as stealing, burglary, and running away from home (APA, 2000). ODD generally appears on the average by 6 years of age, whereas CD appears around 9 years (Loeber & Farrington, 2000). Key risk factors for CD but not ODD have been found to include poverty, family discord, and a family history of APD (Hinshaw & Lee, 2003).

Delinquents may or may not be diagnosed with CD depending on the nature of their symptoms. It has been found that delinquency may be transient and not involve the infliction of pain on others that is a hallmark of CD (Moffitt & Caspi, 2001). Socialized delinquency such as gang involvement has not been linked to CD and later APD. In contrast, in undersocialized persons, CD has been linked to APD, and these children are generally identified at an early age (Hinshaw & Lee, 2003). Under-socialized CD involves assaultive, aggressive behaviors that are generally committed alone (Quay, 1987). These children are at the highest risk for developing APD in adulthood (Semrud-Clikeman & Ellison, 2009). Moreover, in a large epidemiological study, 90% of youths diagnosed with CD were found to have previously met criteria for ODD while the vast majority of children with ODD (90%) did not progress to CD or APD (Hinshaw, 2002).

The transition from CD in adolescence to APD in adulthood has also been studied. The basic findings indicate that adults with APD almost always met CD criteria early in development, but only a small minority of youth with CD go on to meet criteria for APD (Zoccolillo, 1992). The most important indicators as to whether a diagnosis of CD leads to APD appear to be early onset and persistence of aggressive and antisocial behaviors, particularly for boys (Robins, 1986). For girls, CD is a strong predictor for internalizing disorders and antisocial behaviors.

Genetic Influences

One question that is frequently raised is the heritability of APD. Heritability refers to genetic influences on the individual that can be modified and influenced significantly by the environment of the individual (Hinshaw, 1999). Findings have indicated that heritability is strongest for ADHD

symptomatology, moderate for APD, and small for less severe forms of APD (Edelbrock, Rende, Plomin, & Thompson, 1995), with the strongest heritability for childhood onset of CD and APD (Taylor, Iacono, & McGue, 2000). Moreover, the heritability of APD seems to increase with age, with adolescents showing stronger genetic contributions to aggression, whereas for children such contributions are small (Jacobson, Prescott, & Kendler, 2002). It has also been strongly suggested that for persistent CD and APD, the heritable effects are transactional with the environment such that dysfunctional families, aberrant parenting and socialization practices, peer rejection, and academic failure contribute to more severe APD (Lahey, Waldman, & McBurnett, 1999). The influences most affected by genes are temperamental irritability, disinhibition, and sensation seeking, which are also mediated by the environment (Maccoby, 2000).

Psychobiological Influences

Research utilizing neuroimaging is just beginning, and the findings should be viewed with caution. In summary, findings indicate that adolescents diagnosed with early-onset CD with aggression and under-socialized behavior patterns have been found to show low cortical arousal and autonomic reactivity, which has also been found with adults with APD (Quay, 1993). In contrast, adolescents with late onset CD and who are nonaggressive show arousal and reactivity indices that are elevated compared to normal controls (Lahey, McBurnett, Loeber, & Hart, 1995). These findings suggest that the system that involves behavioral activation and reward is stronger than the behavioral inhibition system in youths with CD who are under-socialized and aggressive (Lahey et al., 1995; Quay, 1993). It has also been suggested that genetic abnormalities found in persons with psychopathy may be related to a deficient neural system where the amygdala does not form the connections between punishment and behavior (Blair, 2006). This dissociation would result in people with CD or APD not learning to avoid actions that harm others and not responding to punishment when such acts are committed. Further study is needed to more fully understand what neural networks may be involved or aberrant in these patients.

Comorbidity of CD/ODD/APD and ADHD

Studies have found that similar risk factors are present in the history of children and adults with externalizing disorders that include high sensation-seeking behaviors, low avoidance of dangerous situations, and a history of chaotic and disruptive family environments including parental alcoholism, marital conflict, and child abuse/neglect (Kuperman, Schlosser, Lidral, & Reich, 1999). Similarly, conduct problems present in childhood have been found to relate to later problems with aggressive behavior, delinquency, and substance abuse in adolescence and young adulthood (Barkley & Murphy, 2010; Biederman, Faraone, & Spencer, 1993). It has been suggested that ADHD can be best represented on a continuum with ADHD plus CD being the most severe form of the disorder, ADHD with ODD an intermediate form, and ADHD without comorbidity the least severe form (Biederman, Newcorn, & Sprich, 1991).

Subsequent studies have suggested that a common vulnerability is present between hyperactive and antisocial behaviors. Using structural equation modeling with 206 families, Patterson, DeGarmo, and Knutson (2000) concluded that disruptive parental discipline resulted in hyperactivity and antisocial behaviors. They also concluded that multiple disorders are more severe than single disorders and that genetic and environmental aspects contribute to such comorbidity.

Twin studies have sought to further understand the variance present in ADHD, CD, and ODD. Structural equation modeling using monozygotic and dizygotic twin pairs has found significant genetic contributions to disruptive behaviors with each disorder due to unique genetic factors (Nadder, Silberg, Eaves, & Maes, 1998; Silberg et al., 1996). To more fully explore the relation between genetic and environmental factors, Burt and colleagues (2001) examined the correlations among genetic, shared environment, and non-shared environmental components in CD, ADHD, and ODD in dizygotic and monozygotic twin pairs. Findings indicated that CD is primarily influenced by genetic factors, whereas ADHD and ODD are strongly influenced by genetic and shared environmental factors. The shared environmental factor that appeared to be most influential was the presence of psychosocial adversity within the family system. More specifically, parental discipline was found to influence the child's behavior

as well as to be influenced, in turn, by the child/adolescent. In this bidirectional schema, the parent influences the child/adolescent but is also influenced by the child/adolescent, thus, shared influences are important to understand for these three disorders. ADHD and conduct problems do continue into adulthood for some patients. These findings may shed light as to the relation of these disorders between childhood and adulthood.

Intermittent Explosive Disorder (IED)

Intermittent explosive disorder (IED) is a diagnosis applied to individuals who are repeatedly and impulsively aggressive and overreact to the situation at hand (APA, 2000). Although IED was initially thought to be a relatively rare disorder, more recent studies have found the incidence to range around 6% of the population (Coccaro, Posternak, & Zimmerman, 2005). This disorder has been found to result in significant social and occupational impairment, and there is beginning evidence that there may be a generational transmission of this type of aggressive behavior (McCloskey, Berman, Nobelett, & Coccaro, 2006).

One of the issues for IED is the lack of specificity of the symptoms. *DSM IV-TR* excludes disorders that may be similar to IED (i.e., bipolar disorder, APD, ADHD, CD). There is no guideline as to how frequent the aggressive behaviors must be or how severe (Coccaro, 2003). A diagnosis of IED requires several discrete episodes of aggressiveness that result in assault on a person or property destruction, that the aggression be out of proportion to the triggering situation, and that another diagnosis would account for the symptoms such as APD, borderline personality disorder, CD, or ADHD. *DSM-IV-TR* does not require the aggression to be impulsive or explosive. Some have suggested that the criteria should include verbal aggression as well as specifying that the aggressive frequency occurs two or more times a week for at least a month and be impulsive in nature (Coccaro, Kavoussi, Berman, & Lish, 1998; McCloskey et al., 2006). These criteria, referred to as research criteria, found that participants identified by the research criteria showed more behavioral aggression than those diagnosed solely by *DSM IV-TR*.

Biological Basis for IED

Findings have implicated the serotonin system for IED with selective serotonin reuptake inhibitors (SSRI) being found to reduce aggression in adults with IED (Coccaro & Kavoussi, 1997). There have been few studies of children with IED and no published clinical trials on adults as to the efficacy of SSRIs. Whereas cognitive behavioral treatments (CBT) have been found to be helpful for people with anger issues (DiGuisseppe & Tafrate, 2003), the intensity of the anger seen in IED has been suggested to be similar to that of abusive spouses whose response to CBT has been less efficacious (Babcock, Green, & Robie, 2004). The use of manualized and multi-component cognitive–behavioral therapy was found to improve anger control for patients with IED compared to wait-list subjects using both small group and individual treatment settings (McCloskey, Noblett, Deffenbacher, Gollan, & Coccaro, 2008). Although a reduction in anger as well as aggressive behavior was found in these patients, the participants reported that they continued to be highly reactive and to respond quickly to provocation. Thus, the CBT did help to improve the control, but the tendencies continued to be strong and difficult to manage. One might wonder if CBT in conjunction with medication may be more successful in working with these patients.

Some studies have evaluated the similarity of bipolar disorder in adolescents and IED. A number of symptoms overlap between the two disorders, particularly in disinhibition and aggression. To study whether there are biological similarities between these two disorders, Davanzo and colleagues (2003) used magnetic resonance spectroscopy with adolescents with bipolar disorder or IED. The patients with bipolar disorder showed differences in the anterior cingulate cortex compared to those with IED or controls. These findings were interpreted to suggest that medication for mood may assist children and adolescents with bipolar disorder more effectively than those with IED and that these disorders, while symptomatically similar, are biologically different.

Electroencephalogram (EEG) and evoked response potential (ERP) findings suggest an abnormality in the positive wave seen at 100 milliseconds (P100). Children and adolescents with a history of strong aggressive and explosive behaviors were found to show a very pronounced

P100 compared to controls (Bars, Hegrend, Simpson, & Munger, 2001). This marker for aggressive and explosive behavior may be related to a deficit in the descending inhibitory pathway that allows one to modulate responsivity to sensory input. If this inhibitory system is faulty, it may explain the hair-trigger responses frequently seen in children and adults with IED.

Summary

The empirical evidence for the lifespan of a specific disorder is inconsistent across diagnoses. For example, no studies were located that discussed differences that may be present between adults and children/adolescents in the expression of IED. Studies of IED have been focused on the impulsive aggressiveness seen as well as defining this disorder. Empirical support for IED is present, but the overlap of IED with bipolar disorder in childhood as well as CD makes it difficult to determine what separates these disorders. Larger epidemiological studies that evaluate the background of IED, risk factors, and how the disorder may evolve with development would be very helpful. Neuroimaging as well as ERP studies targeting adolescents and adults with IED and comparing to people diagnosed with bipolar or borderline personality disorder may also serve to elucidate what differences, if any, exist neurologically between these frequently confused disorders.

For ADHD, there are fewer differences between children and adults with ADHD than would be expected. Neuropsychological and neuroimaging findings do not suggest major differences between the ages. Executive functioning may more negatively impact occupational functioning for adults with ADHD. Women appear to be more likely to be identified in adolescence or adulthood compared to men. Comorbidity issues also appear to differ for the genders, with men showing more externalizing behaviors and women showing more problems with dysthymia and borderline personality disorder. Studies using neuroimaging of adult women with ADHD have not been completed at this time, and most of the neuroimaging findings across the ages concentrate on boys and men. This area of research is relatively unexplored, and further study is certainly strongly recommended.

Finally, CD and ODD in early childhood paired with aggression and solo acts of cruelty appear to be the strongest predictors of later APD. Heritability of APD is strong for those children who show early difficulties with irritable temperament, lack of rhythmicity, and aggression, and who also live in families where there is a great deal of marital discord and parental psychopathy, particularly in the fathers. The presence of CD or ODD in childhood has not been found to be predisposing for the majority of adolescents for APD. However, adolescents with CD who also have violent tendencies that appeared very early and involved cruelty to others and disregard for people's rights are highly likely to show significant problems in adulthood and qualify for a diagnosis of APD. Moreover, the causal pathway for APD in adulthood is likely complex and involves interplay among biology, psychology, sociology, and culture and complicates our ability to develop interventions as well as to identify these children at the earliest ages when interventions may be most helpful.

The change in psychiatric and psychological functioning from childhood to adulthood is inextricably linked to changes in brain maturation and function. It may well be that myelination and gray matter development over time changes how the disorder is manifested. Early studies are beginning to demonstrate, at least for ADHD, that brain maturation may be delayed for children and adolescents with ADHD (Shaw et al., 2007). For some of these patients, this delayed maturation of white matter may be related to improvement in functioning when the white matter development approaches that of clients without ADHD. For other patients, this delayed maturation may continue throughout adulthood, thus explaining why some clients require medication until adolescence whereas others require medication throughout the lifespan. Similar studies have not been conducted with patients with APD or with IED and such avenues should be further explored.

INTERNALIZING DISORDERS

Among the most common forms of mental illness, the internalizing disorders comprise mood and anxiety psychopathologies. In the adult population, anxiety has been estimated to be present in nearly 20% of the

population, with mood disorders such as depression at about 9.5% (2005). Many children experience an episode of mood-related symptoms at some time, but these are often transient and may not necessarily persist into adulthood. However, because the adult symptoms of depression and anxiety can be so debilitating, identifying and understanding the risks and protective factors in childhood internalizing disorders is an area of considerable research attention.

One of the most difficult aspects of diagnosis and treatment is the overlap and co-occurrence of the various internalizing disorders across the lifespan. A developmental trend with certain diagnoses tending to be observed at different ages within the population has been observed. Anxiety is usually the earliest diagnosis observed, followed by externalizing disorders, dysthymic disorder, major depressive disorder (MDD), and substance abuse (Kovacs & Devlin, 1998). Longitudinal studies have shown the strong relationship between internalizing disorders in childhood and subsequent adult internalizing pathologies (Keenan, Feng, Hipwell, & Klostermann, 2009; Reef, Diamantopoulou, Meurs, Verhulst, & Ende, 2009), although some studies have found that disruptive disorders in childhood also predict mood disorders in adults (Kosterman et al., 2010). However, when coexisting internalizing symptoms are considered, it appears that externalizing behaviors alone, without early emergence of comorbid internalizing symptoms, are unlikely to lead to an adult mood disorder (Reef et al., 2009). Thus, internalizing disorders in childhood appear to be a good predictor of internalizing disorders in adulthood. However, the nature of the disorders may shift across the lifespan both epidemiologically within the community and along a heterotypic trajectory within each individual.

Anxiety Disorders

Nine *DSM-IV-TR* disorders sharing core symptoms related to anxiety are diagnosed in children. One of these, separation anxiety disorder (SAD), is regarded as specific to childhood onset, whereas panic disorder, agoraphobia, generalized anxiety disorder (GAD), social phobia, specific phobia, obsessive-compulsive disorder (OCD), posttraumatic stress disorder

(PTSD) and acute stress disorder, are considered to be diagnosable throughout the lifespan (Albano, Chorpita, & Barlow, 2003; APA, 2000). Even though SAD is the one specific childhood-onset diagnosis, it has been found to be present in about 6% of adults, with about 20% of these cases having onset in adulthood (Shear, Jin, Ruscio, Walters, & Kessler, 2006). Thus, anxiety disorders of all types appear to be present across ages.

Although fears and worries are naturally a part of childhood, anxiety is the most prevalent form of childhood psychopathology. It moves from normative childhood fear to a disorder when the daily functioning of the child is disturbed by a response that is consistently out of proportion to a presumed threat. Normative development includes an escalation of anxiety, particularly to strangers, and fear of separation that usually begins to resolve at about 2 years of age, clearing for most by about age 6. Such transient symptoms of anxiety may also be experienced due to life events without progressing to functional impairment, and in the majority of cases, this is so. But for some, anxiety persists to the level of dysfunction and precedes poor adult functioning. For the 15% of children for whom fears persist, physiological symptoms including high heart rate, elevated startle responses, and high levels of cortisol may foreshadow a progression toward an anxiety disorder later in childhood (Kagan, Reznick, & Snidman, 1987).

Prevalence estimates of all types of anxiety in school-aged children and adolescents vary with age. In a longitudinal study of a community population comprising 6,674 persons aged 10–16 (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003), the 3-month prevalence rate for any anxiety disorder was found to be highest in 10-year-olds (4.6%). As expected, SAD was generally diagnosed early and was largely extinguished by age 16. Simple phobia followed a similar pattern, with greater numbers at younger ages and tapering off with age. Thus, it may be expected that anxious symptoms involving difficulty going to school and fears regarding specific stimuli, such as thunder, recede as children mature. In contrast, difficulty with social situations and more generalized worry as seen in unspecified social phobia and GAD seem to be more consistent across school ages and into young adulthood. There appears, as well, to be a general progression involving a decrease of anxiety symptoms from later childhood to early adolescence followed by a slight increase in symptoms

from middle to late adolescence (Costello et al., 2003; Van Oort, Greaves-Lord, Verhulst, Ormel, & Huizink, 2009).

In adults, anxiety disorders may take the same or different form if child anxiety preceded the adult diagnosis. For example, panic disorder is rarely seen in children (Merikangas, 2005) but is usually preceded by other types of anxiety earlier in life (Eaton et al., 1998), especially separation anxiety (Costello, Egger, & Angold, 2005; Klein, 1995). GAD in childhood is a more stable predictor of anxiety in adults, but it is also a predictor of depression (Keenan et al., 2009). In adulthood, anxiety has been found to be related to having a disability (Brenes et al., 2005), lower levels of education (Dahl & Dahl, 2010), and lower levels of cognitive performance (Gerstorf, Siedlecki, Tucker-Drob, & Salthouse, 2009).

In young and middle adulthood, GAD is the most likely diagnosis, but in a large epidemiological study, panic disorder was more common in those 65 years and older (King-Kallimanis, Gum, & Kohn, 2009). In general, anxiety disorders are less common late in life and onset late in life is not frequent (Wolitzky-Taylor, Castriotta, Lenze, Stanley, & Craske, 2009). In other words, anxiety is not likely in late adulthood if it was not present earlier in life. However, despite risk factors such as living alone and ill physical health, anxiety in elder persons is often overlooked as a mental health condition (Brenes et al., 2005; Wolitzky-Taylor et al., 2009).

Gender

Females are twice as likely as males to be diagnosed with anxiety disorders (Leach, Christensen, Mackinnon, Windsor, & Butterworth, 2008), although this influence across the lifespan is variable. Gender has been found to be a predictor of subsequent anxiety diagnoses in childhood (Ferdinand & Verhulst, 1995), but it appears to have less influence in predicting anxiety in adolescence (Essau, Conradt, & Petermann, 2002) and adulthood (Leach et al., 2008). Likewise, the prevalence rates for girls in early childhood are much higher, but this difference narrows approaching adolescence (Howell, Brawman-Mintzer, Monnier, & Yonkers, 2002). For children and adults, the rates of recovery are not similar for males and females (Howell et al., 2002). One study found that men and women have different responses to

SSRIs. Women showed a poorer response to SSRIs when baseline severity and age of onset are accounted for (Simon et al., 2006).

Neuropsychological Presentation

Results of neuropsychological functioning in children and adults are not consistent. Some of these differences might be attributed to changes in the way anxiety disorders have been diagnosed over the years, specifically the transition from *DSM-III* to *DSM-IV-TR*. Additionally, the subtype of anxiety disorder may be important to consider along with severity, comorbidity, and age of onset. Unlike the more robust literature on depression, anxiety has been studied less. OCD is the most studied disorder (Airaksinen, Larsson, & Forsell, 2005), with findings centering on deficits in executive functioning, visual memory, attention, and processing speed in young adults. Episodic (neutral word) memory and Trails B deficits have been observed in a small study of adults with OCD and panic disorder with and without agoraphobia, whereas verbal fluency and perceptual-motor speed were intact (Airaksinen et al., 2005). Panic disorder has been associated with cognitive deficits (Lucas, Telch, & Bigler, 1991), but such deficits have been found to be associated with comorbid depression (Kaplan et al., 2006). GAD in adults has not been associated with cognitive impairment (Airaksinen et al., 2005), but this finding is based on only 7 subjects. In children, overanxious anxiety disorder, a *DSM-III* diagnosis related to the *DSM-IV-TR* GAD, was found to be associated with poorer performance on a word-learning task, but no differences were found on a visual-motor reproduction and memory task (Toren et al., 2000).

Neural Correlates

Evidence has mounted suggesting that anxiety is related to an attentional bias toward stimuli that are perceived to be threatening (Eysenck, Derakshan, Santos, & Calvo, 2007). The amygdalar–prefrontal circuitry is hypothesized as central to such difficulties, including managing attention to threat and the interpretation of ambiguous stimuli (Bishop, 2007). Bishop

(2009) demonstrated that higher anxiety was associated with poor functioning in the dorso-lateral-prefrontal-cortex (DLPFC) circuitry associated with controlling one's attention in response to conflict. Notably, this finding was related to trait rather than state anxiety, suggesting a relation to a stable vulnerability rather than to transient moods. Dysregulation in activation of the anterior cingulate cortex and DLPFC have been associated with sentences that illicit worry in participants with GAD compared to normal controls. The GAD participants showed persistent activation of these areas during resting states *after* the stimuli were removed (Paulesu et al., 2010). In social anxiety disorder, the amygdala has been consistently implicated as dysregulated, and decreased activation has been observed following treatment (Freitas-Ferrari et al., 2010). No imaging studies in children were found, but one EEG study did suggest differences in frontal activation in children with anxiety disorders (Baving, Laucht, & Schmidt, 2002).

Comorbidity of Anxiety and Depression

Young children who are diagnosed with an anxiety disorder are most likely to have a co-occurring externalizing disorder, whereas older children and adults with anxiety are more likely to have co-occurring mood disorders. There has been the suggestion that anxiety and depression may be two phases of the same underlying pathology (Kessler et al., 2008; Williamson, Forbes, Dahl, & Ryan, 2005). Evidence for this comes from studies indicating that depression occurring in childhood is most often preceded by anxiety, whereas adults with a first depressive episode are less likely to have a comorbid anxiety disorder (Kovacs, Gatsonia, Paulauskas, & Richards, 1980; Parker et al., 1999). Data from the National Comorbidity Survey indicate that onset of GAD is a predictor for depression, but the reverse is not true (Kessler et al., 2008). Twin studies have suggested that there is a genetic overlap (Silberg et al., 1996) and the risk association between anxiety and depression appears to be greater for girls (Hammen & Rudolph, 2003). Although the genetic and neural mechanisms of both anxiety and depression have not been fully determined, there is reason to believe that the presence of one may include a high likelihood of the other.

Moreover, those with both disorders are expected to have more severe symptoms resulting in greater functional impairment and a longer course of illness.

Mood Disorders

Twenty years ago, depression was just beginning to be recognized as a disorder that could occur in children. Since then, considerable research has been focused on the onset and trajectory of depression from early childhood into late adulthood. Depression and its many diagnostic subtypes do occur both in children and adults, although the presentation varies across the lifespan. The diagnosis of depressive disorders in children is particularly difficult because downward extension of the adult *DSM-IV-TR* diagnoses do not adequately capture symptoms occurring early in life (Hammen & Rudolph, 2003).

The *DSM-IV-TR* recognizes that the presentation of depressive symptoms in children differs from adults only in that children may appear irritable rather than dysthymic (APA, 2000). In children, comorbidity with externalizing disorders is frequent. Because the children may appear disruptive and behaviorally challenged, the presence of depression may be overlooked. Younger children are less likely than adolescents to report subjective dysphoria, but may show a depressed appearance and have more somatic symptoms (Hammen & Rudolph, 2003). Depressed adolescents are likely to sleep more than depressed children, whereas adults are more likely to have difficulty sleeping. Comorbid anxiety and behavioral disorders are common in both children and adolescents, but young children are more likely to have separation anxiety, whereas adolescents are more likely to have an eating or substance abuse problem (Hammen & Rudolph, 2003).

The lifetime rate of depression disorders in young children is very low, with dysthymia more common than MDD. The most commonly occurring diagnosis in young children is Depression Not Otherwise Specified (NOS; Costello et al., 2003). Depression rates rise approaching adolescence, but are still lower than those for adults. Results from the National Comorbidity Study indicated a lifetime prevalence of MDD at 14% for adolescents aged 15–18 years (Kessler, Avenevoli, & Ries Merikangas, 2001). Major

depression appears to peak in early adulthood and lessen with age. Rates for respondents to the National Comorbidity Study-Replication who were aged ≥ 65 years had the lowest rate of MDD at 9.8 for lifetime and 2.6 for 12-month occurrences (Kessler et al., 2010). Similar results were observed in a large European epidemiological study (Angst et al., 2002).

The majority of young children who have experienced depression do not progress to having adult depressive disorders (Hammen & Rudolph, 2003). Recurring episodes along with a family history of depression increase the chances of continuity, and the progression toward a depressive disorder in adulthood may begin with behavioral problems (Mason et al., 2004) or anxiety as well (Beesdo, Pine, Lieb, & Wittchen, 2010). Retrospectively, having a major depressive episode by the age of 21 in young adults has been predicted by depressive and anxiety symptoms in early childhood (Reinherz, Giaconia, Hauf, Wasserman, & Paradis, 2000).

Depression in pre-pubescence does not seem to predict depression in adulthood very well, although it may predict a variety of other disorders, such as behavioral and conduct problems (Hammen & Rudolph, 2003). In contrast, depression occurring in adolescence does seem to have consistent continuity toward adult recurrence. One large clinical study found that nearly two-thirds of adolescents with symptoms of depression experienced an episode of major depression in early adulthood (Hammen & Rudolph, 2003). Depression in childhood and adolescence is also related to other adult disorders, including substance abuse, personality disorders, social problems (McClintock, Husain, Greer, & Cullum, 2010), and poor occupational and economic outcomes (Hammen & Rudolph, 2003). In older adults, depression appears to be less influenced by physical disability than for younger ages. Although many physical problems increase with age, the incidence of MMD significantly decreases with age across adulthood (Kessler et al., 2010). It has been hypothesized that some elderly depression may be related to vascular changes in the frontal and limbic systems that regulate norepinephrine and serotonin (McClintock et al., 2010).

The developmental trajectory of the manic and bipolar depressive diagnoses in children is less well understood (Kessler et al., 2001). Most of the prevalence data on child and adolescent mania has been with clinical samples. Estimates of childhood bipolar I, bipolar II and cyclothymia have typically been at 1% or lower (Kessler et al., 2001). In a large community

sample, the 3-month estimate of any type of bipolar disorder among children aged 9–16 years of age was less than 0.1% (Costello et al., 2003). However, much higher numbers of children and adolescents, 5–11%, report manic-like symptoms lasting for only a few hours or days, which is below the threshold for bipolar I (Carlson & Kelly, 1988). An additional confusion is that symptoms of mania in pre-pubescent children may be difficult to differentiate from symptoms of ADHD (Carlson, 1998; Kessler et al., 2001). Thus, this is an area for which more research is needed.

Gender

Before the age of 10, large differences in the occurrence of depression between males and females is not observed (Mazza, Fleming, Abbott, Haggerty, & Catalano, 2010; Whiffen & Demidenko, 2006). In adolescence gender becomes a strong predictor of depression, with girls more likely to experience depression than boys. Two studies of gender influence on the trajectory of depression found differences between genders on the type of depression seen. Heath and Camarena (2002) observed that more than twice as many boys as girls were more likely to have a single experience of a high level of depression and a subsequent decrease in symptoms. In contrast, nearly three times as many girls as boys experienced increasing depressive symptoms over the 3 years of the study. In a community sample following more than 900 children from the second grade to the eighth grade, Mazza and colleagues (2010) found similar results, with depressive symptoms arising relatively equally between girls and boys in early childhood, but dropping below baseline for boys in adolescence and dropping slightly for girls in early adolescence and then persisting.

It is commonly reported that, post-adolescence, females are twice as likely to experience depression as males (McClintock et al., 2010). The reasons for this difference are not well understood, but some suggest that, rather than a difference in the incidence of depressive symptoms, there is a significant difference in the way that depression is displayed. Men are more likely to engage in aggression and drinking compared to women, and men report fewer symptoms of depression (Brownhill, Wilhelm, Barclay, & Schmied, 2005). Moreover, in communities where drinking alcohol is less

tolerated (Egeland & Hostetter, 1983; Loewenthal, MacLeod, Cook, Lee, & Goldblatt, 2003), the gender gap closes. Thus, it may be that in adulthood, depression in men and women looks quite different.

Neuropsychological Presentation

Depression, particularly MDD, has been associated with reduced functioning in attention, concentration, memory, and processing speed. Chronic depression has been associated with higher levels of anxiety, substance abuse, personality disorders, somatic complaints, and poorer social functioning. The severity of a depressive episode has been found to be also related to higher levels of disability, which leaves open the question of whether severity or duration is more important to consider (McClintock et al., 2010).

Decreases in cognitive functioning, including mental flexibility, attention, working memory, and inhibition control, have been found to be associated with the recurring depression. However, there is evidence that after an episode of depression resolves, cognitive functioning does return to premorbid levels (McClintock et al., 2010). In children, depression has been associated with difficulty learning new material, which may in turn be related to attentional deficits (Semrud-Clikeman & Ellison, 2007). Like adults, children may present with slower reaction speed on timed tests and difficulty with work completion and memory in both verbal and visual tasks (McClintock et al., 2010), highlighting the importance of looking for depression when children present with a variety of school-based and behavioral problems (Baron, 2004; Semrud-Clikeman & Ellison, 2007).

Cognitive impairments among depressed patients with psychotic features are more severe than for unipolar depressed patients without psychosis, but less severe than is found in schizophrenia (Hill, Keshavan, Thase, & Sweeney, 2004). Thus, studies that did not differentiate between those with psychosis and those without may overestimate the degree of neuropsychological impairment associated with unipolar depression (Hill et al., 2009). Bipolar depression may also infer more severe neuropsychological deficits (McClintock et al., 2010), though less research has been completed with this group.

Neural Correlates

In a meta-analysis of brain volume differences in MDD, reductions were seen in areas of the brain that are involved in emotional processing and regulation of stress (Koolschijn, van Haren, Lensvelt-Mulders, Pol, & Kahn, 2009). The largest differences were seen in the anterior cingulate and the orbitofrontal cortex. Smaller but significant differences in the prefrontal cortex, hippocampus, putamen, and caudate were additionally seen in the preponderance of studies. Positron emission tomography (PET) studies and functional magnetic resonance imaging (fMRI) studies have also found differences in the anterior cingulate and frontal cortex (McClintock et al., 2010), suggesting that the volumetric differences in persons with MDD may be related to differences in functioning as well.

The areas implicated in these findings are related to the regulation of stress. The anterior cingulate and the pre- and orbitofrontal cortices are involved in providing a cognitive override to the body's initial limbic system response to negative stimuli. The hypothalamic-pituitary-adrenal (HPA) axis is also involved in MDD. Increased levels of cortisol are present in patients during presentation of MDD, in remission, and even in 2-week-old infants born to parents with bipolar disorder (Ellenbogen, Santo, Linnen, Walker, & Hodgins, 2010). Genetic susceptibility to depression has been suggested by the association of genes known to regulate the availability of serotonin in the brain (Koolschijn et al., 2009; McClintock et al., 2010). In one study involving geriatric patients, frontal volumes of depressed patients medicated with antidepressants had greater frontal volumes than those who were medication-naïve (Laveretsky et al., 2005), suggesting that medications may confer some protection against frontal lobe loss in this population.

SUMMARY

The internalizing disorders present in a variety of ways across the lifespan. Most importantly, research has shown that having an episode of anxiety or depression in early childhood doesn't necessarily predict mental illness later in life. However, most adults with the most recurring internalizing disorders

do have onset in childhood. At this time, there is no reliable indication of which children are likely to progress; thus, early intervention is important not only to relieve symptoms for children, but also to confer resilience on those for whom progression is likely. Adolescence appears to be an important time in the development of lasting internalizing disorders, especially depression, because presence of depression in adolescence is more indicative of a possible long-term problem. In adulthood, men may show different symptoms than women regarding depression; thus, it is important to look for underlying depression in men for whom externalizing behaviors and substance abuse are present. Our eldest population experiences anxiety, especially panic disorder, and depression, though their symptoms may be overlooked and erroneously blamed on failing health. Vascular depression may be a possibility for older persons presenting with symptoms.

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