Not much is known about neurodevelopmental factors involved in the pathophysiology of child and adolescent depression. Neuroendocrine and sleep EEG research paradigms have been used in the majority of published studies examining the neurobiological correlates of early-onset depression. Although these procedures have their merits, the “window to the brain” afforded by these methods is extremely limited. Emerging neuroimaging technologies will provide a unique opportunity to investigate the brain mechanisms underlying child and adolescent depression. To date, however, the application of these techniques in the study of early-onset depression is in its infancy.

The existence of major depressive disorder (MDD) in children and adolescents was controversial until relatively recently, and the diagnosis of MDD was not included in any child psychiatric text prior to the late 1970s (Puig-Antich & Gittleman, 1982). Research over the past two decades, however, has clearly demonstrated that children are capable of experiencing episodes of depression which meet standard DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th ed.) criteria for MDD (Birmaher et al., 1996c; Ryan et al., 1987). In addition, MDD in children and adolescents is common, recurrent, and associated with significant morbidity and mortality (Birmaher et al., 1996c). Epidemiological studies estimate that the prevalence of depression is 2 percent in children (Kashani et al., 1983) and 5–8 percent in adolescents (Lewinsohn, Clarke, Seeley & Rohde, 1994). Early-onset episodes of depression are associated with significant and persistent functional impairment (Puig-Antich et al., 1993), and within five years of the onset of MDD, 70 percent of clinically referred depressed children and adolescents will experience a recurrence (Kovacs et al., 1984; Rao et al., 1995). In addition, longitudinal follow-up studies estimate that as many as 5–10 percent of depressed adolescents will complete suicide within fifteen years of their initial episode of MDD (Rao, Weissman, Martin, & Hammond, 1993; Weissman et al., 1999).

Despite similarities in the clinical picture and longitudinal course of MDD in children, adolescents, and adults, there are notable differences in the neurobiological...
correlates and treatment response of depressed patients in these different age cohorts that warrant careful consideration. Most notably, depressed children and adolescents do not show evidence of hypercortisolemia as is frequently reported in adults (Kaufman & Ryan, 1999; Ryan & Dahl, 1993), and depressed children and adolescents fail to respond to tricyclic antidepressants (Hazell, O’Connell, Heathcote, Robertson, & Henry, 1995; Keller et al., in press).

These and other findings reviewed in this chapter make it unclear whether or not child-, adolescent-, and adult-onset depression are the same or distinct disorders. In this chapter we review extant data on the neurobiological correlates and treatment response of depressed children and adolescents, and highlight differences in research findings across the lifecycle. Alternate explanations to account for the discrepancies are delineated, and clinical and preclinical studies that provide support for these alternate explanations are discussed. Directions for future research are outlined, with emphasis placed on the role of utilizing neuroimaging approaches. The application of these techniques, and the cross fertilization of clinical and basic research strategies will help to elucidate the neurodevelopmental processes involved in the pathophysiology of child and adolescent depression (Cicchetti & Cannon, 1999), and help to determine if child-, adolescent-, and adult-onset depression are one and the same disorder.

The data reviewed in this chapter are very consistent with the principles of developmental psychopathology emphasized throughout this text (Cicchetti & Rogosch, 1996). For example, the field of developmental psychopathology emphasizes the mutual interplay between normality and psychopathology. This concept is highlighted in the discussion of the constraints in our knowledge about the pathophysiology of early-onset affective disorders which is due to the limits in our understandings of the typical development of the neural substrates underlying the affective and cognitive processes that are disturbed in depressed children. The concept equifinality is delineated repeatedly as well, since there are multiple pathways to the etiology of child and adolescent depression. Multifinality is also stressed, as there are a range of outcomes associated with early-onset affective disorders (e.g., sustained recovery, recurrence, new onset bipolar disorder). Preliminary data suggest that the neurobiology of depression in children and adolescents with different etiological pathways and developmental trajectories is distinct. A central theme reiterated throughout this chapter is the concept of heterogeneity, with careful attention to the pathways to early onset affective disorders, and the outcomes of depressed children, recommended in attempting to uncover relevant subtypes of child- and adolescent-onset mood disorders, and the underlying pathophysiology associated with each.

**NEUROBIOLOGICAL CORRELATES AND TREATMENT RESPONSE OF DEPRESSION ACROSS THE LIFECYCLE**

Although there are significant differences in the neurobiological correlates and treatment response of depression in children, adolescents, and adults, there are also a few similarities. In this chapter, the similarities are discussed first, followed by a discussion of the discrepancies in research findings across the lifecycle. In some of the research where inconsistencies have been reported, children and adolescents differ from one another, and only one cohort is similar to adults, with the group similar to adults changing as the child matures. Similarities, children and adolescents (For a more detailed review, see Diaz, 2001.)

### Similar Findings

**Dexamethasone Suppression Test (DST)** has been more extensively used for the assessment of the HPA axis in children and adolescents than any other test. This test has been used to investigate the role of the HPA axis in the pathophysiology of depression in children and adolescents (Kaufman & Charney, 1995). Results have been mixed, with some studies suggesting that the HPA axis is intact in children and adolescents with depression, while other studies have found evidence of HPA axis hyperactivity. However, a recent meta-analysis of DST studies conducted in child and adolescent depression suggests that DST non-suppression is more commonly observed in depressed children and adolescents (Kaufman & Charney, 1995).

<table>
<thead>
<tr>
<th>Measure</th>
<th>DST (% Non-suppression)</th>
<th>24-hour Basal Cortisol</th>
<th>Nighttime Cortisol</th>
<th>ACTH post-CRH</th>
<th>Replicability Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Replicability Code</td>
<td>+/- = Inconsistent finding</td>
<td>+ = One controlled study</td>
<td>++ = Replicated finding</td>
<td>-- = Uncertain replicability</td>
<td></td>
</tr>
</tbody>
</table>

Table 19.1. HPA Axis Measures

As reviewed in this chapter, DST non-suppression may be a predictor of treatment response in children and adolescents with depression. In a recent study, DST non-suppression was positively correlated with treatment response to antidepressant medication (Kaufman & Charney, 1995). These findings suggest that DST non-suppression may be a useful clinical marker for predicting treatment response in children and adolescents with depression.

### References

to adults changing depending on the parameter under investigation. In other studies, children and adolescents are similar to each other, but both differ from adults. (For a more detailed review of the literature, readers are referred to Kaufman et al., 2001.)

### Similar Findings Reported across the Lifecycle

**Dexamethasone Suppression Test.** The Dexamethasone Suppression Test (DST) has been more extensively studied in children and adolescents than any other psychobiological parameter. Dexamethasone is a synthetic substance like cortisol that has been used to investigate the integrity of feedback mechanisms in the Hypothalamic-Pituitary-Adrenal (HPA) axis. Administration of dexamethasone normally causes the HPA axis to shut down and cortisol levels to decrease markedly. DST nonsuppression suggests that the normal feedback mechanisms in place to shut off the HPA axis are deficient. Approximately 50–70 percent of adults with depression are considered DST nonsuppressors, and have elevated cortisol secretion after dexamethasone administration. As reviewed by Dahl et al. (1992), there have been twenty-nine studies that conducted the DST in depressed children and adolescents. The results of these studies are summarized in Table 19.1. Half the studies were conducted with preadolescents, and the majority (79%) utilized inpatient samples. Approximately half of the published reports included twenty or more depressed children or adolescents, and a comparable number of controls. Averaging across studies, rates of nonsuppression were somewhat higher among children than adolescents, and about twice as high in subjects from inpatient settings than subjects from outpatient settings. An estimated 50–70 percent of depressed children and 40–60 percent of depressed adolescents were reported to be DST nonsuppressors. The rates of DST nonsuppression reported in these studies are more or less comparable to the rates reported in adult samples (APA, 1987; Carroll, 1982). Also consistent with the studies conducted in adults, higher rates of nonsuppression were reported in children and adolescents with endogenous symptoms.

### Table 19.1. HPA Axis Measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>Children</th>
<th>Adolescents</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Finding</td>
<td>Replicability</td>
<td>Finding</td>
</tr>
<tr>
<td>DST (% Non-suppression)</td>
<td>50–70% ++</td>
<td></td>
<td>40–60% ++</td>
</tr>
<tr>
<td>24-hour Basal Cortisol</td>
<td>Normal ++</td>
<td></td>
<td>Normal ++</td>
</tr>
<tr>
<td>Nighttime Cortisol</td>
<td>Elevated +/-</td>
<td></td>
<td>Elevated +/-</td>
</tr>
<tr>
<td>ACTH post-CRH</td>
<td>Normal +</td>
<td></td>
<td>Normal +</td>
</tr>
</tbody>
</table>

*Replicability Code:*

+/- = Inconsistent findings reported
+ = One controlled study
++ = Replicated finding
### Table 19.2. Double-Blind Placebo-Controlled Clinical Trials

<table>
<thead>
<tr>
<th></th>
<th>Children</th>
<th>Adolescents</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Effective</td>
<td>Effective</td>
<td>Effective ++</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>-</td>
<td>Effective ++</td>
<td>Effective ++</td>
</tr>
<tr>
<td>TCA Medications</td>
<td>Ineffective</td>
<td>Ineffective ++</td>
<td>Effective ++</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Ineffective</td>
<td>Ineffective ++</td>
<td>Effective ++</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Ineffective</td>
<td>Ineffective ++</td>
<td>Effective ++</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>Ineffective</td>
<td>Ineffective ++</td>
<td>Effective ++</td>
</tr>
<tr>
<td>Desipramine</td>
<td>-</td>
<td>Ineffective ++</td>
<td>Effective ++</td>
</tr>
</tbody>
</table>

**Replicability Code:**
- = One controlled study
++ = Replicated finding

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### Treatment with Selective Serotonin Reuptake Inhibitors

As mentioned in the introduction, tricyclic antidepressants (TCAs), which include the older antidepressant medications like imipramine, are no more effective than placebo in the treatment of child and adolescent depression (Keller et al., 2001). In contrast, selective serotonin reuptake inhibitors (SSRIs) preliminarily appear effective in this age cohort. Emslie and colleagues (1997) conducted a randomized, double-blind, placebo-controlled eight-week clinical trial of fluoxetine (e.g., Prozac) in ninety-six child and adolescent outpatients with nonpsychotic MDD. At the end of the study, using the intent to treat sample, significantly more patients who received fluoxetine were rated "much" or "very much" improved on the Clinical Global Impression Scale (56% versus 33%). After week five of treatment, there were also significant differences between the two groups on depression symptom severity ratings. The significant differences in depression severity ratings were maintained for each subsequent assessment point, with the gap between the two groups maximal at the conclusion of the study. In addition, equivalent response rates were found for patients twelve and younger (N = 48) and those thirteen and above (N = 48). These results are consistent with the findings of Keller and colleagues (2001) demonstrating efficacy of the SSRI paroxetine over placebo in the treatment of adolescent depression. (See Table 19.2 for a summary of double-blind pediatric placebo-controlled clinical trials.)

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### Table 19.3. EEG Sleep

<table>
<thead>
<tr>
<th>Measure</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>REM Latency</td>
<td>Normal</td>
</tr>
<tr>
<td>REM Density</td>
<td>Normal</td>
</tr>
<tr>
<td>Delta Sleep</td>
<td>Normal</td>
</tr>
</tbody>
</table>

**Replicability Code:**
+/- = Inconsistent findings
+ = One controlled study
++ = Replicated findings

---

### Research Questions

#### EEG Sleep

EEG sleep assessment various aspects of sleep that are among the better studied behaviors (e.g., Kupfer, 1987). The sleep latency, sleep continuity, and the rapid eye movement (REM) period, in particular, are well known. Alterations in EEG sleep are common in depression; however, inpatient versus outpatient differences (see Ryan & Dahl, 1990) and REM latency differences (see Rintelmann & Ziegler, 1987) have been reported. A number of studies, including our own (Table 19.3, no significant sleep differences found).

#### Growth Hormone

Growth hormone results similar to the sleep latency results in studies with larger sample sizes, may be better explained by blunted GH response to dexamethasone. When comparing early blunted GH response to the dexamethasone-induced hypogonadism produced by L-Dopa (Jense

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(Robbins, Alessi, Yanchyshyn, & Colfer, 1983), psychotic features (Freeman, Proznanski, Grossman, Buchsbaum, & Banegas, 1985), and a prior history of MDD (Klee & Garfinkel, 1984). In the one study that assayed dexamethasone levels (Birmaher et al., 1992), as expected, plasma dexamethasone levels correlated negatively with plasma cortisol levels. MDD and normal control subjects, however, did not differ in rates of dexamethasone metabolism.

---

### Neurobiology of Sleep

**EEG Sleep.** EEG sleep research assess various aspects of sleep that are among the better studied behaviors (e.g., Kupfer, 1987). The sleep latency, sleep continuity, and the rapid eye movement (REM) period, in particular, are well known. Alterations in EEG sleep are common in depression; however, inpatient versus outpatient differences (see Ryan & Dahl, 1990) and REM latency differences (see Rintelmann & Ziegler, 1987) have been reported. A number of studies, including our own (Table 19.3, no significant sleep differences found).

#### Growth Hormone

Growth hormone results similar to the sleep latency results in studies with larger sample sizes, may be better explained by blunted GH response to dexamethasone. When comparing early blunted GH response to the dexamethasone-induced hypogonadism produced by L-Dopa (Jense

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(Robbins, Alessi, Yanchyshyn, & Colfer, 1983), psychotic features (Freeman, Proznanski, Grossman, Buchsbaum, & Banegas, 1985), and a prior history of MDD (Klee & Garfinkel, 1984). In the one study that assayed dexamethasone levels (Birmaher et al., 1992), as expected, plasma dexamethasone levels correlated negatively with plasma cortisol levels. MDD and normal control subjects, however, did not differ in rates of dexamethasone metabolism.
Research Suggesting Children and Adolescents Differ from One Another

**EEG Sleep.** EEG sleep studies utilize electrodes to monitor changes in brain waves to assess various aspects of sleep architecture. EEG changes associated with MDD in adults are among the best-replicated findings in biological psychiatry (Reynolds, Gillen, & Kupfer, 1987). The most consistently reported sleep alterations include prolonged sleep latency, sleep continuity disturbances, reduced time until first rapid eye movement (REM) period, increased REM density, and decreased delta (Stage 3 and Stage 4) sleep. Alterations in EEG sleep measures consistent with findings reported in adults are more common in depressed adolescents than in depressed children, and more frequent in inpatient versus outpatient cohorts. As reviewed elsewhere (Kaufman & Ryan, 1999; Ryan & Dahl, 1993), six of the eight EEG sleep studies conducted with adolescents reported reduced REM latency, and four of the eight studies reported REM density differences (see Table 19.3). Of the studies conducted with children, only one reported REM latency differences and no other EEG sleep findings (Emslie, Rush, Weinberg, 1993). The remaining three studies conducted with this age group failed to detect differences between depressed and control children on any of the EEG sleep summary measures, despite inclusion of inpatients, ample sample size in two studies, and excellent methodology in all three studies (Dahl et al., 1991a; Puig-Antich et al., 1982; Young, Knowles, MacLean, Boag & McConville, 1982). As summarized in Table 19.3, no studies with children or adolescents have detected delta (Stage 3 and 4) sleep differences between depressed and control subjects.

**Growth Hormone Probes.** In contrast to the EEG sleep findings reviewed above, Growth Hormone (GH) probe studies with children have produced quite robust results similar to those reported in depressed adults, and predominantly negative results in studies with adolescents. Most studies with adolescents, however, had very small sample sizes, making conclusions in this area tentative. The results of studies examining GH probes in depressed children and adolescents are summarized in Table 19.4. When compared to normal controls, depressed children have been reported to have blunted GH response to clonidine (Jensen & Garfinkel, 1990; Meyer et al., 1991); insulin induced hypoglycemia (Meyer et al., 1991; Puig-Antich et al., 1984; Ryan et al., 1994); L-Dopa (Jensen & Garfinkel, 1990); and GH releasing hormone (Ryan et al., 1994).

---

### Table 19.3. EEG Sleep Parameters

<table>
<thead>
<tr>
<th>Measure</th>
<th>Children Finding</th>
<th>Adolescents Finding</th>
<th>Adults Finding</th>
<th>Replicability Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>REM Latency</td>
<td>Normal</td>
<td>Decreased</td>
<td>Decreased</td>
<td>++</td>
</tr>
<tr>
<td>REM Density</td>
<td>Normal</td>
<td>Increased</td>
<td>Increased</td>
<td>+/−</td>
</tr>
<tr>
<td>Delta Sleep</td>
<td>Normal</td>
<td>Normal</td>
<td>Decreased</td>
<td>++</td>
</tr>
</tbody>
</table>

*Relevability Code:*

+/- = Inconsistent findings published

+ = One controlled study

++ = Replicated finding
Table 19.4. GH Response to Several Neuroendocrine Probes

<table>
<thead>
<tr>
<th>Probe</th>
<th>Children Finding</th>
<th>Replicability</th>
<th>Adolescents Finding</th>
<th>Replicability</th>
<th>Adults Finding</th>
<th>Replicability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine</td>
<td>Blunted ++</td>
<td></td>
<td>Normal +</td>
<td></td>
<td>Blunted ++</td>
<td></td>
</tr>
<tr>
<td>ITT</td>
<td>Blunted ++</td>
<td></td>
<td>-</td>
<td>-</td>
<td>Blunted ++</td>
<td></td>
</tr>
<tr>
<td>L-Dopa</td>
<td>Blunted ++</td>
<td></td>
<td>Normal +</td>
<td></td>
<td>Blunted ++</td>
<td></td>
</tr>
<tr>
<td>GHRH</td>
<td>Blunted +</td>
<td></td>
<td>-</td>
<td>-</td>
<td>Blunted +/-</td>
<td></td>
</tr>
<tr>
<td>Dextroamphetamine</td>
<td>-</td>
<td></td>
<td>Normal +</td>
<td></td>
<td>Blunted +</td>
<td></td>
</tr>
<tr>
<td>Desipramine</td>
<td>-</td>
<td>-</td>
<td>Blunted +</td>
<td></td>
<td>Blunted ++</td>
<td></td>
</tr>
</tbody>
</table>

**Replicability Code:**
+/- = Inconsistent findings published  
+ = One controlled study  
++ = Replicated finding

In comparison, no overall group differences were found between depressed and control adolescents in GH secretion after administration of clonidine (Jensen & Garfinkel, 1990), L-Dopa (Jensen & Garfinkel, 1990), or Dextroamphetamine (Waterman et al., 1997). One study did report blunted GH secretion in adolescents after Desmethylimipramine administration; however, findings were restricted to depressed adolescents with suicide ideation and plan (Ryan et al., 1988).

**Children and Adolescents Similar to Each Other – Both Differ from Adults**

**Basal Cortisol.** Approximately one-half of depressed adults show evidence of cortisol hypersecretion (Schildkraut, Green, & Mooney, 1989). As stated above, classic cortisol hypersecretion as frequently reported in depressed adults is rare in depressed children and adolescents (see Table 19.1). To the extent that dysregulation of basal cortisol is found in subjects in this age range, it appears more subtle, and is manifest as alterations in the normal diurnal pattern of cortisol secretion. Rather than have increased twenty-four-hour cortisol secretion, depressed youngsters are more likely to only have elevated cortisol output close to the period of sleep onset, a time when the HPA axis is normally quiescent. Two studies examining cortisol secretion in depressed children failed to detect differences between depressed and normal control children on any of the summary measures of twenty-four-hour plasma cortisol samples, and hypercortisolemia was reported in less than 10 percent of the subjects (Birmaher et al., 1992; Puig-Antich et al., 1989a). In two other combined investigations of depressed children and adolescents that did not collect twenty-four-hour specimens, nighttime cortisol was reportedly increased in the depressed subjects (Goodyer et al., 1996; Kutcher et al., 1991). One other report similarly found increased cortisol secretion after sleep onset in depressed inpatient/suicidal adolescents, but no overall difference in twenty-four-hour mean cortisol secretion (Dahl et al., 1991b). This finding was not observed in another large study with predominantly outpatient adolescents (Dahl et al., 1989). Studies with adults with unipolar depression report a correlation between age and cortisol hypersecretion (Asnis et al., 1981; Halbreich, Asnis, Zumoff, Nathan & Shindledecker, 1984).

**Neurobiology of Depressed Adolescents**

This may account for the finding in younger depressed adolescent, and...

**Corticotropin Releasing Hormone (CRH)**

Corticotropin Releasing Hormone (CRH) in depressed patients has been extensively examined. CRH, or pressor, in depressed patients is elevated, and hypersecretion has been documented in young adults (Nemeroff, 1992). In comparison, no overall group differences were found between depressed and control adolescents in GH secretion after administration of clonidine (Jensen & Garfinkel, 1990), L-Dopa (Jensen & Garfinkel, 1990), or Dextroamphetamine (Waterman et al., 1997). One study did report blunted GH secretion in adolescents after Desmethylimipramine administration; however, findings were restricted to depressed adolescents with suicide ideation and plan (Ryan et al., 1988).

**Serotonin Probes**

After administration of serotonin agonists, depressed adults show increased post-challenge prolactin release. In contrast, most studies comparing prolactin secretion after fenfluramine, fluoxetine, or clomipramine in depressed and normal subjects have failed to find significant differences (Weidmer-Mikulski et al., 1991). In a study of adolescents with major depression, however, significantly increased prolactin secretion was observed in depressed adolescents compared to normal controls (Ryan et al., 1994). As in adults, several studies of depressed adolescents report a correlation between age and increased prolactin secretion (see Table 19.1). However, in contrast to adults, depressed adolescents show a significant decrease in prolactin secretion after clomipramine challenge relative to normal controls (Birmaher et al., 1992). This finding was not observed in another large study with predominantly outpatient adolescents (Dahl et al., 1989). Studies with adults with unipolar depression report a correlation between age and prolactin hypersecretion (Asnis et al., 1981; Halbreich, Asnis, Zumoff, Nathan & Shindledecker, 1984).

**Tricyclic Antidepressants (TCAs)**

TCAs do not appear to affect prolactin secretion in children or adolescents (Birmaher et al., 1992, in press). As in adults, depressed children and adolescents receiving TCAs do not show evidence of increased prolactin secretion.
Neurobiology of Child and Adolescent Depression

This may account for the observed differences in rates of hypercortisolemia in child, adolescent, and adult cohorts, but as discussed later, other factors may also contribute.

Corticotropin Releasing Hormone. The cortisol secretion abnormalities observed in depressed adults have been hypothesized to be due to alterations in endogenous Corticotropin Releasing Hormone (CRH) secretion (Gold et al., 1986; Plotsky, Owens, & Nemeroff, 1998). Consequently, several investigators have administered CRH to depressed patients. Adults with MDD have repeatedly been found to have elevated baseline cortisol and blunted ACTH secretion after CRH infusion (see Birmaher et al., 1996a for a review). In contrast, as summarized in Table 19.1, when CRH was administered to a cohort of thirty-four children with MDD and twenty-two normal controls, there were no overall group differences on any of the basal or post-CRH cortisol or ACTH measures (Birmaher et al., 1996a). Likewise, when CRH was administered to a group of twenty-one MDD and twenty normal control adolescents, no group differences were found on any measures (Dorn et al., 1996). Despite adequate sample size, these studies failed to replicate the pattern of results observed in adult depressed samples.

Serotonin Probes. Most studies using serotonergic probes in children (e.g., depressed and aggressive children) report findings that are opposite most studies conducted with adults. After administration of serotonin precursors and serotonin direct and indirect agonists, depressed adults have been reported to have blunted prolactin secretion, with post-challenge prolactin levels found to correlate negatively with dimensional measures of depression, aggression, and/or suicidality (Maes & Meltzer, 1995). In contrast, most studies conducted with either depressed or aggressive children report augmented prolactin secretion after serotonergic presynaptic probes in both diagnostic groups (e.g., fenfluramine, L-5-HTP), and a positive correlation between prolactin levels and dimensional clinical scales (Birmaher et al., 1997; Kaufman et al., 1998b; Pine et al., 1997; Ryan et al., 1992). In depressed adults, postsynaptic 5HT_{1B} serotonergic receptors have been hypothesized to be intact, given the absence of differences in prolactin secretion after m-Chlorophenylpiperazine (mCPP) administration (Anand et al., 1994). This finding in adults is likewise contradicted by a recent report of a small cohort of depressed adolescents who were found to have an augmented prolactin response after administration of the serotonergic postsynaptic probe mCPP (Ghaziuddin, King, Zaccagnini, & Weidmer-Mikhail, 1997). As one study with older adolescents did find depressed adolescents secreted significantly less prolactin after clorimpramine administration than age matched controls (Sallee et al., 1998), more work is needed to understand developmental influences on serotonergic indices. While children, adolescents, and adults all show evidence of serotonergic system dysregulation, the nature of these alterations appear to vary across the lifecycle. Available research studies conducted in depressed children and adolescents are summarized in Table 19.5.

Tricyclic Antidepressant Medications. Unlike in adults, tricyclic antidepressants (TCAs) do not appear effective for the treatment of depression in children and adolescents (Birmaher, Ryan, Williamson, Brent, & Kaufman, 1996b; Keller et al., in press). As indicated in Table 19.2, a number of placebo-controlled clinical trials in depressed children and adolescents failed to demonstrate efficacy of several different TCA medications, including imipramine, amitriptyline, desipramine, and nortriptyline.
Table 19.5. Prolactin Secretion After Serotonergic Probes

<table>
<thead>
<tr>
<th>Probe</th>
<th>Children Finding</th>
<th>Replicability</th>
<th>Adolescents Finding</th>
<th>Replicability</th>
<th>Adults Finding</th>
<th>Replicability</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-5HTP</td>
<td>Augmented</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>Blunted</td>
<td>++</td>
</tr>
<tr>
<td>MCPP</td>
<td>-</td>
<td>-</td>
<td>Augmented</td>
<td>+</td>
<td>Normal</td>
<td>+</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>-</td>
<td>-</td>
<td>Blunted</td>
<td>+</td>
<td>Blunted</td>
<td>++</td>
</tr>
</tbody>
</table>

Replicability Code:

+ = One controlled study
++ = Replicated finding

Conclusions from the early TCA studies were limited due to small sample size (Martin, Kaufman, & Charney, 2000); however, a recent multi-site double-blind, placebo-controlled trial of 275 depressed outpatients 12-19 years of age randomized to paroxetine, imipramine, or placebo provides conclusive evidence regarding the ineffectiveness of TCA medications in this age cohort (Keller et al., 2001). Patients randomized to imipramine received comparable ratings as patients receiving placebo on all of the clinical outcome measures. In contrast, as mentioned earlier, paroxetine proved superior to placebo on measures of affect, global improvement, and remission of depressive symptoms. Given the accumulating negative evidence against the efficacy of TCAs in this age cohort, the increased reporting of adverse side effects with these medications, and the potential for lethality with overdose, TCA medications appear to be of questionable utility in the treatment of depression in children and adolescents.

Summary

Although there are some similarities in the neurobiological correlates and treatment response of depressed children, adolescents, and adults, the differences far outnumber the similarities. Both children and adolescents differ from depressed adults on measures of basal cortisol secretion, ACTH stimulation post-CRH infusion, response to several serotonergic probes, and efficacy of TCA medications. Given the consistent inconsistencies in research findings across the lifecycle, it seems reasonable to pose the question, “Are child-, adolescent-, and adult-onset depression one and the same disorder?”

REASONS FOR DISCREPANCIES IN RESEARCH FINDINGS ACROSS THE LIFECYCLE

There are many precedents in medicine in which earlier- and later-onset forms of disease represent illnesses with distinct neurobiological mechanisms, despite similarity in clinical picture (Childs & Scriver, 1986). A classic example is the comparison of juvenile to adult onset diabetes (Geller & Luby, 1997). While child-onset depression may be distinct from adult-onset depression, there are alternate plausible explanations for the discrepant findings in child, adolescent, and adult studies. The differences in the neurobiological correlates and treatment response of depressed patients across the lifecycle may be due to: (1) developmental factors; (2) stage of illness factors (e.g., number of episodes, total duration of illness). Of these, recurrent unipolar depression is particularly discussed further.

Development

Many of the neural substrates of depression are not established until adolescence and norepinephrine is the primary neurotransmitter that is chronically altered across the lifespan (Rakic & Brown, 1996), or rough until the frontal cortex achieves its full maturity (Rosenberg & Luby, 2001).

The neuron also has been found to be repeatedly interrupted when the function in primates shows no notable changes until 31 months of age in the dorsolateral prefrontal cortex. When imaging studies were more diffuse in the dorso lateral prefrontal cortex, there appeared to be more diffuse changes in the brain regions. These changes suggest that deficits in memory tasks have yet to be reported.
of episodes, total duration of illness); or (3) heterogeneity in clinical outcome (e.g., recurrent unipolar course vs. new onset bipolar disorder). These alternate explanations are discussed further in the remainder of this section.

Developmental Factors

Many of the neurobiological systems implicated in the pathophysiology of adult depression are not fully developed until adulthood. While the expression of serotonin, norepinephrine, and dopamine receptors occur very early in life and are highly synchronized across the cortex (Lidow & Rakic, 1992), the development of monoaminergic storage capacity and synthetic processes is more variable (Goldman-Rakic & Brown, 1982). Serotonin content and synthetic activity matures relatively early (Goldman-Rakic & Brown, 1982), with the adult pattern of serotonergic innervation to the prefrontal cortex achieved by approximately six months in primates (Kye, Woo & Lewis, 1996), or roughly five to six years in humans. In contrast, the development of norepinephrine and dopamine content and synthetic activity continues through puberty, with dopamine innervation to the prefrontal cortex not finalized until early adulthood (Rosenberg & Lewis, 1995).

The neuronal circuits that mediate the performance of various cognitive tasks have also been found to change and become more refined with development. For example, when the functioning of the dorsolateral prefrontal cortex was experimentally temporarily interrupted through the use of reversible cyrogenic inhibition (e.g., cooling), no notable changes in a delayed response performance memory task were reported in primates 18 months or younger, mild deficits (8%) were noted in monkeys 19-31 months of age, and significant (22%) deficits were noted in postpubertal monkeys 34-36 months of age (Alexander 6; Goldman, 1978). These findings suggest that the dorsolateral prefrontal cortex is central in mediating the performance of delayed response memory tasks in mature, but not young, non-human primates (Alexander & Goldman, 1978). Consistent with this pre-clinical work, recent developmental neuroimaging studies examining cortical activity during memory tasks report greater and more diffuse activation in the prefrontal region in children relative to adults (Casey, Giedd, & Thomas, 2000). At younger ages, connections from a wider range of prefrontal brain regions are utilized in the performance of delayed memory tasks. With development, there appears to be refinement of the circuits that mediate memory performance, and increased specialization of the dorsolateral prefrontal cortex for the performance of this type of cognitive task.

Interestingly, deficits in the performance of delayed memory tasks have been repeatedly reported in adult depressed cohorts, especially among older patients with recurrent episodes of illness (Sweeney, Strojwas, Mann, & Thase, 1998). Adults with depression have also been found to have reduced structure and function in the dorsolateral prefrontal cortex in neuroimaging studies (Drevets, Gadde, & Krishnan, 1999). In contrast, depressed children do not appear to have difficulties in the performance of delayed memory tasks. While there is a need for more work in this area, preliminary data suggest that deficits in visual-spatial reasoning are more prominent than memory deficits in youngsters with depression (Frost, Moffitt, & McGee, 1989; McClure, Rogeness, & Thompson, 1997; McGee, Anderson, Williams, & Silva, 1986). Neuroimaging studies have yet to examine the structure and function of the dorsolateral prefrontal
cortex in pediatric depressed cohorts. Studies that assess oculomotor basal ganglia-thalamocortical circuits that mediate the performance of visual-spatial reasoning tasks, as opposed to dorsolateral and other prefrontal cortical circuits utilized in delayed memory paradigms, may be more fruitful in neuroimaging studies of early onset depression (Alexander, DeLong, & Strick, 1986). If there are true differences in neuropsychological correlates of depression in juvenile and adult samples, and the differences reflect true differences in affected underlying neuronal pathways, the examination of both types of tasks in functional neuroimaging studies in children, adolescents, and adults could provide valuable insights into potential developmental changes in the neural circuits that mediate depression across the lifecycle.

Stage of Illness Factors

Based on findings from preclinical studies, it has been hypothesized that the biological correlates and treatment response of patients with recurrent episodes of depression may differ from patients with a single episode of MDD (Post, 1992). Through kindling mechanisms, and stress-induced neurotoxicity and alterations in neurotrophic factors. recurrent episodes of depression may enhance neurobiologic alterations associated with depression (for further discussion of these mechanisms, see the following authors: Duman & Charney, 1999; Kupfer, 1991; Post, 1992). In accordance with these assertions, hippocampal volume reductions are significantly more common in adult depressed patients with recurrent episodes of disorder than patients with single episodes of MDD, with degree of hippocampal atrophy found to correlate significantly with lifetime duration of depressive illness (Sheline, Wang, Gado, Csernansky, & Vannier, 1996). Given the demonstrated importance of stage of illness on hippocampal volume measures, it is not surprising that the one study that examined hippocampal volume in children and adolescents with Posttraumatic Stress Disorder (N = 43), about half of whom met criteria for comorbid MDD, failed to find evidence of hippocampal atrophy (De Bellis et al., 1999). Developmental factors are likely also relevant, however, as preclinical studies have found age dependent changes in sensitivity to NMDA receptor blockade neurotoxicity in corticolimbic regions, with cell death minimal or absent in childhood, and reaching peak in early adulthood (Farber et al., 1995).

As most children and adolescents who participated in the studies reviewed in this chapter only had one episode of depression, differences from adult studies may be attributable to differences in the proportion of patients with recurrent episodes of disorder included in the investigations. Consistent with this hypothesis, adults with recurrent depression are more likely to have EEG sleep alterations than adults experiencing a first episode of depression (Thase et al., 1995). There is also some evidence to suggest that HPA axis alterations may be more likely in depressed children with recurrent illness than in depressed children experiencing their first episode (Klee & Garfinkel, 1984). In addition, when post-hoc analyses were conducted in one study comparing prolactin values after serotonergic challenge in depressed children with and without a prior history of MDD, similar to findings in adults, children with recurrent depression secreted significantly less prolactin than children with single episodes of disorder (Birmaher et al., 1997). Therefore, differences in the neurobiological correlates of depression across the lifecycle may reflect course of illness factors — and not fundamental differences in the pathophysiology of the disorder. Careful classification of patients by stage of illness...
(e.g., first episode vs. recurrent), and repeat longitudinal neurobiological assessments after a recurrence will help to resolve this question.

Heterogeneity in Clinical Outcome

Given the protracted period of risk for the development of affective disorders, studies with child and adolescent probands have a high likelihood of including subjects who will change their group status over time. For example, although not reported in all studies (Weissman et al., 1999), several studies have reported that as many 20–40 percent of children and adolescents with depression experience a manic episode within five years of their initial episode of MDD (Rao et al., 1996; Strober, Lampert, Schmidt, & Morrell, 1993). In one longitudinal follow-up study of depressed adolescents who completed a comprehensive psychobiological protocol during their index episode of depression (Rao et al., 1996), differences between depressed and normal control subjects on measures of basal cortisol secretion were only evident after removal of subjects who switched to Bipolar Disorder. Utilization of the longitudinal clinical course data was essential in "cleaning" the Time 1 biological data.

Children and adolescents who serve as “normal” controls in studies of the neurobiological correlates of early onset depression may also switch group status over time. In the longitudinal study referenced above, 23 percent of the “normal” controls had an episode of MDD during the seven-year interval follow-up (Rao et al., 1996). These subjects likewise differed from “true normal controls” on several of the Time 1 psychobiological measures. For example, controls who developed depression over the follow-up interval had significantly higher REM density and a trend toward reduced REM latency when compared to controls with no disorder at follow-up. In high-risk studies, youngsters at risk for MDD have also been found to have biological alterations similar to depressed children prior to the onset of any affective disorder. Like depressed children, when compared to low-risk normal controls, high-risk children have been found to have augmented prolactin secretion after L-5-HTP administration and blunted growth hormone secretion after GHRH administration (Birmaher et al., 2000). Given the protracted period of risk for the onset of depression, studies that failed to utilize normal controls at low familial risk for affective disorder may have obscured group differences in neurobiological studies with child and adolescent probands. These findings highlight the need for careful characterization of normal controls, and the importance of longitudinal follow-up data to “clean” Time 1 psychobiological measures.

Summary

As discussed in this section, differences in the neurobiological correlates and treatment response of depressed patients across the lifecycle may be due to: (1) developmental factors; (2) stage of illness factors (e.g., number of episodes, total duration of illness); or (3) heterogeneity in clinical outcome (e.g., recurrent unipolar course vs. new onset bipolar disorder). There is compelling evidence to support each of these possibilities. Unfortunately, available data preclude definitive conclusions regarding the merits of these alternate hypotheses. Further systematic research will be required to determine if child-, adolescent-, and adult-onset depression are one and the same disorder.
DIRECTIONS FOR FUTURE RESEARCH

The pattern of findings observed in the neurobiological correlates and treatment response of depressed children, adolescents, and adults is not entirely consistent nor easily understood (e.g., DST nonsuppression, normal basal cortisol secretion, normal ACTH post-CRH infusion). The incorporation of neuroimaging measures in neurobiological studies of early-onset affective disorders will allow for more direct examinations of similarities, differences, and potential developmental changes in the neural circuits implicated in the pathophysiology of depression across the lifecycle. As stated previously, most studies of the neurobiological correlates of early-onset depression have utilized neuroendocrine paradigms. Although these methods have their merits, especially for the study of the Hypothalamic–Pituitary–Adrenal axis stress system, the “window to the brain” afforded by these methods is extremely limited. To determine if child-, adolescent-, and adult-onset depression are one and the same disorder, we recommend: (1) utilizing the same neuroimaging paradigms in child, adolescent, and adult depressed cohorts; (2) carefully characterizing subjects’ stage of illness; and (3) conducting longitudinal clinical and repeat neurobiological assessments of patients of different ages at various stages of illness.

Important foci for future research in early-onset affective disorders are discussed in the remainder of this section. The first two sections discuss research methods that have not been applied, or only little applied to the study of early-onset affective disorders (e.g., neuroimaging, genetics). The next two parts discuss factors affecting heterogeneity in depressed cohorts (e.g., family history of psychiatric illness, life events, and traumatic experiences), and the last section discusses gender influences on depression.

Central Measures of Brain Function

As stated in the introduction, the development of new, noninvasive imaging techniques afford a unique opportunity to investigate the brain mechanisms underlying child- and adolescent-onset depression. The methods typically considered “noninvasive” include structural and functional Magnetic Resonance Imaging (MRI), Magnetic Resonance Spectroscopy (MRS), and Diffusion Tensor Imaging (DTI), as these methods do not require the injection of radioactive tracers and have no known adverse side effects. The application of these procedures in children and adolescents with unipolar depression is in its infancy, however, with only a few published reports and abstracts of imaging studies produced to date.

Structural MRI studies are easily accomplished in pediatric populations (Rosenberg et al., 1997), and permit the identification of neuroanatomical variations associated with early onset MDD. Steingard and colleagues (Steingard et al., 1996) conducted the only published report of structural MRI in children and adolescents with depressive disorders (e.g., major depression and dysthymia). Children with depressive disorders were found to have reduced frontal lobe/cerebral volume ratios and increased lateral ventricular/cerebral volume ratios when compared to psychiatric control subjects. The finding of reduced frontal lobe volume is consistent with results of studies conducted with adults, but lateral ventricular enlargement has not typically been reported in non-delusional mid-life depression (Drevets et al., 1999). These findings need to be replicated and future studies extended to include normal control comparison subjects and the examination of associated MRI and PET studies of metabolism and function in the same region of the brain.

In depressed patients, reduced amygdala volume has been reported (Drevets et al., 1999). In a subset of depressed adolescents under way at V preferred by Drevets et al., reduced amygdala volume was found in depressed adolescents compared to normal controls. In addition, Steingard and colleagues (Steingard et al., 1996) reported a 10-15% reduction in the volume of the hippocampus in twins with a history of depressive illness. In one patient (area 25) has a reported transient sadness and reduced amygdala volumes (Sheline, Gado, & Mowry, 1997).

Depressed adolescents with unipolar depression have been reported to have reduced amygdala volume in half who had a transient sad mood (Sheline, Gado, & Mowry, 1997). The results have been consistent with others (e.g., Rosenberg et al., 1997). The reduced hippocampal volume in depressed adolescents may be related to the predictive factor of family history of psychiatric illness (Rosenberg et al., 1997).

In the hippocampus and other subcortical structures, there are many known primary disturbances. With changes related to some structural changes, there may be secondary changes related to some structural changes, and others (e.g., 1996; Mervall et al., 1993; Hauser et al., 1996; Mervall et al., 2000; Sheline et al., 2000). The subgenual and other subcortical structures may be related to some structural changes, there may be secondary changes related to some structural changes, and others (e.g., 1996; Mervall et al., 1993; Hauser et al., 1996; Mervall et al., 2000; Sheline et al., 2000).
examination of more refined subregions of the frontal lobes. In particular, given replicated MRI and Positron Emission Tomography (PET) studies showing reduced structure and function in the dorsolateral (Brodmanns area 9) region of the prefrontal cortex, this region needs to be examined in child and adolescent cohorts.

In depressed adults, in the subgenual prefrontal cortex (e.g., Brodmanns area 24), an area ventral to the genu of the corpus callosum and sometimes referred to as the anterior cingulate, gray matter volume reductions as high as 40 percent have also been reported (Drevets et al., 1997). Preliminary yet to be published structural MRI work under way at Washington University in adolescent twins with adolescent or earlier onset MDD suggest subgenual prefrontal cortex/anterior cingulate volume is similarly reduced in early-onset depression (Botteron, Raichle, Heath, & Todd, 1999). In addition, the volume reduction appears to represent a “scar” marker, as it is observed in identical twins with a history of MDD, but not present in co-twins without a history of affective illness. In adults, increased blood flow in the subgenual cingulate (Broadmanns area 25) has also been reported in normal controls during experimentally induced transient sadness and in depressed patients during episodes of illness (Mayberg et al., 1997).

Depressed adults have also been reported to have reductions in amygdala volume (Sheline, Gado, & Price, 1998). Preliminary results from the ongoing twin study cited above suggest that adolescent twins with adolescent or earlier onset MDD similarly have reduced amygdala volume (Botteron et al., 1999). Interestingly, the volume reduction in this region appears to represent a potential putative “risk” marker, and was observed in identical twins with a history of MDD, and in co-twins without a history of affective illness. Longitudinal follow-up of this cohort will be very informative in determining the predictive significance of this marker over time.

Hippocampal volume assessments have not been obtained in children and adolescents with primary affective disorders. As mentioned previously, no hippocampal volume reductions were reported in a study of children and adolescents with PTSD, half who had comorbid MDD (De Bellis et al., 1999). Reduction in hippocampal volume has been reported in several (Bremner et al., 2000; Shah et al., 1998; Sheline et al., 1996; Mervaala et al., 2000), but not all studies of adults with depression (Axelson et al., 1993; Hauser et al., 1989; Vakili et al., 2000). In two of the positive studies, degree of hippocampal atrophy was found to correlate with total duration of illness (Bremner et al., 2000; Sheline et al., 1996). This raises questions as to whether these changes represent primary disturbances associated with the onset of disorder, or secondary brain changes related to recurrence and extended glucocorticoid exposure. There may be some structural abnormalities associated with depression in adults which represent primary disturbances and are evident across the lifecycle (e.g., frontal lobe; amygdala), and others (e.g., hippocampal atrophy) which are only evident later in development or secondary to biological alterations (e.g., excess cortisol) associated with persistence and recurrence of disorder. More research is needed in this area.

Preclinical studies have shown that the dorsolateral prefrontal cortex, the cingulate, and other subcortical structures including the hippocampus are functionally linked. The subgenual cingulate projects directly to the dorsolateral prefrontal cortex, and there are many bidirectional indirect pathways between these structures through several different limbic and paralimbic nodes including the hippocampus, posterior cingulate, and anterior insula. The importance of these regions in mediating mood and
attention and emotional homeostasis has been implicated in multiple neuroimaging studies with depressed (Baxter et al., 1989; Bench et al., 1992; Mayberg et al., 1999) and normal control (George et al., 1995; Lane, Reiman, Ahern, Schwartz, & Davidson, 1997; Mayberg et al., 1999) adults. The relevance of these neural circuits in child- and adolescent-onset depression has yet to be established and will require utilization of functional neuroimaging techniques.

Functional MRI (fMRI) studies permit the identification of the different regions in the brain that are utilized in processing different types of information or solving various types of problems. There is one ongoing investigation of functional MRI in depressed children and adolescents. Consistent with the structural MRI findings reported above (Botton et al., 1999), preliminary reports from this study suggest depressed adolescents have reduced amygdala activation when processing fearful and neutral faces compared to adolescents with anxiety disorders and normal controls (Thomas et al., 2001). Therefore, both structural and functional abnormalities have been reported in the amygdala in association with early-onset MOD.

In addition to structural and functional MRI methodology, Magnetic Resonance Spectroscopy (MRS) is another noninvasive imaging technique that warrants further application in studies of child and adolescent depression. MRS allows for the direct monitoring of brain neurochemistry, and can be used to quantify steady-state metabolic levels of neurotransmitters such as glutamate-amino acid butyric acid (GABA), and compounds involved in membrane phospholipid metabolism. In a recent abstract, Steingard and colleagues (Steingard & Renshaw, 1996) reported that depressed adolescents had a trend toward reduced N-acetyl-L-aspartate (NAA) to creatine and phosphocreatine (CR) ratios in the orbitofrontal cortex when compared to normal controls (Brodmann area 47). As NAA is thought to arise largely from neurons, the preliminary data reported by Steingard and colleagues suggest the possibility that abnormal development of the orbitofrontal cortex may be associated with early-onset depression. In studies with adults, abnormalities of the orbitofrontal cortex appear to be linked to serotonergic processes. Adults with depression have been found to have reduced serotonergic receptor binding in the orbitofrontal cortex (Biver et al., 1997), and recovered depressed adult patients that experience a relapse in symptoms after experimentally induced depletion of tryptophan, the amino acid that is the precursor to serotonin, show decreased metabolism in this region as well (Bremner et al., 1997). In addition, in a recent postmortem study of adult depressed patients (Rajkowska et al., 1999), cortical thickness was found to be significantly reduced in the rostral orbitofrontal cortex (Brodmann areas 10 and 47). The reduced cortical volume was associated with a reduction in the size of the largest class of neurons located in supragranular layers, and an increase in density of small neurons found in this area. Consistent with the data discussed above, primate studies have found that the neurons in this region are targets of serotonergic input. The overall smaller neuronal size in this cortical region was attributed to neuronal shrinkage or a developmental deficiency, rather than neuronal loss by the authors of the study. If neuronal loss had occurred, density of large neurons would have been decreased without associated increases in the density of small neurons (Rajkowska et al., 1999). Additional MRS studies examining phospholipid metabolism, structural MRI studies, and postmortem studies in child and adolescent depression will help to determine the potential relevance of the orbitofrontal cortex in the pathophysiology of early-onset depression.
The use of MRS technology to examine GABA is also of interest in the study of child and adolescent depression given: emerging conceptualizations of the role of GABA in mood disorders (Petty, 1995); a report documenting reduced plasma GABA in a subset of depressed children and adolescents (Prosser et al., 1997); a recent MRS study demonstrating reduced cortical GABA in depressed adults (Sanacora et al., 1999); and new insights into the unique mechanism of action of SSRI medications (Guidotti & Costa, 1998). While both TCA and SSRI medications enhance serotonergic transmission and reduce glutamate N-methyl-D-aspartate (NMDA) glutamate receptor function (Kilts, 1994), amelioration of depressive symptoms with SSRI treatment is uniquely correlated with increases in the neurosteroid 3-alpha, 5-alpha, tetrahydroprogesterone (ALLO). ALLO binds with high affinity to GABA receptors, and potently facilitates GABA transmission at these sites (Gambarama, Ghiglieri, & Graziella de Montis, 1995). In contrast, Imipramine and other TCA agents that are ineffective in child- and adolescent-onset depression do not promote changes in brain ALLO or GABA transmission. The use of MRS methodology to study glutamate in early-onset depression is warranted as well, as preclinical studies with glutamatergic agents produce animals with the two most prominent characteristics of patients with early-onset depression: animals with learned helplessness which is nonresponsive to TCA treatments (Petty, McChesney, & Kramer, 1985), and animals who display “depression-like” behaviors in the absence of hypercortisolemia (Biagini et al., 1993).

Diffusion Tensor Imaging (DTI) is another noninvasive neuroimaging methodology that permits the evaluation of the integrity of white matter tracts – axonal pathways (Pierpaoli, Jezzard, Basser, Barnett, & Di Chiro, 1996). The use of DTI may be of special interest in studies designed to investigate the neurobiology of affective disorders in children with a history of significant trauma. Preclinical research examining the effects of early stress in mature animals, and clinical studies of adults with Posttraumatic Stress Disorder, suggest that stress early in life is associated with changes in the Hypothalamic–Pituitary–Adrenal (HPA) axis, central Corticotropin Releasing Hormone (CRH) system, and the hippocampus, a brain structure vulnerable to the neurotoxic effects of stress-induced elevations in circulating glucocorticoids (e.g., cortisol) and amino acids (e.g., glutamate).

Emerging evidence in human and nonhuman primates suggests that the neurobiological changes associated with early stress may vary at different developmental periods. HPA axis changes are not especially robust in juvenile samples, and contradictory findings have been reported (Kaufman & Charney, 1999). In addition, early stress may not be associated with the same pattern of brain changes in adult and juvenile samples. To the best of our knowledge, there is only one published structural MRI study in prepubescent nonhuman primates subjected to early stress, and the one previously cited published structural MRI study in maltreated children and adolescents with PTSD (De Bellis et al., 1999; Sanchez, Hearn, Do, Rilling, & Herndon, 1998). Neither study reported hippocampal atrophy. Both studies, however, reported reductions in the medial and caudal portions of the midbody of the corpus callosum.

The corpus callosum contains the majority of inter-hemispheric axonal projections in the brain. The medial and caudal portions of the midbody of the corpus callosum contains inter-hemispheric projections from the auditory cortices, posterior cingulate, retrosplenial cortex, insula, and somatosensory and visual cortices to a lesser extent. It also includes connections from the inferior parietal lobe to the contralateral inferior
holism or

To date there are no published reports examining genetic markers in child and adolescent depression. Several of the regions with interhemispheric projections through the medial and caudal portions of the midbody of the corpus callosum have connections with prefrontal cortical areas, and are involved in circuits that mediate the processing of emotional stimuli and various memory functions. Given emerging evidence regarding volumetric changes in the corpus callosum in prepubescent nonhuman primates subjected to early stress, and children and adolescents with a history of early trauma – and the silence of the interhemispheric projections in the regions showing volumetric changes – the utilization of DTI to examine the integrity of corpus callosum white matter tracts in depressed children with a history of abuse may be informative. As discussed later, the neurobiology of depression may be different in children with a history of significant trauma and children who develop depression independent of any psychosocial adversity. The use of DTI in traumatized and nontraumatized depressed cohorts may help to further illuminate these differences.

Although the application of neuroimaging paradigms is in its infancy in the study of child- and adolescent-onset depression, the potential gains possible with the application of these new techniques are far reaching. The use of these techniques with normal and depressed clinical child, adolescent, and adult cohorts will help to identify potential developmental differences in the pathophysiology of depression across the lifecycle. Once the structures and circuits implicated in the pathophysiology of child and adolescent depression are identified, hypotheses regarding the neurodevelopmental processes involved in the etiology of early-onset depression can be tested in preclinical research studies. The interplay of normal developmental, clinical, and preclinical studies will help to advance understandings of the mechanisms involved in the onset, maintenance, and recurrence of depressive disorders across the lifecycle.

Genetics Studies

To date there are no published reports examining genetic markers in child and adolescent depressed probands. In addition, there are no family-based association studies demonstrating linkage in unipolar depression. Two case-control studies with adult depressed probands provide evidence for an association with a polymorphism in the tyrosine hydroxylase locus (Serretti et al., 1998; Souery et al., 1996), and another case-control study reported association with a polymorphism at the serotonin transporter locus (Collier et al., 1996). Consistent with much of the literature on psychiatric genetics, however, controversial findings have since been published refuting these associations (Frisch et al., 1999; Kunugi et al., 1999; Serretti et al., 1998).

Child and adolescent probands are a promising group for future genetic studies. Several family studies suggest MDD during childhood or adolescence (onset < 20 years) is associated with significantly greater risk of MDD in first- and second-degree relatives (Kupfer, Frank, Carpenter, & Neiswanger, 1986). There are emerging data, however, that suggest early onset MDD is associated with increased rates of alcoholism and antisocial personality disorder in relatives. There also appear to be greater rates of the co- transmission of these disorders (Harrington et al., 1997; Kovacs, Iandelli, & Rende et al., 1998). Since nonadditive effects are known to be important in homogenous families. Two particular studies have examined these relations with nonadditive disease expression in homogenous families.

Depressed patients differ from depressed patients with relatives of other diagnoses, with reduced subgenus disease transmission with Familial Depression Project and the European project on familial depression. In contrast, de-pressed patients develop depression with familial depression with distinct subtypes.

Much has been learned about the genetic basis of depression through studies of pedigrees. It has been found that the etiology of depression involves at least four candidate genes as well as many modifier genes. Although it is clear that there are different biological pathways involved in the etiology of depression, the details of these pathways and their interactions are yet to be elucidated. As complexity increases, it becomes apparent that the genetics of depression are not a simple matter of identifying genes that are associated with depression, but rather a complex interplay of genetic and environmental factors.
Neurobiology of Child and Adolescent Depression

1997; Kovacs, Devlin, Pollock, Richards, & Mukerji, 1997; Puig-Antich et al., 1989b; Rende et al., 1997; Williamson et al., 1995). Genetic studies may therefore need to use more refined definitions of phenotypes that include familial factors to establish linkage in homogenous subgroups of depressed patients (Angst & Merikangas, 1997).

Two particular valuable phenotypes to examine include Winokur's (Winokur, 1982) Depressive Spectrum Disorders and Familial Pure Depressive Disorders depression subtypes. Depressed patients with Depressive Spectrum Disorders have a family history of alcoholism or antisocial personality disorder with or without a family history of depression. In contrast, depressed patients with Familial Pure Depressive Disorders have a family history of depression and no family history of alcoholism, antisocial personality disorder, or mania.

Depressed patients with a family history of Depressive Spectrum Disorders may differ from depressed patients with Familial Pure Depressive Disorders on genetic and other important parameters. For example, in studies with adults, depressed patients with relatives with Depressive Spectrum Disorders were found to be less likely to have reduced subgenual prefrontal cortex volumes than depressed patients with relatives with Familial Pure Depressive Disorders (Drevets, 1998). This highlights the value of obtaining family history measures in imaging and other neurobiological studies of early onset MDD, as these measures may help to explain significant variance in psychological parameters, and help to identify meaningful subgroups of depressed patients with distinct etiologies and associated pathophysiology.

Much has been written about the definition of phenotypes to be used in genetic studies of psychiatric illness (Angst & Merikangas, 1997; Leboyer et al., 1998). In addition, it has become increasingly clear that mental disorders such as depression are genetically complex. As recently defined by Hyman (1999), the term genetically complex implies that there is no single genetic locus that causes the disorder. Rather, multiple alleles at multiple loci are believed to interact to produce vulnerability to depression. Although it is possible that some genes exert an independent main effect on the etiology of depression, it is likely that some of the relevant genes confer vulnerability to depression only in the presence of other specific alleles found at other loci. These nonadditive effects of genes are referred to as epistasis. In addition, in different families, different combination of genes may be responsible for vulnerability to depression. Modifier genes that influence age of onset of disorder rather than actual vulnerability to disease have also been identified for other medical conditions, and are likely relevant in the etiology of early onset depression as well (see Hyman, 1999, for further discussion).

As complicated as the genetics of depression appears to be, the Human Genome Project and the Brain Molecular Anatomy Project promise to greatly aid in the elucidation of the genetic basis of depression across the lifecycle. The Brain Molecular Anatomy Project is sponsored by the National Institute of Mental Health and National Institute of Neurological Disorders and Stroke. It is aimed at facilitating the discovery of genes expressed in the brain and then putting them on anatomical maps. Given the episodic nature of depression, and as discussed in the next section, the impact of experience on its etiology, genes involved in synaptic plasticity are attractive targets in understanding individual differences in vulnerability to depression. Despite considerable evidence that neuronal activity influences the function of circuits in the developing and adult brain, the molecular signals responsible for longer-term adaptations remain largely obscure (McAllister, Katz, & Lo, 1999). Neurotrophins have emerged as attractive candidates...
for such signaling molecules, and have been proposed to play a central role in a variety of forms of synaptic plasticity. Consistent with this hypothesis: neurotrophins have been found to be present in sites of CNS development and adult plasticity; neurotrophin expression and secretion is activity dependent; and neurotrophins have been found to regulate aspects of neuronal function that change activity in neural circuits, including synaptic function, membrane excitability, neuronal morphology, and neuronal connectivity (McAllister et al., 1999). Recent studies have also demonstrated that antidepressant medications promote the expression of the neurotrophin brain-derived neurotrophic factor (BDNF) in certain populations of neurons in the hippocampus and cerebral cortex (Duman, Heninger, & Nestler, 1997). The importance of these changes is highlighted by the discovery that stress can decrease the expression of BDNF and lead to atrophy in these same stress-vulnerable hippocampal neurons. These findings lead to a molecular and cellular hypothesis of depression that posits stress-induced vulnerability to depression is mediated by intracellular mechanisms that decrease neurotrophic factors necessary for the survival and optimal function of particular neurons in key circuits implicated in the pathophysiology of depression (Duman et al., 1997). Genes encoding and regulating neurotrophic factors may be important candidates to study in future genetic investigations of affective disorders in children, adolescents, and adults.

The research potentials afforded by the Human Genome and Brain Molecular Anatomy projects, as well as some of the emerging technologies discussed in the next section, are profound. As recently discussed by Watson and Akil (1999), there will be many challenges in defining the genes involved in depression and other psychiatric disorders, elucidating their functions, and understanding their interactions with developmental and environmental factors. Through collaborations among geneticists, neurobiologists, and clinicians, however, much progress in understanding the pathophysiology of these disorders is possible.

Life Events and Early Childhood Trauma

While genetic and environmental factors have traditionally been conceptualized as independent contributors to the etiology of depression, twin studies have highlighted the interdependence of these factors. Specifically, twin studies with adult and adolescent probands suggest genetic factors influence: (1) risk of exposure to traumatic events; and (2) sensitivity to the negative impact of environmental stressors (Kendler, 1998; Kendler et al., 1995; Silberg et al., 1999). In accordance with these data, several studies have demonstrated that depressed children and adolescents are significantly more likely than controls to have experienced adverse life events in the year preceding the onset of their depression (Goodyer, Herbert, Tamplin, Secher, & Pearson, 1997; Williamson et al., 1998). Nevertheless, not all depressed children and adolescents have a history of significant life stressors.

There are preliminary data to suggest that children and adolescents who develop depression independent of a history of adversity may differ significantly on a number of parameters than those who develop depression in the context of such experiences. For example, depressed abused and depressed nonabused children have been found to differ on a number of neurobiological indices. Specifically, consistent with preclinical studies examining the impact of early adverse rearing conditions on serotonergic function (Kraemer et al., 1999), depressed children have been found to be significantly more prolactinized than controls (Kaufman et al., 1997).

In addition to depression, traumatized children and adolescents are at high risk for subsequent psychiatric disorders, compared to controls. For example, traumatized children are at significantly elevated rates of a history of subsequent depression, suicide attempts, and psychiatric disorders. This finding has implications for the development of early intervention strategies for children who have experienced traumatic events.

Preclinical studies (e.g., stress exposure, neurochemical changes) of the role of stress in depression and anxiety have been conducted in mice and other animal models. These studies have provided insights into the neural mechanisms underlying the effects of stress on depression and anxiety. For example, studies have found that stress exposure can lead to changes in the expression of genes involved in the regulation of neurotransmitter systems, including the serotonergic system. These changes have been associated with alterations in the function of key neurotransmitter receptors, such as the 5-HT_1A receptor (Chalmers, Li, & Koob, 1999).

Evolving cloning strategies, such as Human Genome Project or mRNAs in the brain, have been used to scan the genome and identify genes that may be involved in the pathophysiology of depression and other psychiatric disorders.
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function (Kraemer, 1992), depressed abused children have been found to secrete significantly more prolactin after L-5-HTP administration than depressed nonabused children (Kaufman et al., 1998b). In addition, while HPA axis alterations are rare in nontraumatized depressed children, they have been reported in several studies of depressed abused children (Hart, Gunner, & Cicchetti, 1996; Kaufman, 1991; Kaufman et al., 1997).

In addition to differing on numerous neurobiological parameters, depressed abused and depressed nonabused children have also been found to have different patterns of psychiatric disorders among their first-degree relatives (Kaufman et al., 1998a). When compared to controls, both depressed abused and depressed nonabused children have significantly elevated rates of depression in their first-degree relatives, with more than 50 percent of the first-degree relatives of both depressed cohorts having a lifetime history of MDD. The relatives of the depressed abused children, however, also have elevated rates of alcoholism and antisocial personality disorder. In fact, 77 percent of the depressed abused children had relatives with Depressive Spectrum Disorders. In contrast, 62 percent of the depressed nonabused children met Winokur's (1982) criteria for Familial Pure Depressive Disorder subtype. The relatives of the nonabused depressed children were also significantly more likely to meet criteria for non-PTSD anxiety disorders. This finding is also of significant interest, as Weissman and colleagues (1984) found offspring of depressed patients with comorbid anxiety (e.g., Panic) disorders to be two times more likely to develop child onset depression than offspring of depressed patients without anxiety disorders. While both depressed abused and depressed nonabused children have high familial loading of depression, the pattern of psychiatric illness in the relatives of these two groups of children suggest a different underlying vulnerability to depression in the two cohorts. These studies highlight the need for further systematic examination of familial/genetic and experiential factors in studies of the neurobiological correlates and treatment of early-onset depression.

Preclinical studies will help to identify the mechanisms by which experiential factors (e.g., stress) confer vulnerability to depression, and examine genetic factors that effect sensitivity to these experiences. For example, chronic stress has been found to decrease 5HT\textsubscript{1A} receptor number and binding in the hippocampus, and produce changes in mineralocorticoid and glucocorticoid receptor ratios in this same region (Lopez, Chalmers, Little, & Watson, 1998). Examination of this sort of animal model of depression in mice strains with high versus low behavioral responses to stress will allow for an examination of differences in the expression of genes due to inherent differences between the high stress and low stress breeds, and differences resulting from the stress and nonstress experimental conditions. Candidate genes of interest to examine mRNAs for would include corticotropin releasing hormone, glucocorticoid receptors, 5HT receptors, and other genes known to be involved in the stress response (Watson & Akil, 1999).

Evolving methodologies, such as gene chips and complimentary DNA (cDNA) clones derived from the expressed sequence tag (EST) data base developed as part of the Human Genome Project, will allow for the simultaneous study of thousands of genes or mRNAs involved in the complex genetics of depression and other brain disorders (Watson & Akil, 1999). Currently, in conducting the stress reactivity experiment described above, 5–10 genes could be examined. The evolving technologies of gene chips that contain 10,000 or more oligonucleotides of 10 to 20 nucleotides per chip can be used to scan thousands of genes simultaneously. ESTs are fragments of DNA sequences
Gender Influences on Depression

Among pre-adolescents, MDD occurs at approximately the same rate in boys and girls. With the onset of adolescence, the gender ratio of depression shifts to 2:1. Paralleling the gender distribution of depression observed in adult cohorts, female adolescents are approximately two times more likely to develop depression than male adolescents (Angold, Costello, & Worthman, 1998; Birmaher et al., 1996c). Although the shift in gender distribution of depression that occurs in adolescence appears to be linked to changes in pubertal status, more research is needed to understand the mechanisms responsible for this shift, and the overall 2-3-fold increased rate of depression that occurs in adolescence.

Oxytocin is one neurohormone hypothesized to influence the shift in the gender distribution of depression that occurs with the onset of puberty (Cyranowski, Frank, Young, & Shear, 2000), but currently there are no data examining this. The relationship between sex steroid levels and depressed mood has been examined in several investigations of normal adolescents, but no studies of depressed teenagers. In nonclinical samples of adolescents, low testosterone has been associated with higher ratings of sad affect in boys (Susman et al., 1987). Interestingly, in depressed men with low basal testosterone secretion, testosterone replacement therapy in an open clinical trial was found to be an effective augmentation treatment for SSRI refractory MDD (Seidman & Rabkin, 1998). Within normal samples of girls, the rapid increase of estradiol that corresponds with puberty onset has also been associated with higher ratings of depression (Warren & Brooks-Gunn, 1989). Investigations with adult women have not consistently reported abnormal circulating levels of estrogen in association with Premenstrual Mood Syndrome (PMS); however, several studies suggest a role of gonadal steroids in precipitating symptoms of PMS (Rubinow, Schmidt, & Roca, 1998).

Little data exist on PMS in adolescence. Studies with normal adolescents suggest that close to 90 percent of female adolescents experience at least one PMS symptom of moderate or greater severity (Cleckner-Smith, Doughty, & Grossman, 1998; Fisher, Trieller, & Napolitano, 1989). In normal adolescents, physical PMS symptoms are associated with greater ratings of emotional distress (Freeman, Rickels, & Sondheimer, 1993), and in a study of normal health and development, it was estimated that up to 14 percent of female adolescents met diagnostic criteria for PMS (Raia et al., 1992).

PMS has not been systematically evaluated in most clinical or neurobiological research studies with depressed adolescents. The role of sex steroids in the pathophysiology of early-onset affective disorders warrants further investigation given the data reviewed in this section, and preclinical studies which suggest a role for sex steroids in mediating serotonin levels (Cologer-Clifford et al., 1996). Focused studies of sex steroids in depressed adolescence would be particularly informative.

Summary

This section reviewed the role of sex steroids in the pathophysiology of child and adolescent depression, and the interaction of environmental factors.
mediating serotonergic functioning and stress reactivity. Both testosterone and estrogen influence multiple parameters of serotonergic tone (Rubinow et al., 1998; Simon, Cologer-Clifford, Lu, McKenna, & Hu, 1998). Sex steroids also affect gene expression of hypothalamic CRH and hippocampal and hypothalamic glucocorticoid receptor mRNA levels (Patchev & Almeida, 1998). Consequently, it has been suggested that better understanding of gender differences in neuroendocrine response to stress will enhance understanding of the development of disorders like depression which have a higher prevalence in women (Jezova, Jurankova, Mosnarova, Kriska, & Skultetyova, 1996). Focused preclinical work in this area will help to refine hypotheses on the role of sex steroids in the pathophysiology of early-onset depression, and attainment of sex steroid measures in clinical studies may help to delineate gender influences on the pathophysiology of depression.

Summary

This section reviewed a range of research strategies to be used to unravel the neurodevelopmental factors and processes that promote the development of depression in children and adolescents. A key theme reiterated throughout the section is the concept of heterogeneity — heterogeneity in pathways to the etiology of depression, and heterogeneity in the outcome of children with depression. If the onset of depressive symptoms appears independent of any life stressors, within the context of a history of child maltreatment, or in association with the onset of the menstrual cycle, the underlying pathophysiology is apt to be different. Likewise, the neurobiology of depression in children with single episodes of disorder, a recurrent course of illness, or a switch to bipolar disorder preliminarily appears to be distinct. Familial loading for psychopathology and depressive subtypes are also important factors to consider in future studies. The utilization of neuroimaging and genetic research approaches with carefully characterized samples will help to unravel the neuroanatomical structures and circuits implicated in the etiology of early-onset MDD. This work must proceed, however, in close association with normal developmental studies, as the neural circuits that mediate the control of affect at different developmental stages is poorly understood. The longitudinal follow-up of high risk and clinical populations will also help to identify primary disturbances associated with the onset of disorder, and secondary alterations associated with recurrence and/or persistence of depressive symptomatology.

The mechanisms responsible for the development of depression may change with age. While those who study adult depression have developed cogent theories of potential mechanisms responsible for the etiology of depression, like those of Nemeroff and colleagues which focuses on alterations in the stress hormone CRH (Heim, Owens, Plotsky, & Nemeroff, 1997), the application of these theories is apt to be limited in early-onset affective illness. Given the relative absence of HPA axis and hippocampal volume changes in juvenile depressed samples, and emerging data focusing on other structures such as the amygdala in nontraumatized populations, and the corpus callosum in those with a history of significant early adversity, alternate theories are required to explain the pathophysiology of early-onset mood disorders. The research will require an iterative process, and will benefit greatly from a strong cross-fertilization between developmental, basic, and clinical research approaches.
CONCLUSION

Depression in children and adolescents is common, recurrent, and associated with significant morbidity and mortality. Over the past fifteen years we have learned that we cannot extrapolate down from what we know about depression in adults. There are many differences in the neurobiological correlates and treatment response of depressed children, adolescents, and adults. Systematic longitudinal research that carefully accounts for developmental, stage of illness, familial, and experiential factors is required to understand the pathophysiology of depression across the lifecycle. The application of multidisciplinary research approaches will help to elucidate the neurodevelopmental processes involved in the pathophysiology of child and adolescent depression, and help to determine if child-, adolescent-, and adult-onset depression are one and the same disorder.

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