CHAPTER 30

Harnessing the Neuroscience Revolution to Enhance Child and Adolescent Psychotherapy

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Interest in the field of clinical neuroscience has exploded in the past decade (Weingarten & Strauman, 2015). However, direct contributions of neuroscience to clinical assessment and treatment are rare. It is natural and appropriate for clinicians and policymakers to ask where and when translational gains from neuroscience will emerge in clinical practice. In this chapter we identify a number of paths through which neuroscience might inform superior assessment and treatment of children and adolescents in the future. We focus on three potential contributions that neuroscience can make to clinical assessment and treatment. First, neuroscience might be used to identify individuals who are more or less likely to respond to specific psychosocial treatments. Given that a substantial minority of people fail to improve in treatment, even with our most empirically supported approaches, identifying people who are likely to fail and why might point us toward innovative new approaches for improving clinical outcomes. Second, neuroscience might facilitate the process of matching individuals to treatments from which they are most likely to benefit, in part by identifying clinically meaningful subgroups within specific diagnoses. Finally, neuroscience can potentially identify mechanisms of effective clinical change, allowing for the development of more efficient evidence-based treatments. We use the term "neuroscience" throughout the chapter to refer to the application of neuroscience to study cognitive and affective processes, and their development in humans.

After a brief review of common neuroscience methods, we discuss existing research within these three broad themes. Clinical applications of neuroscience remain limited, particularly with children and adolescents. Thus, we focus primarily on what is *possible* in terms of these applications (for additional review, see Fournier & Price, 2014; Weingarten & Strauman, 2015). At the same time, it is important to

acknowledge the current practical constraints of integrating neuroscience methods into clinical practice. Accordingly, we end with a discussion of obstacles, limitations, and future directions that might facilitate the application of neuroscience to clinical intervention for children and adolescents. As translational research in children is still limited, we discuss relevant research on children and adolescents where possible and highlight examples from research with adults when pediatric research is not available. Many of the reviewed neuroimaging studies focus on neural networks involved in salience and reward processing. The primary brain regions in each of these networks are depicted in Figures 30.1 and 30.2, respectively. We focus on incorporating neuroscience methods into the evaluation of evidence-based treatments. We do not cover treatments that are not empirically supported.

THE TOOLS OF NEUROSCIENCE

A variety of noninvasive neuroimaging methods for examining the structure and function of the human brain are commonly used to study clinical questions. Of

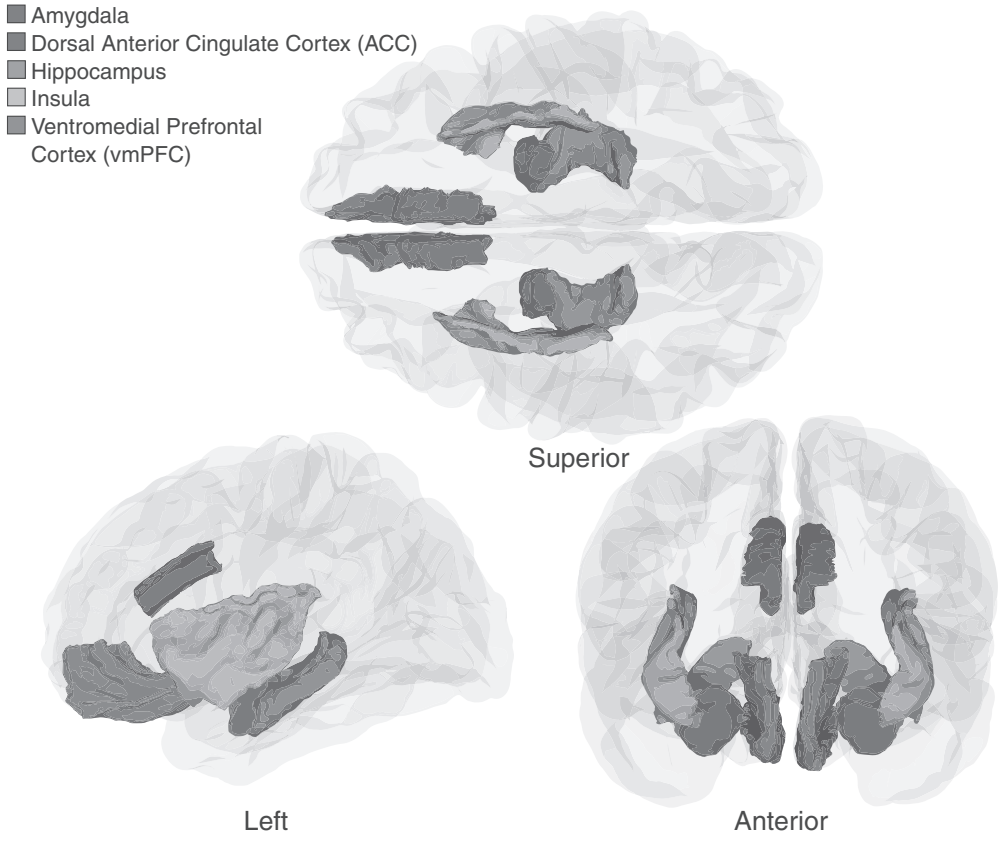

FIGURE 30.1. Key brain regions involved in fear learning and salience processing (brain data from Freesurfer: *http://surfer.nmr.mgh.harvard.edu*). A color version of this figure is available at *www.guilford.com/weisz-forms*.

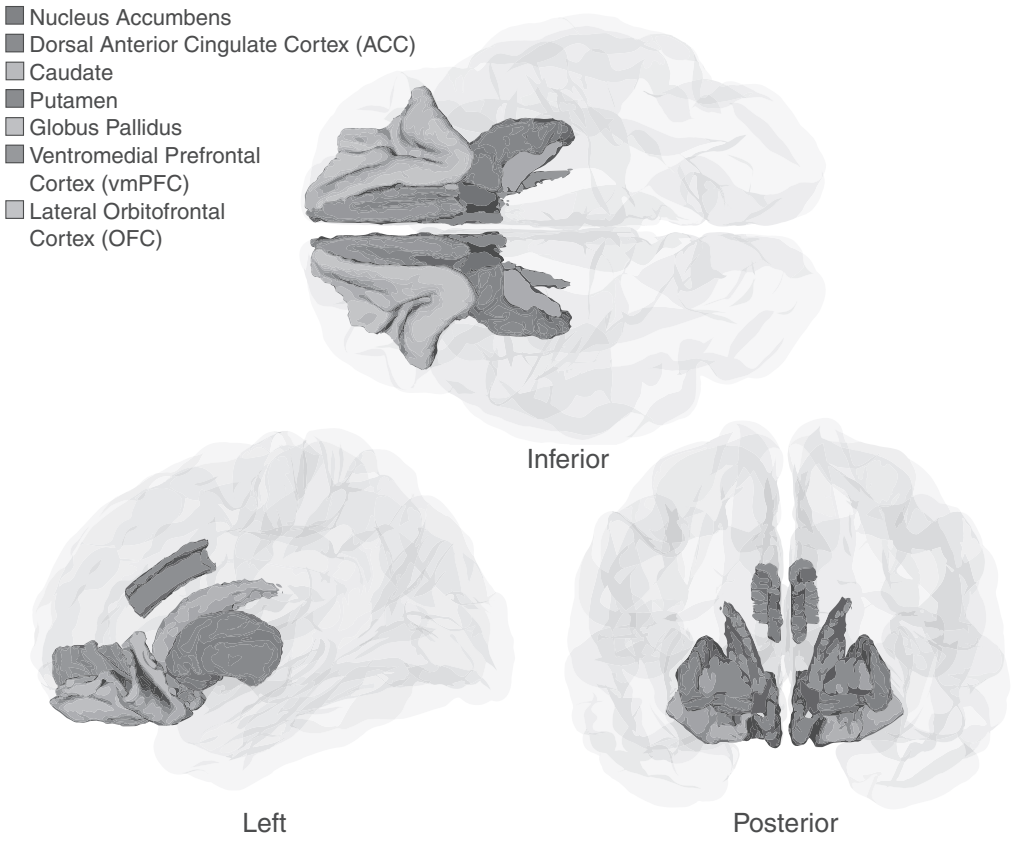

FIGURE 30.2. Key brain regions involved in reward processing (brain data from Freesurfer: *http://surfer.nmr.mgh.harvard.edu*). A color version of this figure is available at *www.guilford.com/weisz-forms*.

these, magnetic resonance imaging (MRI) and functional MRI (fMRI) are the most commonly used tools. Both methods exploit differences in the magnetic properties of brain tissues to construct images (Huettel, Song, & McCarthy, 2014). MRI is used to acquire high-resolution images of brain structure that provide information on the volume, surface area, and thickness of brain structures and is frequently used to measure structural differences between clinical and nonclinical populations, as well as deviations from typical developmental trajectories. fMRI is used to measure blood-oxygenation-level-dependent (BOLD) signal, which can be used to model neural activity. Most fMRI studies measure brain activity in the context of an experimental task. MRI techniques also may be used to measure the structural and functional connections between different brain regions. The integrity of structural connections between brain regions (i.e., white matter) can be estimated using diffusion tensor imaging (DTI), an MR image that is sensitive to directionality of diffusion in brain tissues. Functional connections between different brain regions can be measured by examining the degree to which regions activate together (using fMRI) either at rest (i.e., resting state functional connectivity) or in the context of an experimental task.

Although MRI methods have become predominant, other tools can be used to examine brain function. Electroencephalography (EEG) is a method of recording electrical activity in the brain through electrodes placed on the scalp. These electrodes can measure electrical properties of the brain at rest, as well as event-related potentials (ERPs) at particular locations in response to experimental stimuli. Relative to fMRI, EEG is less accurate in estimating the location of activity within the brain, but provides greater specificity of the timing of neural responses (Horwitz, Friston, & Taylor, 2000). A related technique, magnetoencephalography (MEG), measures magnetic perturbations caused by intracellular currents to acquire temporally and spatially specific information about brain activity (Krish, 2014). MEG has rarely been used to study psychosocial treatments. Finally, positron emission tomography (PET) scanners image the distribution of radioactive materials following an injection. By using contrast agents that act as analogues to glucose or other chemicals important to brain function, a variety of neural processes can be examined (Horwitz et al., 2000). PET methods are infrequently used with children.

USING NEUROSCIENCE TO PREDICT TREATMENT RESPONSE

Evidence-based psychotherapies have been shown to be broadly effective in treating children and adolescents (Weisz, Weiss, Han, Granger, & Morton, 1995). However, many children do not respond, even in highly controlled clinical trials, and treatment effects are generally smaller in real-world clinical settings than in efficacy trials (Weisz, Ugueto, Cheron, & Herren, 2013). To date, behavioral markers and diagnostic data routinely collected in clinical practice have provided few clues about which children are most likely to respond to treatment. Neuroscience can reveal differences in neural structure and function among children whose behavioral presentation is similar or identical, and these brain-related differences in otherwise equivalent cases might predict response to treatment better than behavioral measures. Identifying individual differences in neural structure and function that predict response to treatment may be especially relevant in children, where self-report methods are challenging and disagreement among reporters is the norm (De Los Reyes, Aldao, & Augenstein, Chapter 31, this volume; De Los Reyes & Kazdin, 2005). The measurement of individual differences in neural structure and function may in turn lead to the discovery of new behavioral instruments for use in clinical settings.

Recent research on the treatment of social anxiety disorder (SocAD) in adults provides an example of how neuroimaging tools can be used to predict treatment response. Although medication and cognitive-behavioral therapy (CBT) have both been shown to be efficacious in treating SocAD, a meaningful proportion of individuals do not respond to treatment in clinical trials, although more intensive combined therapies are associated with better response rates (e.g., Blanco et al., 2010). Recent evidence suggests that neural measures may have greater predictive utility than standard clinical measures in predicting treatment response among individuals with SocAD. For example, several studies have found that individuals with SocAD who exhibit greater pretreatment response to negative facial emotion in the dorsal and ventral occipitotemporal cortex (higher-order visual processing regions of the brain) respond better to CBT (Doehrmann et al., 2013; Klumpp, Fitzgerald,

& Phan, 2013). Together with clinical severity data, differences in task-related brain activity in these regions accounted for 41% of variability in treatment response in one study (Doehrmann et al., 2013). In a related study, when information about structural and functional connectivity provided by DTI and resting state fMRI was included in models of treatment prediction along with clinical severity data, response to CBT treatment was predicted with 81% accuracy (Whitfield-Gabrieli et al., 2016). In both of these studies, pretreatment clinical severity data and other behavioral indicators accounted for only 12% of treatment outcome variance.

Neuroscience approaches have recently been applied to predict treatment response in children and adolescents with anxiety, mood, and trauma-related disorders. For example, McClure et al. (2006) found that greater pretreatment amygdala activity (see Figure 30.1) while viewing fearful (vs. happy) faces was associated with higher clinician reports of symptom improvement in children receiving CBT or medication for anxiety disorders. A similar pattern was observed in a study of trauma-focused CBT for PTSD, where greater amygdala response to threatening versus neutral facial expressions was associated with faster PTSD symptom reduction in adolescent girls (Cisler et al., 2015). In adolescent depression, greater activity in the nucleus accumbens and caudate while anticipating a possible monetary reward in a guessing task predicted reduced posttreatment anxiety symptoms and a steeper rate of improvement in adolescents undergoing CBT (Forbes et al., 2010; see Figure 30.2). In children, as in adults, preliminary but promising evidence suggests that neural measures convey information about prospective treatment response that is not captured by existing clinical measures. Future research is needed to expand on this knowledge base and identify the mechanisms underlying these associations.

Neuroimaging technology is currently insufficiently advanced for practical direct measurement of these biomarkers in a typical clinical setting. However, neural models of treatment response may lead to similarly predictive models using behavioral or psychophysiological tools that are easier to measure in clinical settings (we discuss this possibility at greater length in the final section of the chapter). In clinical practice, these measures might allow for more effective triage of cases to more intensive and effective treatments (e.g., combined CBT and medication), leading to more rapid improvement for clients and less time spent on therapies that are unlikely to be effective.

USING NEUROSCIENCE TO FACILITATE INDIVIDUALIZED CARE

In the face of long-standing evidence that many evidence-based treatments are broadly similar in effectiveness (e.g., CBT and interpersonal psychotherapy for adolescent depression), clinicians are often faced with the issue of deciding which treatment will be most effective for a particular client. However, there are few clear guidelines to help clinicians make such decisions or to suggest the utility of one treatment over another. Neuroscience may facilitate the discovery of innovative tools for clinicians to select the most effective treatments for their clients by revealing biomarkers of response to specific treatments and differentiating clinically relevant subtypes of specific forms of psychopathology. Research on major depressive disorder (MDD) has already begun to explore these topics.

Although several psychotherapies and pharmacotherapies for adolescents with MDD have received substantial empirical support, at least 15% of adolescents with MDD do not respond even to our best treatments (March et al., 2007; Weisz, McCarty, & Valeri, 2006). While alternative treatments for adolescents who do not respond to an initial MDD treatment can be effective (Brent et al., 2008), it remains true that many youth spend substantial amounts of time undergoing treatments that, ultimately, will not be effective, increasing the amount of time they spend experiencing depression and the associated risks for negative sequelae, including self-harm. The availability of clear indicators suggesting a particular therapy for a particular adolescent with depression could fundamentally change the course of treatment in these cases. Currently, few reliable indicators exist (Hollon et al., 2005; Sherrill & Kovacs, 2004).

Neuroimaging studies have begun to reveal a number of biomarkers that predict treatment response in adults. While many of these biomarkers predict treatment response across treatment methods (Konarski et al., 2009; Siegle et al., 2012), there is already some evidence for biomarkers that predict variable response to *specific* treatments. In one study comparing CBT to medication for adults with MDD using PET, reduced resting state glucose metabolism in the insula—an area of the brain that has been associated with emotional and interoceptive awareness—was associated with greater remission during CBT but poor response to medication treatment, whereas adults with increased insula metabolism responded better to medication than to CBT (McGrath et al., 2013). In a follow-up study, the symptoms of nonresponders reassigned to combined therapy were more likely to remit if their added treatment component matched the appropriate biomarker (Dunlop, Kelley, McGrath, Craighead, & Mayberg, 2015). One possible explanation for these findings is that the lower glucose metabolism in the insula corresponds to a reduced level of emotional and interoceptive awareness that may be addressed with CBT better than with medication, although additional research is needed to identify the specific cognitive and affective processes that might be influenced by variation in resting state glucose metabolism in the insula. Investigation of these types of treatment-selective biomarkers could lead to novel recommendations about which individuals with MDD might preferentially respond to CBT versus medication.

Further possibilities for individualized treatment come from neuroscience studies of subtypes of specific forms of psychopathology. Traditionally, diagnostic categories have been established according to symptom clusters outlined in the *Diagnostic and Statistical Manual for Mental Disorders* (DSM). These categories may obscure distinct endophenotypes that contribute to similar symptomatic presentations despite distinct neurobiological and etiological characteristics (Charney et al., 2002). By identifying biologically distinct characteristics of specific endophenotypes, neuroscience may provide evidence for heterogeneity within particular diagnostic clusters and, potentially, inform assessment and treatment options. For example, anhedonia—an experience characterized by difficulty feeling pleasure—is a common feature of MDD (Goldstein & Klein, 2014; Pechtel, Dutra, Goetz, & Pizzagalli, 2013) and has been shown to predict treatment nonresponse in adults and adolescents (McMakin et al., 2012; Vrieze et al., 2013). Pizzagalli and colleagues have shown that anhedonia is associated with atypical structure and function in neural networks involved in reward processing that are distinct from other symptoms of

depression and anxiety. Specifically, anhedonia—but not other symptoms of depression—is associated with reduced volume of the nucleus accumbens (see Figure 30.2) and blunted nucleus accumbens response to reward (Wacker, Dillon, & Pizzagalli, 2009). If neuroscience can provide tools to identify endophenotypes of MDD and other disorders on a case-by-case basis, then clinicians may ultimately be able to select treatments that specifically target the key neural and behavioral characteristics of those endophenotypes. For example, behavioral activation is an empirically supported treatment for MDD that specifically targets anhedonia and has been shown to produce functional changes in brain structures associated with reward processing, including greater activity in the caudate while anticipating a reward, and in the paracingulate gyrus and orbital frontal cortex when receiving one (Dichter et al., 2009; see Figure 30.2). Although clinical instruments for assessing anhedonia via self- and collateral reports exist, neuroscience advances may contribute new and less subjective measures of anhedonia that are informed by studies of underlying neurobiology and not simply reports of clients or their parents, a point to which we return at the end of this chapter.

Neuroscience may also aid treatment research by identifying subtypes of psychopathology related to differences in environmental experience. For example, children who have experienced maltreatment are at elevated risk for developing MDD and many other forms of psychopathology (Kilpatrick et al., 2003; McLaughlin et al., 2012), and respond more poorly to treatments for MDD than do youth without maltreatment exposure (Nanni, Uher, & Danese, 2012), particularly CBT (Barbe, Bridge, Birmaher, Kolko, & Brent, 2004; Lewis et al., 2010). Differences in neural structure and function might explain this elevated risk for psychopathology and poor treatment response. For example, maltreated youth exhibit greater amygdala response to negative cues—a pattern associated with anxiety and other forms of internalizing psychopathology (e.g., Thomas et al., 2001) and greater recruitment of the prefrontal cortex during attempts to regulate emotion using cognitive reappraisal (McLaughlin, Peverill, Gold, Alves, & Sheridan, 2015). This pattern suggests that cognitive reappraisal requires greater cognitive resources for maltreated than for nonmaltreated youth, and that greater practice in cognitive restructuring might be necessary for it to be effective for them. Other work suggests that maltreatment is associated with blunted response to reward in the ventral striatum (Hanson, Hariri, & Williamson, 2015), an area largely overlapping the nucleus accumbens. This is the same pattern described earlier in association with anhedonia (Pechtel et al., 2013). This pattern suggests that behavioral activation might be a particularly useful treatment option for maltreated children with MDD, although we are unaware of studies testing this possibility. Taken together, it has been argued that MDD, and potentially other forms of psychopathology, in maltreated youth constitute a distinct clinical subtype requiring alternative treatments (Teicher & Samson, 2013). By identifying neurobiological differences that might explain why treatments are less effective in maltreated youth, neuroscience may allow clinical scientists to hypothesize and test individualized courses of treatment for children and adolescents with a history of maltreatment.

If replicated, these and similar studies could inform a new generation of clinical assessments designed not only to assess symptomatology but also to provide clues as to the treatment most likely to be effective for a particular client. Neuroscience

approaches might ultimately contribute to the development of behavioral measures that discriminate between neural states corresponding to different treatment sensitivities and might be more feasible for use in clinical settings. Eventually, advances in technology (e.g., mobile scanners) may even allow neuroimaging tools to be incorporated into routine assessment. In either case, more rapid prescription of individualized courses of care would facilitate faster clinical gains, resulting in better quality care, and less time and money spent on treatments that are unlikely to be effective.

USING NEUROSCIENCE TO IDENTIFY MECHANISMS OF TREATMENT CHANGE

Clinical psychology has reached a stage of treatment research where the question has shifted from what works to *how* and *for whom* our evidence-based treatments work. Although hundreds of evidence-based treatments for children and adolescents exist, few treatment studies propose or evaluate a specific and justifiable mechanism through which the effect of a treatment on clinical gains is mediated (Kazdin, 2007; Weersing & Weisz, 2002). There is an urgent need for this type of research on treatment mechanisms, as understanding the mechanisms through which our treatments work will allow us to optimize treatments to be most effective, make treatment more efficient by retaining only essential elements, better predict individual differences in treatment response, and identify new therapeutic methods and opportunities (Kazdin, 2007). By articulating neurobiological mechanisms underlying the etiology and maintenance of psychopathology and treatment efficacy, and providing new ways to observe these mechanisms in the brain, neuroscience provides a unique source of information about how and why our treatments work and how we can improve them.

We provide an illustrative example of how neuroscience can help clarify the mechanism of treatment for CBT for posttraumatic stress disorder (PTSD). Exposure to trauma creates powerful associations between fear and the people, sights, sounds, and smells that were present during the traumatic event. These fear memories are readily recalled when survivors of trauma are exposed to stimuli associated with the traumatic experience. In the normal course of recovery following a traumatic event, most people gradually begin to associate these feared stimuli with safety as they repeatedly encounter them without threat; this process is known as extinction learning. However, the original fear memory coexists with these safety memories and can be reinstated in specific circumstances (Bouton, 2002, 2004). Many theoretical accounts of PTSD propose that the disorder reflects a failure of extinction learning and the retrieval of that learning, resulting in poor inhibition of fear (Jovanovic & Ressler, 2010; Milad & Quirk, 2012). In essence, safety (or extinction) memories are difficult to create or retrieve for individuals who develop PTSD following a trauma, resulting in persistent fear responses to cues associated with the traumatic event; these persistent fear responses are reflected in the intrusion symptoms of PTSD (Norrholm et al., 2011). A proposed mechanism for the effectiveness of exposure treatments for PTSD, which have strong empirical support (Cohen, Deblinger, Mannarino, & Steer, 2004; Foa, McLean, Capaldi, & Rosenfield,

2013), is that they alleviate PTSD symptoms by supporting fear extinction (Rothbaum & Davis, 2003). However, it is difficult to verify that the mechanism of change in exposure therapy in PTSD actually involves improvements in the ability to retain and retrieve extinction memories using behavioral methods alone.

Neuroscience provides a direct method for measuring fear extinction learning and retrieval. Evidence from both animal and human studies documents the central role of the amygdala (see Figure 30.1) in both the acquisition of fear (Delgado, Olsson, & Phelps, 2006; Johansen, Cain, Ostroff, & LeDoux, 2011) and in extinction learning (Phelps, Delgado, Nearing, & LeDoux, 2004). During successful retrieval of extinction learning, the ventromedial prefrontal cortex (vmPFC) is activated and inhibits the amygdala and, accordingly, the original fear memory (Milad & Quirk, 2012; Phelps et al., 2004). Research in neuroscience has already established differences in brain structure and function in individuals with PTSD consistent with hypothesized learning and neural mechanisms, with individuals with PTSD showing greater amygdala activity and reduced vmPFC activity during retrieval of extinction learning (Milad et al., 2008, 2009). Simpler biomarkers can also be used to measure these processes outside the scanner, most notably, skin conductance response (a measure of sympathetic nervous system activation that reflects greater arousal and fear) and fear-potentiated startle (Jovanovic & Ressler, 2010; Norrholm et al., 2011; Phelps et al., 2004).

We are unaware of research examining whether improvements in the retention of extinction learning are a mechanism explaining successful treatment of PTSD with exposure therapy, despite long-standing theoretical speculation that this is the mechanism underlying exposure therapy. Examination of the effects of PTSD treatment on the learning processes and underlying neural systems involved in fear extinction would allow us to test whether exposure is working the way we expect, to monitor progress, and to test conceptual models of the etiology and maintenance of PTSD. If treatment effects and corresponding improvements in symptomatology correspond to theoretical projections, it becomes possible to improve treatments based on these models, including novel pharmacological adjuncts to evidence-based treatments (Davis, Ressler, Rothbaum, & Richardson, 2006; Ganasen, Ipser, & Stein, 2010) as well as innovations in behavioral treatment (Monfils, Cowansage, Klann, & LeDoux, 2009; Schiller et al., 2010). Although these mechanisms have yet to be examined in PTSD, recent research suggests that children and adolescents who do not respond to CBT for anxiety disorders exhibit blunted reduction in skin conductance responses during fear extinction relative to treatment responders and nonanxious children (Waters & Pine, 2016). This finding provides some support for the clinical relevance of fear learning processes, and the neural circuitry that supports them, to treatment outcomes in children and adolescents.

Most intriguingly, close integration of treatment with neurobiological models of psychopathology allows us to explore innovative theories that could explain shortcomings in our treatment methods. For example, recent neuroscience research suggests that, rather than representing a simple deficit in recall of fear extinction memories, PTSD may ultimately result from a failure to discriminate between contexts associated with safety and those associated with threat, possibly related to structural and functional differences in the hippocampus (Garfinkel et al., 2014; O'Doherty, Chitty, Saddiqui, Bennett, & Lagopoulos, 2015; Rougemont-Bücking et

al., 2011). Further investigation supporting a context-processing account of PTSD could lead to novel improvements in treatment approaches. For example, it is possible that contextual modulation during exposure therapy (e.g., by changing where exposure is conducted, either *in vivo* or through virtual reality) would improve treatment outcomes. This approach has received some support in research on simple phobia (Vansteenwegen et al., 2007). In PTSD, this hypothesis is premature but potentially promising if a context processing account of PTSD continues to receive support. However, because contextual processing is quite challenging to study with behavioral methods, direct comparison of these competing theories is currently possible only with neuroscience methods.

Neuroscience research on mechanisms underlying the etiology and maintenance of child and adolescent psychopathology is particularly valuable, because developmental changes in relevant neural systems may identify periods of greater or lesser sensitivity to individual treatments. For example, the model of PTSD reviewed earlier focused on disruptions in the retrieval of extinction memories related to trauma-relevant cues in adults with PTSD. Recent translational work spanning rodent and human research suggests meaningful developmental variation in extinction learning, with impaired extinction learning occurring during adolescence in both rodents and humans (Pattwell et al., 2012). Although replication of this finding is critical, it suggests that modification of core elements of exposure-based treatments for PTSD might improve treatment efficacy in adolescents. In particular, delivering treatment elements involving exposure for an extended period of time might be needed to facilitate fear extinction in adolescents. Future research is needed to examine this possibility directly.

LIMITATIONS, OBSTACLES, AND FUTURE DIRECTIONS

Although clinical neuroscience has made tremendous strides in recent years and has potential to improve treatment practices, there is still much to learn. The burden of proof lies with researchers to produce neuroscience research with clear translational applications, and a number of obstacles and limitations will need to be overcome before the clinical potential of neuroscience to improve psychosocial treatments for children and adolescents can be fully realized.

Perhaps the most obvious conclusion at this stage is the need for more neuroscience research specifically examining disorders of childhood and their treatment. Although extensive neuroscience research focuses on associations of brain structure and function with mental health and increasingly with treatment, much of this research has been conducted in adults. However, developmental variations in behavior and psychopathology are frequently paralleled by broad developmental changes in the brain. These developmental changes have important implications for understanding the etiology and treatment of psychopathology in children and adolescents. For example, it has been argued that the elevated risk for onset of MDD, anxiety, risk behaviors, and substance use that occurs during adolescence is related to the greater salience of aversive and appetitive cues but reduced capacity to modulate responses to these cues during this developmental period, and that these behavioral changes are explained by the earlier functional development of

structures that respond to emotional salience (e.g., the amygdala) and reward (e.g., the ventral striatum) relative to regions in the prefrontal cortex that modulate and inhibit activation in these subcortical structures (Casey & Jones, 2010; Galvan et al., 2006; Hare et al., 2008; Somerville, Jones, & Casey, 2010; Steinberg, 2008). Increasing awareness of the profound changes in neural structure and function that accompany development and the numerous implications that these changes have for understanding child and adolescent psychopathology have led to an explosion of research in developmental neuroscience. Yet these advances have yet to be applied in a systematic way to treatment research. For example, the seminal adolescent "imbalance" theory described earlier has potential implications for adapting evidence-based treatments of both internalizing and externalizing problems to be more attuned to the unique neurodevelopmental features of adolescence. For example, heightened sensitivity of the ventral striatum to reward during this developmental period may make adolescents particularly likely to respond to treatments that target reward-related processes, such as behavioral activation. We are unaware of research examining this or other hypotheses on the treatment implications of this theory. It is crucial that clinical neuroscience continue to ask developmental questions and that translational research is conducted with the specific goal of exploring the clinical implications and utility of new discoveries in developmental neuroscience.

A second key issue involves the degree to which it is practical and logistically feasible to incorporate neuroscience measures into clinical research with children and adolescents. There are many practical obstacles to the use of these tools with children in research and clinical contexts. MRI data acquisition is both expensive and time consuming. As scanning procedures can generate anxiety and require children to be separated from their parents, special training and practice are typically required when scanning children, especially children with psychopathology. Of particular concern with children is the importance of remaining still during the scan to generate data that are free of motion-related artifacts, which requires training and sometimes practice in a mock scanner (Raschle et al., 2009). Even after data have been acquired, additional expertise is required for preprocessing and analysis (see Huettel et al., 2014, for an overview). Other methods such as EEG also require substantial investments of time and money, as well as meaningful amounts of data processing.

Although we believe that neuroscience provides important tools for improving treatment methods, it would be unreasonable for clinicians to accept exponentially increased assessment costs and the need for technicians with advanced skills in computer programming and image analysis with either enthusiasm or much hope of improved care for their clients. To that end, realizing the clinical potential of neuroscience for child and adolescent treatments will require close collaboration between neuroscientists and treatment researchers, each of whom bring necessary but not sufficient skills to tackle these challenges. We are confident that advances in technology, especially more portable and cheaper data acquisition tools, as well as improved analysis software, will continue to reduce the cost and burden of conducting neuroscience research, although it is not clear whether this progress will produce a degree of automation and quality control sufficient to make routine neuroimaging feasible in clinical contexts.

Although advances in technology may indeed render the direct application of neuroscience methods to treatment more feasible, it is more realistic in the near future that neuroscience will enable better treatments by identifying more easily measureable correlates of clinically relevant biomarkers. Numerous behavioral tasks already exist that are reliably associated with neural function and have potential applications to treatment. For example, anhedonia is associated with a unique pattern of behavior on reward learning tasks as compared to other symptoms of depression, and this behavioral pattern is strongly associated with the atypical neural phenotype that characterizes anhedonia, which we have previously discussed. Specifically, individuals with anhedonia do not change their behavior (e.g., respond more quickly or accurately) to stimuli involving a greater probability of reward, and this behavioral pattern also predicts increases in anhedonia over time (Pizzagalli, Jahn, & O'Shea, 2005). Reward learning tasks require only a computer to administer and can be scored automatically. Incorporatving these behavioral tasks into intake assessments for depression could help to identify a group of clients for whom a treatment specifically targeting anhedonia, such as behavioral activation, might be appropriate. Indeed, some research in adults has suggested that behavioral activation may be more effective than cognitive therapy for severe depression, which is often characterized by anhedonia (Dimidjian et al., 2006). Tasks assessing attention bias to threat (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007), cognitive control (Schoemaker et al., 2012), and adaptation to emotional conflict (Etkin, Egner, Peraza, Kandel, & Hirsch, 2006)—among many other cognitive and affective functions—might hold similar promise in this regard.

Many steps remain before the full potential of neuroscience to effect clinical gains in pediatric treatment can be realized. More neuroscience research needs to be conducted in child and adolescent samples with specific translational goals in diagnosis or treatment evaluation, and treatment researchers should incorporate neural measures within intervention studies in order to capture data on neural mechanisms of effective clinical change. As we learn more about clinical biomarkers, researchers will need to investigate related behavioral and physiological measures that are practical in clinical settings. Finally, effective training and dissemination strategies for neuroscience-informed methods will need to be developed.

CONCLUDING COMMENTS

Neuroscience provides great promise in informing future treatments of children and adolescents. It has the potential to reveal individual differences in neural function that are related to variability in treatment response. Investigation of these differences and the discovery of easily administered measures of these biomarkers may allow us to make better-informed judgments about the most effective treatments for individual clients, particularly in domains where meaningful subgroups respond differentially to specific treatments. Investigation of the neural correlates of child and adolescent psychopathology and its treatment has the potential to reveal the mechanisms by which our clients get better. This may provide new insights into treatments that are known to be effective and generate new questions about how

treatments can target disruptions in brain development that result in psychopathology.

There remains much to learn about these topics. Special effort will be needed to conduct neuroscience research with both a specific focus on the assessment and treatment of child and adolescent psychopathology and a clear goal of clinically relevant discovery. Nevertheless, we believe that neuroscience has the potential to enrich our understanding of psychopathology and its treatment. This, in turn, may allow us to develop more effective treatments for children and adolescents in the future.

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REFERENCES

Barbe, R. P., Bridge, J. A., Birmaher, B., Kolko, D. J., & Brent, D. A. (2004). Lifetime history of sexual abuse, clinical presentation, and outcome in a clinical trial for adolescent depression. *Journal of Clinical Psychiatry, 65*(1),478–483.

Bar-Haim, Y., Lamy, D., Pergamin, L., Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (2007). Threat-related attentional bias in anxious and nonanxious individuals: A meta-analytic study. *Psychological Bulletin, 133,* 1–24.

Blanco, C., Heimberg, R. G., Schneier, F. R., Fresco, D. M., Chen, H., Turk, C. L., et al. (2010). A placebo-controlled trial of phenelzine, cognitive behavioral group therapy and their combination for social anxiety disorder. *Archives of General Psychiatry, 67,* 286–295.

Bouton, M. E. (2002). Context, ambiguity, and unlearning: Sources of relapse after behavioral extinction. *Biological Psychiatry, 52,* 976–986.

Bouton, M. E. (2004). Context and behavioral processes in extinction. *Learning and Memory, 11,* 485–494.

Brent, D., Emslie, G., Clarke, G., Wagner, K. D., Asarnow, J. R., Keller, M., et al. (2008). Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression. *Journal of the American Medical Association, 299,* 901–913.

Casey, B. J., & Jones, R. M. (2010). Neurobiology of the adolescent brain and behavior: Implications for substance use disorders. *Journal of the American Academy of Child and Adolescent Psychiatry, 49,* 1189–1201.

Charney, D. S., Barlow, D. H., Botteron, K., Cohen, J. D., Goldman, D., Gur, R. E., et al. (2002). Neuroscience research agenda to guide development of a pathophysiologically based classification system. In D. J. Kupfer, M. B. First, & D. A. Regier (Eds.), *A research agenda for DSM-V* (pp. 31–83). Arlington, VA: American Psychiatric Association.

Cisler, J. M., Sigel, B. A., Kramer, T. L., Smitherman, S., Vanderzee, K., Pemberton, J., et al. (2015). Amygdala response predicts trajectory of symptom reduction during trauma-focused cognitive-behavioral therapy among adolescent girls with PTSD. *Journal of Psychiatric Research, 71,* 33–40.

Cohen, J. A., Deblinger, E., Mannarino, A. P., & Steer, R. (2004). A multi-site, randomized

controlled trial for children with abuse-related PTSD symptoms. *Journal of the American Academy of Child and Adolescent Psychiatry, 43,* 393–402.

Davis, M., Ressler, K., Rothbaum, B. O., & Richardson, R. (2006). Effects of D-cycloserine on extinction: Translation from preclinical to clinical work. *Biological Psychiatry, 60,* 369–375.

Delgado, M. R., Olsson, A., & Phelps, E. A. (2006). Extending animal models of fear conditioning to humans. *Biological Psychology, 73,* 39–48.

De Los Reyes, A., & Kazdin, A. E. (2005). Informant discrepancies in the assessment of childhood psychopathology: A critical review, theoretical framework, and recommendations for further study. *Psychological Bulletin, 131,* 483–509.

Dichter, G. S., Felder, J. N., Petty, C., Bizzell, J., Ernst, M., & Smoski, M. J. (2009). The effects of psychotherapy on neural responses to rewards in major depression. *Biological Psychiatry, 66,* 886–897.

Dimidjian, S., Hollon, S. D., Dobson, K. S., Schmaling, K. B., Kohlenberg, R. J., Addis, M. E., et al. (2006). Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the acute treatment of adults with major depression. *Journal of Consulting and Clinical Psychology, 74,* 658–670.

Doehrmann, O., Ghosh, S. S., Polli, F. E., Reynolds, G. O., Horn, F., Keshavan, A., et al. (2013). Predicting treatment response in social anxiety disorder from functional magnetic resonance imaging. *JAMA Psychiatry, 70,* 87–97.

Dunlop, B. W., Kelley, M. E., McGrath, C. L., Craighead, W. E., & Mayberg, H. S. (2015). Preliminary findings supporting insula metabolic activity as a predictor of outcome to psychotherapy and medication treatments for depression. *Journal of Neuropsychiatry and Clinical Neurosciences, 27,* 237–239.

Etkin, A., Egner, T., Peraza, D. M., Kandel, E. R., & Hirsch, J. (2006). Resolving emotional conflict: A role for the rostral anterior cingulate cortex in modulating activity in the amygdala. *Neuron, 51,* 871–882.

Foa, E. B., McLean, C. P., Capaldi, S., & Rosenfield, D. (2013). Prolonged exposure vs supportive counseling for sexual abuse–related PTSD in adolescent girls: A randomized clinical trial. *Journal of the American Medical Association, 310,* 2650–2657.

Forbes, E. E., Olino, T. M., Ryan, N. D., Birmaher, B., Axelson, D., Moyles, D. L., et al. (2010). Reward-related brain function as a predictor of treatment response in adolescents with major depressive disorder. *Cognitive, Affective, and Behavioral Neuroscience, 10,* 107–118.

Fournier, J. C., & Price, R. B. (2014). Psychotherapy and neuroimaging. *Focus: The Journal of Lifelong Learning in Psychiatry, 12,* 290–298.

Galvan, A., Hare, T. A., Parra, C. E., Penn, J., Voss, H., Glover, G., et al. (2006). Earlier development of the accumbens relative to orbitofrontal cortex might underlie risk-taking behavior in adolescents. *Journal of Neuroscience, 26,* 6885–6892.

Ganasen, K. A., Ipser, J. C., & Stein, D. J. (2010). Augmentation of cognitive behavioral therapy with pharmacotherapy. *Psychiatric Clinics of North America, 33,* 687–699.

Garfinkel, S. N., Abelson, J. L., King, A. P., Sripada, R. K., Wang, X., Gaines, L. M., et al. (2014). Impaired contextual modulation of memories in PTSD: An fMRI and psychophysiological study of extinction retention and fear renewal. *Journal of Neuroscience, 34,* 13435–13443.

Goldstein, B. L., & Klein, D. N. (2014). A review of selected candidate endophenotypes for depression. *Clinical Psychology Review, 34,* 417–427.

Hanson, J. L., Hariri, A. R., & Williamson, D. E. (2015). Blunted ventral striatum development in adolescence reflects emotional neglect and predicts depressive symptoms. *Biological Psychiatry, 78,* 598–605.

Hare, T. A., Tottenham, N., Galvan, A., Voss, H. U., Glover, G. H., & Casey, B. J. (2008).

Biological substrates of emotional reactivity and regulation in adolescence during an emotional go-nogo task. *Biological Psychiatry, 63,* 927–934.

Hollon, S. D., Jarrett, R. B., Nierenberg, A. A., Thase, M. E., Trivedi, M., & Rush, A. J. (2005). Psychotherapy and medication in the treatment of adult and geriatric depression: Which monotherapy or combined treatment? *Journal of Clinical Psychiatry, 66*(1), 478–468.

Horwitz, B., Friston, K. J., & Taylor, J. G. (2000). Neural modeling and functional brain imaging: An overview. *Neural Networks, 13,* 829–846.

Huettel, S. A., Song, A. W., & McCarthy, G. (2014). *Functional magnetic resonance imaging* (3rd ed.). Sunderland, MA: Sinauer.

Johansen, J. P., Cain, C. K., Ostroff, L. E., & LeDoux, J. E. (2011). Molecular mechanisms of fear learning and memory. *Cell, 147,* 509–524.

Jovanovic, T., & Ressler, K. J. (2010). How the neurocircuitry and genetics of fear inhibition may inform our understanding of PTSD. *American Journal of Psychiatry, 167,* 648–662.

Kazdin, A. E. (2007). Mediators and mechanisms of change in psychotherapy research. *Annual Review of Clinical Psychology, 3,* 1–27.

Kilpatrick, D. G., Ruggiero, K. J., Acierno, R., Saunders, B. E., Resnick, H. S., & Best, C. L. (2003). Violence and risk of PTSD, major depression, substance abuse/dependence, and comorbidity: Results from the National Survey of Adolescents. *Journal of Consulting and Clinical Psychology, 71,* 692–700.

Klumpp, H., Fitzgerald, D. A., & Phan, K. L. (2013). Neural predictors and mechanisms of cognitive behavioral therapy on threat processing in social anxiety disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 45,* 83–91.

Konarski, J. Z., Kennedy, S. H., Segal, Z. V., Lau, M. A., Bieling, P. J., McIntyre, R. S., et al. (2009). Predictors of nonresponse to cognitive behavioural therapy or venlafaxine using glucose metabolism in major depressive disorder. *Journal of Psychiatry and Neuroscience, 34,* 175–180.

Krish, S. D. (2014). Magnetoencephalography. In C. Senior, T. Russell, & M. S. Gazzaniga (Eds.), *Methods in mind* (pp. 291–326). Cambridge, MA: MIT Press.

Lewis, C. C., Simons, A. D., Nguyen, L. J., Murakami, J. L., Reid, M. W., Silva, S. G., et al. (2010). Impact of childhood trauma on treatment outcome in the Treatment for Adolescents with Depression Study (TADS). *Journal of the American Academy of Child and Adolescent Psychiatry, 49,* 132–140.

March, J. S., Silva, S., Petrycki, S., Curry, J., Wells, K., Fairbank, J., et al. (2007). The Treatment for Adolescents with Depression Study (TADS): Long-term effectiveness and safety outcomes. *Archives of General Psychiatry, 64,* 1132–1143.

McClure, E. B., Adler, A., Monk, C. S., Cameron, J., Smith, S., Nelson, E. E., et al. (2006). fMRI predictors of treatment outcome in pediatric anxiety disorders. *Psychopharmacology, 191,* 97–105.

McGrath, C. L., Kelley, M. E., Holtzheimer, P. E., Dunlop, B. W., Craighead, W. E., Franco, A. R., et al. (2013). Toward a neuroimaging treatment selection biomarker for major depressive disorder. *JAMA Psychiatry, 70,* 821–829.

McLaughlin, K. A., Greif Green, J., Gruber, M. J., Sampson, N. A., Zaslavsky, A. M., & Kessler, R. C. (2012). Childhood adversities and first onset of psychiatric disorders in a national sample of US adolescents. *Archives of General Psychiatry, 69,* 1151–1160.

McLaughlin, K. A., Peverill, M., Gold, A. L., Alves, S., & Sheridan, M. A. (2015). Child maltreatment and neural systems underlying emotion regulation. *Journal of the American Academy of Child and Adolescent Psychiatry, 54,* 753–762.

McMakin, D. L., Olino, T. M., Porta, G., Dietz, L. J., Emslie, G., Clarke, G., et al. (2012). Anhedonia predicts poorer recovery among youth with selective serotonin reuptake

inhibitor-treatment resistant depression. *Journal of the American Academy of Child and Adolescent Psychiatry, 51,* 404–411.

Milad, M. R., Orr, S. P., Lasko, N. B., Chang, Y., Rauch, S. L., & Pitman, R. K. (2008). Presence and acquired origin of reduced recall for fear extinction in PTSD: Results of a twin study. *Journal of Psychiatric Research, 42,* 515–520.

Milad, M. R., Pitman, R. K., Ellis, C. B., Gold, A. L., Shin, L. M., Lasko, N. B., et al. (2009). Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder. *Biological Psychiatry, 66,* 1075–1082.

Milad, M. R., & Quirk, G. J. (2012). Fear extinction as a model for translational neuroscience: Ten years of progress. *Annual Review of Psychology, 63,* 129–151.

Monfils, M. H., Cowansage, K. K., Klann, E., & LeDoux, J. E. (2009). Extinction–reconsolidation boundaries: Key to persistent attenuation of fear memories. *Science, 324,* 951–955.

Nanni, V., Uher, R., & Danese, A. (2012). Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: A meta-analysis. *American Journal of Psychiatry, 169,* 141–151.

Norrholm, S. D., Jovanovic, T., Olin, I. W., Sands, L. A., Karapanou, I., Bradley, B., et al. (2011). Fear extinction in traumatized civilians with posttraumatic stress disorder: Relation to symptom severity. *Biological Psychiatry, 69,* 556–563.

O'Doherty, D. C. M., Chitty, K. M., Saddiqui, S., Bennett, M. R., & Lagopoulos, J. (2015). A systematic review and meta-analysis of magnetic resonance imaging measurement of structural volumes in posttraumatic stress disorder. *Psychiatry Research: Neuroimaging, 232,* 1–33.

Pattwell, S. S., Duhoux, S., Hartley, C. A., Johnson, D. C., Jing, D., Elliott, M. D., et al. (2012). Altered fear learning across development in both mouse and human. *Proceedings of the National Academy of Sciences USA, 109,* 16318–16323.

Pechtel, P., Dutra, S. J., Goetz, E. L., & Pizzagalli, D. A. (2013). Blunted reward responsiveness in remitted depression. *Journal of Psychiatric Research, 47,* 1864–1869.

Phelps, E. A., Delgado, M. R., Nearing, K. I., & LeDoux, J. E. (2004). Extinction learning in humans: Role of the amygdala and vmPFC. *Neuron, 43,* 897–905.

Pizzagalli, D. A., Jahn, A. L., & O'Shea, J. P. (2005). Toward an objective characterization of an anhedonic phenotype: A signal-detection approach. *Biological Psychiatry, 57,* 319–327.

Raschle, N. M., Lee, M., Buechler, R., Christodoulou, J. A., Chang, M., Vakil, M., et al. (2009). Making MR imaging child's play—pediatric neuroimaging protocol, guidelines and procedure. *Journal of Visualized Experiments, 29,* e1309.

Rothbaum, B. O., & Davis, M. (2003). Applying learning principles to the treatment of posttrauma reactions. *Annals of the New York Academy of Sciences, 1008,* 112–121.

Rougemont-Bücking, A., Linnman, C., Zeffiro, T. A., Zeidan, M. A., Lebron-Milad, K., Rodriguez-Romaguera, J., et al. (2011). Altered processing of contextual information during fear extinction in PTSD: An fMRI study. *CNS Neuroscience and Therapeutics, 17,* 227–236.

Schiller, D., Monfils, M. H., Raio, C. M., Johnson, D. C., LeDoux, J. E., & Phelps, E. A. (2010). Preventing the return of fear in humans using reconsolidation update mechanisms. *Nature, 463,* 49–53.

Schoemaker, K., Bunte, T., Wiebe, S. A., Espy, K. A., Dekovič, M., & Matthys, W. (2012). Executive function deficits in preschool children with ADHD and DBD. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 53,* 111–119.

Sherrill, J. T., & Kovacs, M. (2004). Nonsomatic treatment of depression. *Psychiatric Clinics of North America, 27,* 139–154.

Siegle, G. J., Thompson, W. K., Collier, A., Berman, S. R., Feldmiller, J., Thase, M. E., et al. (2012). Towards clinically useful neuroimaging in depression treatment: Is subgenual cingulate activity robustly prognostic for depression outcome in cognitive therapy across studies, scanners, and patient characteristics? *Archives of General Psychiatry, 69,* 913–924.

Somerville, L. H., Jones, R. M., & Casey, B. (2010). A time of change: Behavioral and neural correlates of adolescent sensitivity to appetitive and aversive environmental cues. *Brain and Cognition, 72,* 124–133.

Steinberg, L. (2008). A social neuroscience perspective on adolescent risk-taking. *Developmental Review, 28,* 78–106.

Teicher, M. H., & Samson, J. A. (2013). Childhood maltreatment and psychopathology: A case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. *American Journal of Psychiatry, 170,* 1114–1133.

Thomas, K. M., Drevets, W. C., Dahl, R. E., Ryan, N. D., Birmaher, B., Eccard, C. H., et al. (2001). Amygdala response to fearful faces in anxious and depressed children. *Archives of General Psychiatry, 58,* 1057–1063.

Vansteenwegen, D., Vervliet, B., Iberico, C., Baeyens, F., Van den Bergh, O., & Hermans, D. (2007). The repeated confrontation with videotapes of spiders in multiple contexts attenuates renewal of fear in spider-anxious students. *Behaviour Research and Therapy, 45*(6), 1169–1179.

Vrieze, E., Pizzagalli, D. A., Demyttenaere, K., Hompes, T., Sienaert, P., de Boer, P., et al. (2013). Reduced reward learning predicts outcome in major depressive disorder. *Biological Psychiatry, 73,* 639–645.

Wacker, J., Dillon, D. G., & Pizzagalli, D. A. (2009). The role of the nucleus accumbens and rostral anterior cingulate cortex in anhedonia: Integration of resting EEG, fMRI, and volumetric techniques. *NeuroImage, 46,* 327–337.

Waters, A. M., & Pine, D. S. (2016). Evaluating differences in Pavlovian fear acquisition and extinction as predictors of outcome from cognitive behavioural therapy for anxious children. *Journal of Child Psychology and Psychiatry, 57*(7), 869–876.

Weersing, V. R., & Weisz, J. R. (2002). Mechanisms of action in youth psychotherapy. *Journal of Child Psychology and Psychiatry, 43,* 3–29.

Weingarten, C. P., & Strauman, T. J. (2015). Neuroimaging for psychotherapy research: Current trends. *Psychotherapy Research, 25,* 185–213.

Weisz, J. R., McCarty, C. A., & Valeri, S. M. (2006). Effects of psychotherapy for depression in children and adolescents: A meta-analysis. *Psychological Bulletin, 132,* 132–149.

Weisz, J. R., Ugueto, A. M., Cheron, D. M., & Herren, J. (2013). Evidence-based youth psychotherapy in the mental health ecosystem. *Journal of Clinical Child and Adolescent Psychology, 42,* 274–286.

Weisz, J. R., Weiss, B., Han, S. S., Granger, D. A., & Morton, T. (1995). Effects of psychotherapy with children and adolescents revisited: A meta-analysis of treatment outcome studies. *Psychological Bulletin, 117,* 450–468.

Whitfield-Gabrieli, S., Ghosh, S. S., Nieto-Castanon, A., Saygin, Z., Doehrmann, O., Chai, X. J., et al. (2016). Brain connectomics predict response to treatment in social anxiety disorder. *Molecular Psychiatry, 21,* 680–685.