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A translational neuroscience framework for the development of socioemotional functioning in health and psychopathology

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Abstract

The development of socioemotional functioning is a complex process that occurs over a protracted time period and requires coordinating affective, cognitive, and social faculties. At many points in development, the trajectory of socioemotional development can be deleteriously altered due to a combination of environmental insults and individual vulnerabilities. The result can be psychopathology. However, researchers are just beginning to understand the neural and genetic mechanisms involved in the development of healthy and disordered socioemotional functioning. We propose a translational developmental neuroscience framework to understand the transactional process that results in socioemotional functioning in both healthy and disordered populations. We then apply this framework to healthy socioemotional development, pediatric anxiety, pediatric depression, and autism spectrum disorder, selectively reviewing current literature in light of the framework. Finally, we examine ways that the framework can help to frame future directions of research on socioemotional development and translational implications for intervention.

Understanding the processes underlying healthy socioemotional functioning, as well as altered socioemotional functioning, in developmental psychopathology requires integration across domains, such as social, cognitive, and affective functioning (Cicchetti & Blender, 2004). Moreover, this integration must include multiple levels of analysis (e.g., genetics, molecular neurobiology, brain function, cognitive-affective performance, symptoms, and disorders) in order to tease apart the many pathways to disorder versus health (Cicchetti & Blender, 2004; Cicchetti & Dawson, 2002; Masten, 2007). Two individuals may have the same starting point in terms of context in early life, but later in adolescence, one might show adaptive socioemotional functioning while the other might have developed a disorder. Conversely, two individuals might have a disorder yet differ in early life context. These concepts of multifinality (the former situation) and equifinality (the latter situation) can be addressed by tracing different developmental trajectories with multiple levels of analysis (Cicchetti & Rogosch, 1996). For example, the two individuals who had the same contexts yet differed in whether they had a disorder might be distinguished by different genetic profiles as well as different brain activation patterns. Teasing apart the many developmental pathways to health and disorder will depend on bringing together many pieces of information from multiple levels of analysis (Curtis & Cicchetti, 2003).

Moreover, concurrently examining these multiple levels of analysis and their interplay can provide a more integrated understanding of the development of socioemotional functioning because these levels of analysis reciprocally interact with each other (i.e., have transactional relationships; Sameroff, 2010). The transactional nature of these levels of analysis means that it is difficult to assign causation to one level over any other. Thus, considering all of the levels in context with each other rather than in isolation is important in order to have a fuller picture of developmental pathways (Cicchetti & Blender, 2004).

This article builds on the perspectives set forth in prior work, which emphasized a developmental, multilevel approach to the study of psychopathology (e.g., Cicchetti, 2007; Cicchetti & Blender, 2004; Monk, 2008). In addition, our framework also incorporates the concept of transactional models and acknowledges the bidirectional effects between levels of analysis (Sameroff, 2010). We propose a translational developmental neuroscience framework to understand socioemotional functioning in both healthy and disordered populations. We then apply this framework to healthy socioemotional development, pediatric anxiety, pediatric depression, and autism spectrum disorder (ASD), selectively reviewing current literature in light of the framework. Finally, we examine ways that the framework can help to identify future directions of research on socioemotional development.

Translational Developmental Neuroscience Framework

Levels of analysis

The translational developmental neuroscience framework represents a cascade of events across multiple levels of analysis

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(Figure 1). Genetic material likely has varying levels of influence on developmental psychopathology outcomes. Most gene-based studies of developmental psychopathology have traditionally considered only two levels of analysis, such as the prevalence of a particular disorder in individuals with a specific polymorphism. However, genes do not directly cause disorders. Genes instead exert their effects during development by coding for the proteins that in turn affect the maturation of neurons and circuits related to socioemotional functioning. Thus, to understand the functional impact of genes, it is also important to track and understand the cascade of events that follows genotype: DNA transcription to RNA, translation to protein, proteins influencing the development of brain systems, brain mechanisms of sensations, perceptions, and cognitions that can lead to symptoms.

Further up in the levels of analysis in this framework, the brain mediates the link between genetic activity and sensations, perceptions, cognitions and behaviors. Situated at the heart of this transactional developmental neuroscience framework, the brain represents the crossroads that affect or is affected by changes in the other levels of analysis. Thus, integrating functional and structural neuroimaging as another level of analysis into studies on socioemotional functioning can help to explain equifinality and multifinality. Specifically, it can explain how individuals can be homogenous in terms of genotype or environment yet heterogeneous in behavior or disorder outcome or the converse, the same disorder outcome yet with different starting points in terms of genotype or environment (Curtis & Cicchetti, 2003). In particular, the brain could be more sensitive to genetic effects than behavior (Meyer-Lindenberg, 2009). This is borne out in studies that have found brain differences between genotype groups that were not detected by self- or parent-reported symptom measures (e.g., Wiggins et al., 2012, in press).

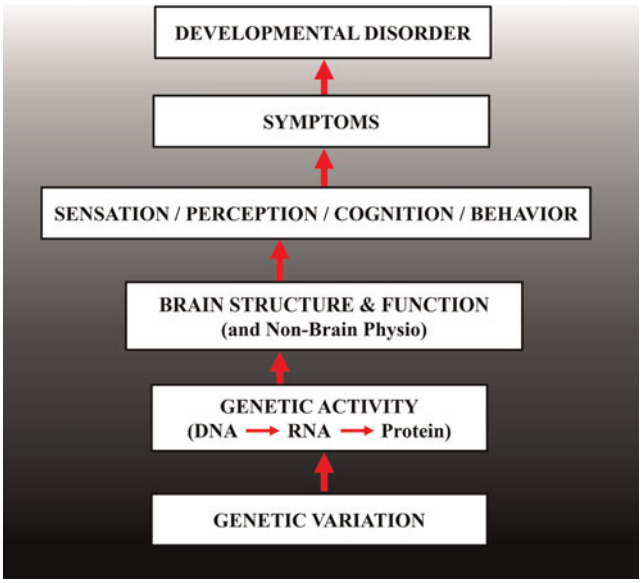

Figure 1. (Color online) The translational developmental neuroscience framework, Step 1. The translational developmental neuroscience framework represents a cascade of events across multiple levels of analysis.

Next, affective–cognitive mechanisms lead to alterations in behavior that may be classified as symptoms as in maladaptive behaviors. Understanding the influences on the lower level affective–cognitive mechanisms that give rise to symptoms is important, because affective–cognitive mechanisms can be a useful target for treatment. For example, attention bias modification treatment targets one probable affective–cognitive mechanism of anxiety symptoms, a tendency to attend to anxiety-provoking stimuli, by training individuals to change this attention bias (Bar-Haim, 2010; Eldar et al., 2012). Self-reported (but not clinician-reported) anxiety symptoms decreased after youths were trained to attend toward happy faces (Britton et al., 2013). Future research could examine whether variations in efficacy of treatments targeting affective–cognitive mechanisms are due to individual differences in other levels of the framework, such as genotype.

Developmental psychopathology is currently diagnosed behaviorally and is based on number, intensity, and duration of symptoms. However, two people diagnosed with the same disorder may present different symptoms from each other; they may have different combinations of the symptoms that make up the criteria for a disorder, and/or one person may have more severe symptoms than the other. These different presentations may represent different etiologies and prognoses although they are still classified as the same disorder. Thus, using disorders as discrete classifications represents a significant limitation in research. Instead of grouping research participants by diagnosis, using dimensional measures that cut across diagnoses is an alternative promoted by initiatives such as the National Institute of Mental Health's Research Domain Criteria. Within our framework, genetic or brain activity linked to variations in symptom severity can elucidate different etiological mechanisms that might be obscured by using discrete diagnostic categories.

Environment influences every level

The environment, broadly defined as all elements outside the individual, cuts across levels (Figure 2), influencing and/or being influenced by each of the levels. For example, genetic activity (specifically, the efficacy of DNA transcription to RNA and translation to protein) can be affected by environmental influences through such epigenetic mechanisms as DNA methylation. The women in one study who were exposed to childhood sex abuse exhibited increased serotonin transporter gene methylation, which in turn was associated with decreased gene expression (Vijayendran et al., 2012). Future research could link methylation status of the serotonin transporter gene to brain function in circuits relevant to socioemotional functioning, such as the amygdala–prefrontal circuit or the default network.

Transactional

This framework also recognizes that influences among the levels can be transactional, such that the direction of influence

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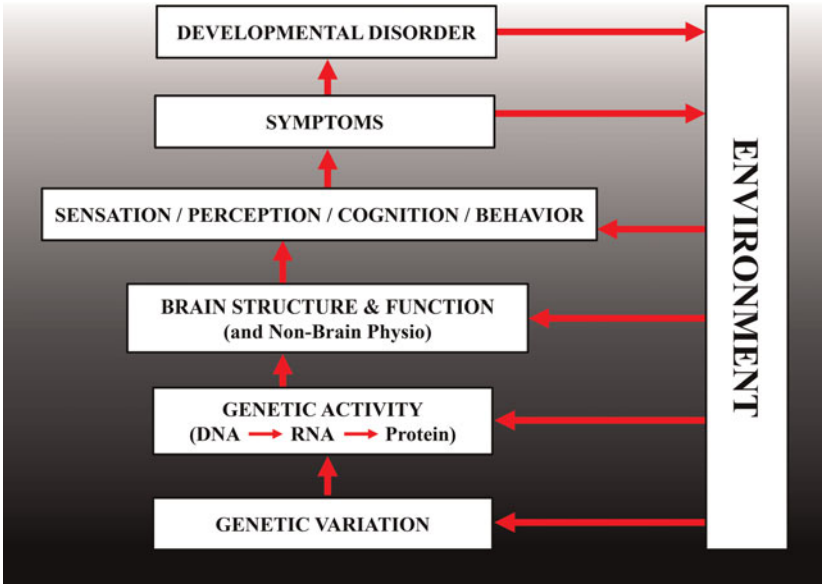

Figure 2. (Color online) The translational developmental neuroscience framework, Step 2. The environment, which is broadly defined as all elements outside the individual, spans all levels and influences and/or is influenced by each of the levels.

flows both ways (Figure 3). For example, the arrows linking environment and behavior/cognition are bidirectional because the environment not only affects behaviors and cognitions but behaviors and cognitions can also change one's environment. In a child who has social impairment, peers may approach and interact with the child less often. Therefore, the child has fewer opportunities to develop social skills. The result is that social impairments continue and even worsen. The present framework builds on this idea of transactional models, whereby the individual is a product of continuous interactions between the individual and experience (Fiese & Sameroff, 1989; Sameroff & Mackenzie, 2003), but also recognizes the transactional nature of the relationships between brain function and behavior as well as brain function and genetic activity. Contrary to the popular notion that the brain causes behavior via a "one-way street," behavior can affect brain function as well. Moreover, genetic activity affects brain function, and brain function (in response to environmental conditions) can affect the efficacy of genetic expression via mechanisms such as methylation.

Developmental

All of the levels are interacting with each other within the context of development. The relationships among levels

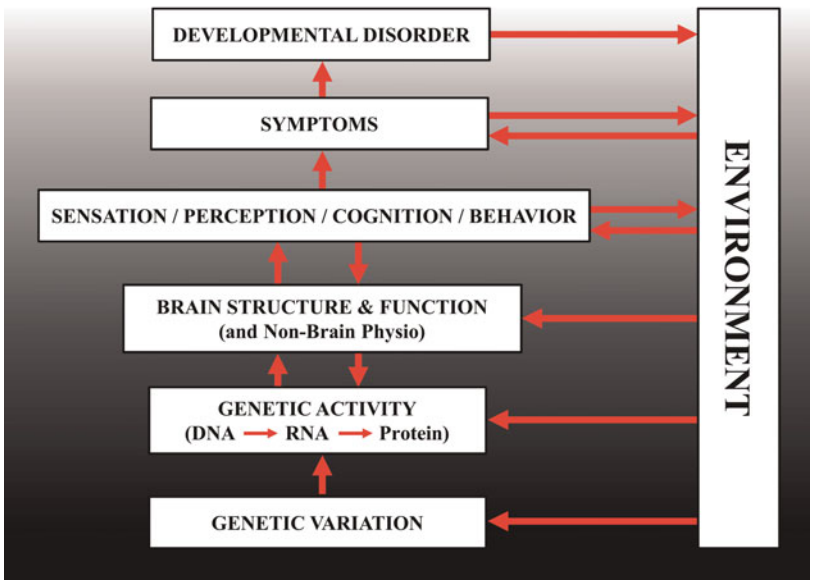

Figure 3. (Color online) The translational developmental neuroscience framework, Step 3. The framework recognizes that influences among the levels can be transactional, such that the direction of influence flows both ways.

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changes, depending on the developmental period (Figure 4). For example, the serotonin transporter's effects on depression-like behaviors hinges on the stage at which development serotonin transporter levels are altered: when serotonin transporter is decreased in early life, rodents have depression-like behaviors that emerge in adolescence. In contrast, when serotonin transporter is reduced in adulthood, depression-like behaviors do not appear (Ansorge et al., 2008).

Translational

This framework is translational as well because it incorporates the interface of basic and clinical science and facilitates the application of basic science to medical and behavioral treatments. The framework gives us a way to conceptualize and study how different levels work together to result in psychopathology. Through this framework, studies that examine any level, from genes to brain to behavior, can be understood in the larger context of normal and abnormal socioemotional functioning. Moreover, the framework also gives us a way to delineate the boundaries among typical, at-risk, and abnormal functioning at any level of analysis and throughout development. Having a larger conceptualization of how all these levels of analysis work together to produce healthy or impaired socioemotional functioning may be instrumental in creating hypothesis-driven treatments.

Concepts

We examine what is known about links in this framework in terms of socioemotional functioning. This framework is naturally broad, so we narrow our application of this framework to a few key areas in this article. We focus on typical development to establish a normative base for the links in this framework. Next, we examine what is known about the links in the framework in individuals diagnosed with disorders in three areas: pediatric anxiety (with a focus on social anxiety features), pediatric depression, and ASD.

In addition, we focus on midchildhood through adolescence. This is a key developmental period as multiple transitions relevant to socioemotional function take place in the shift from preadolescence through adolescence: peers grow in importance; puberty begins and hormone levels change; romantic relationships are initiated; classroom structures change from elementary, to middle, to high school; and importantly, affective disorders often onset in this period (Casey et al., 2010; Eccles et al., 1993; Nelson, Leibenluft, McClure, & Pine, 2005).

In our discussion of brain function, we focus on functional magnetic resonance imagine (fMRI) and the two types of data it provides. The first is the measure of activation in specific brain regions. The second is functional connectivity, which measures the degree to which the changes in blood flow are synchronized between two areas in the brain. As the crossroads of this framework, the brain is subject to multiple influences, and fMRI is a sensitive tool to examine these influences on the brain in the context of socioemotional development in children and adolescents. Functional MRI allows researchers to see how brain structures respond to and interact with particular socioemotional stimuli and situations. Through the tasks utilized in fMRI, researchers can isolate socioemotional functions and the brain systems involved in those functions. In addition, fMRI may also be used to determine brain function when participants are not performing a particular task (e.g., in

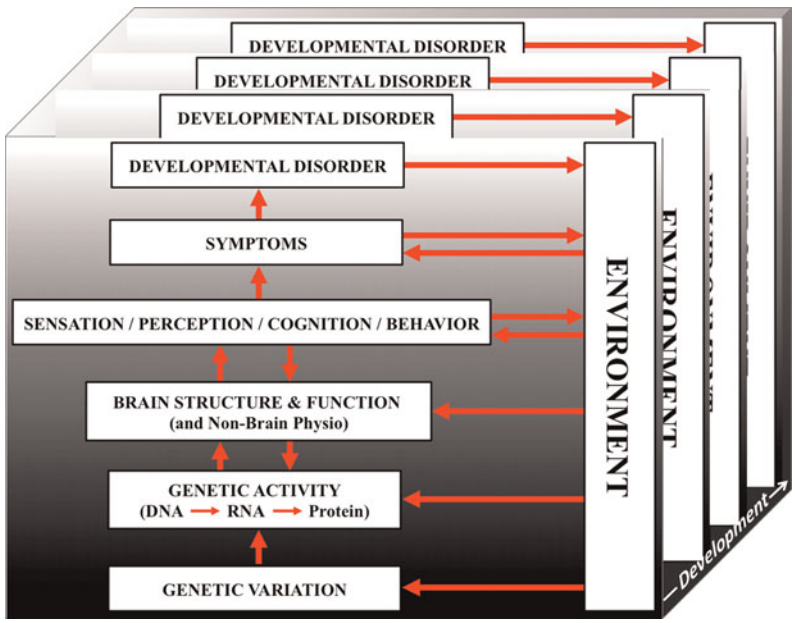

Figure 4. (Color online) The translational developmental neuroscience framework, Step 4. All of the levels interact with each other within the context of development. The relationships among levels changes, depending on the developmental period.

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the absence of a task or at rest). Other methods (structural neuroimaging, EEG) of measuring the brain are complementary to fMRI but are not discussed here in the interest of space. Of note, positron emission tomography scans are generally not done for research purposes in children because of ethical issues surrounding the potential risks associated with injecting radioactive tracer into a developing child; thus, positron emission tomography scans are not a part of this article.

Although many brain structures contribute to socioemotional functioning, we focus on fMRI studies on several key regions that have been most consistently implicated in this domain. First, we include studies examining amygdala activation. The amygdala is thought to be involved in salience detection and may also index distress (Davis, 1999; Davis & Whalen, 2001; LeDoux, 1996, 2000). The amygdala is reliably activated in response to emotional faces and other socioemotional stimuli (Sabatinelli et al., 2011). Second, we include studies examining functional connectivity of the amygdala with the prefrontal cortex. The prefrontal cortex and amygdala form a circuit via reciprocal connections found in adult humans and animal models (Carmichael & Price, 1995; Ongur & Price, 2000; Sarter & Markowitsch, 1984). The ventral, not dorsal, prefrontal cortex is likely the main area through which regulation of the amygdala occurs (Ray & Zald, 2012). Within the ventral prefrontal cortex, the ventromedial regions may be more involved in automatic regulation of the amygdala, whereas the ventrolateral prefrontal cortex is implicated in voluntary regulation of responses (Phillips, Ladouceur, & Drevets, 2008; Ray & Zald, 2012). In MRI studies, stronger functional connectivity suggests greater coordination of amygdala and prefrontal activation. Third, we include studies examining posterior–anterior connectivity of the default network in the context of rest, or absence of a task. These studies serve as a complement to studies on amygdala and prefrontal cortex, the vast majority of which rely on tasks using socioemotional stimuli. Functional connectivity of the default network increases in absence of task and decreases during engagement in a cognitively demanding task (Buckner & Carroll, 2007; Fox, Snyder, et al., 2005; Raichle & Snyder, 2007). The default network is linked to social function, particularly projecting oneself into others' situations or theory of mind (Buckner & Carroll, 2007; Flavell, 1999; Frith & Frith, 2003) and consolidating a narrative of the self (Gusnard, Akbudak, Shulman, & Raichle, 2001), although the primary purpose of the default network is a subject of debate. Default network structures include posterior medial areas, such as the posterior cingulate and precuneus, as well as medial prefrontal areas (Buckner, Andrews-Hanna, & Schacter, 2008). Posterior–anterior connectivity of the default network is the focus of this article because posterior–anterior default network connectivity undergoes the most protracted developmental time course (Fair et al., 2008) and is implicated in a number of disorders, such as autism (e.g., Monk et al., 2009), depression (e.g., Greicius et al., 2007), and schizophrenia (e.g., Garrity et al., 2007).

It is worth noting that the numbers of genetics studies on anxiety, depression, and ASD are vast: a PubMed search for "genetics anxiety" yields 6,920 studies, "genetics depression" yields 14,637 studies, and "genetics autism" yields 4,229 studies. However, there are relatively few studies that quantitatively related genetic information with brain function. Thus, we focus on genetic polymorphisms that are related to amygdala activation, amygdala–prefrontal connectivity, or posterior–anterior default connectivity and can shed light on individual differences in brain function in these areas.

The environment is often defined as any nongenetic influence. Because it is such a broad concept, we utilize a few studies that illustrate how the environment impacts brain function in the circuits of interest in youths. Specifically, we examine adverse environmental influences, such as child maltreatment.

Typical Development

Functional brain development

Amygdala. From the time that fMRI was first used to understand brain development, the amygdala has been the subject of intense investigation. Consistent with findings in studies of adults, healthy youths exhibit amygdala activation to fearful faces (Baird et al., 1999). However, when adults and youths are directly compared on amygdala activation, children exhibit greater amygdala activation to fearful and neutral faces than do adults (Guyer, Monk, et al., 2008; Thomas, Drevets, Whalen, et al., 2001) as well as greater activation to fearful versus neutral faces compared to adults (Monk et al., 2003). Taken together, these studies suggest that amygdala reactivity decreases from childhood into adulthood. Consistent with that view, adolescents in later stages of puberty exhibit less amygdala activation to neutral faces than in earlier stages of puberty (Forbes, Phillips, Silk, Ryan, & Dahl, 2011).

Amygdala–prefrontal connectivity. A few studies examined amygdala–prefrontal functional connectivity in youths. One study demonstrated that 7- to 9-year-old children show weaker connectivity between the amygdala and ventromedial prefrontal cortex than 19- to 22-year-old adults (Qin, Young, Supekar, Uddin, & Menon, 2012). Directional influence of the ventral prefrontal cortex on the amygdala also increases with age (Perlman & Pelphrey, 2011). This pattern of increased coupling between the amygdala and prefrontal cortex across adolescence has been interpreted to be more efficient regulation of the amygdala with age (Casey, Jones, & Hare, 2008). This interpretation is consistent with the protracted developmental timeline for amygdala–prefrontal development (Casey et al., 2008; Gee et al., 2013). Others, however, have challenged the notion that decreased connectivity necessarily means less emotion regulation and, thus, increased risk for poor socioemotional functioning (Crone & Dahl, 2012; Pfeifer & Allen, 2012). Most methods of calculating func-

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tional connectivity are based on correlation between time courses from two brain areas (e.g., amygdala and prefrontal cortex). This limits the interpretation of direction of influence and does not rule out the possibility of a third variable influencing both brain regions.

Default network. Several studies on youth populations have shown that functional connections within the default network, particularly posterior to anterior long-range connections, increase with maturation from childhood through adolescence. Using a variety of methods for calculating connectivity, research has shown that children have weaker posterior–anterior functional connectivity of the default network relative to adults (Fair et al., 2008; Stevens, Pearlson, & Calhoun, 2009; Supekar et al., 2010). In addition, posterior–anterior default network connectivity is positively correlated with age in children and adolescents (Wiggins et al., 2011).

Linking the brain to typical variations in socioemotional functioning

Some work has been done to quantitatively link the amygdala and posterior–anterior connectivity within the default network to socioemotional behaviors in youths. In adolescents, amygdala activation in response to fearful faces positively correlates with scores on social anxiety subscales: peer rejection, humiliation, performing in public, and being separated from loved ones (Killgore & Yurgelun-Todd, 2005). However, amygdala activation is not correlated with the nonsocial aspects of anxiety (Killgore & Yurgelun-Todd, 2005). Greater amygdala activation in adolescents when viewing fearful faces is also related to lower emotional intelligence (ability to effectively utilize social and emotional capacities; Killgore & Yurgelun-Todd, 2007). For the default network, increased connectivity in the anterior portion of the default network (right middle frontal gyrus) is related to decreased anxiety scores in healthy youths but not in adults (Dennis, Gotlib, Thompson, & Thomason, 2011). These studies indicate that incremental differences in brain function are linked to incremental differences in socioemotional functioning.

Genetic influences on the brain and behavior

Serotonin transporter linked polymorphic region gene (5-HTTLPR). One genetic variant that has received considerable interest is *5-HTTLPR*. This genetic variant affects the production of serotonin transporter and consists of short and long alleles, which have a variable number of tandem repeats (Lesch et al., 1996). Within the long allele there is a single nucleotide polymorphism where adenine is substituted for a guanine nucleotide (*rs25531*); a long allele with the adenine substitution results in greater serotonin transporter expression (high expressing) than either a long allele with guanine or the short allele (low expressing; Hu et al., 2006).

Low-expressing *5-HTTLPR* genotypes are associated with multiple socioemotional problems and traits in children and adolescents. Low-expressing *5-HTTLPR* alleles are related to increased aggressive behavior (Beitchman et al., 2003), fear and anxiety traits (Hayden et al., 2007), behavioral inhibition when social support is low (Fox, Nichols, et al., 2005), and affective problem scores when children are living in a one-parent family (Nobile et al., 2009). In addition, the low-expressing alleles have been found to be associated with shyness/social anxiety in two studies (Battaglia et al., 2004, 2005), although another study found that the high-expressing genotype is associated with shyness (Arbelle et al., 2003). The low-expressing *5-HTTLPR* variants are also related to greater externalizing and internalizing behavior but only when another genotype, the long allele of a dopamine receptor genetic variant (dopamine receptor D4 variable number tandem repeat), is also present (Becker, El-Faddagh, Schmidt, & Laucht, 2007; Schmidt, Fox, & Hamer, 2007).

There have been a number of studies examining *5-HTTLPR* in relation to brain activation in adults (e.g., Hariri et al., 2005), but fewer have focused on linking *5-HTTLPR* to brain function in healthy children and adolescents. In healthy adults, *5-HTTLPR* low-expressing genotypes have been linked to increased amygdala activation (Hariri et al., 2005). In a study examining the contribution of *5-HTTLPR* genotype during child and adolescent development, amygdala activation positively correlates with age in children and adolescents with low-expressing genotypes but not high-expressing genotypes (Wiggins, Bedoyan, et al., in press). Moreover, the pattern of greater amygdala activation with the low-expressing genotypes established in healthy adults is not evident until later adolescence (Wiggins, Bedoyan, et al., in press). In the default network, typically developing youths with low-expressing *5-HTTLPR* genotypes show reduced posterior–anterior connectivity compared to youths with the high-expressing genotypes (Wiggins et al., 2012). In addition, healthy youths with the low-expressing genotypes showed attenuated increases in posterior–anterior default network connectivity with age compared to high-expressing genotypes (Wiggins et al., 2012). To summarize, low-expressing *5-HTTLPR* alleles are associated with brain development profiles (increased amygdala activation, decreased default network connectivity) that are related to socioemotional problems (e.g., Dennis et al., 2011; Killgore & Yurgelun-Todd, 2005).

Adverse environmental influences on the brain

Studies of youths that experienced adverse environments earlier in development suggest that these experiences can have lasting effects on brain function in key socioemotional circuits. Two studies on children and early adolescents who were previously institutionalized found that these youths who experienced early adverse rearing environments exhibit increased amygdala activation to faces (Maheu et al., 2010; Tottenham et al., 2011). A prospective study on a community sample also found that girls' life stress during infancy predicts increased cortisol (a hormone related to stress) in childhood as well as decreased connectivity between the amygdala and ven-

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tromedial prefrontal cortex during adolescence at 14 years after the stressors were measured and controlling for recent life stress (Burghy et al., 2012). In this community sample, greater amygdala–ventromedial prefrontal cortex connectivity is related to worse depression symptoms but ameliorated anxiety symptoms in girls (Burghy et al., 2012). These studies illustrate how early environmental influences initiate a cascade of events throughout development that includes alterations in brain function years following environmental stressors. However, no studies have yet examined negative early environments on default network connectivity in youths.

Pediatric Anxiety

Anxiety disorders start early in development, and 12.5 years is the median age of onset for social anxiety disorder (Grant et al., 2005). The specific focus of this section is on social aspects of anxiety, such as social phobia and generalized anxiety disorder, which is characterized by excessive anxiety about a variety of situations but often has social anxiety features (for a review of other types of pediatric anxiety, see Blackford & Pine, 2012).

Functional brain development

Amygdala activation and connectivity with prefrontal cortex. Several studies have demonstrated that children and adolescents with anxiety have greater amygdala activation to negatively valenced emotional expressions. Youths with social phobia (Blair et al., 2011) and with generalized anxiety disorder (Beesdo et al., 2009; McClure et al., 2007; Thomas, Drevets, Dahl, et al., 2001) exhibit increased amygdala activation in response to fearful faces compared to healthy youths. Angry faces presented for a very short period of time (17 ms) and subsequently masked to limit participants' ability to implement regulatory processes also elicits greater amygdala activation in children with generalized anxiety disorder compared to controls (Monk, Telzer, et al., 2008). In a social evaluation task with faces, adolescents with social anxiety and controls rated photographs of peers on how much they would like to interact with that person. They were told that their peers would learn of their ratings and that they would be rated as well. During an fMRI scan, youths were shown pictures of their previously rated peers (either high or low desirability), and rated how interested the peer would be in interacting with the participant. Adolescents with social anxiety show greater amygdala activation than did healthy adolescents when anticipating evaluation from peers they previously rated as undesired for an interaction (Guyer, Lau, et al., 2008). Socially anxious adolescents also had greater functional connectivity between the amygdala and ventrolateral prefrontal cortex while evaluating the interest level of low- versus high-desirability peers; this difference was driven by positive connectivity appearing only in socially anxious adolescents when evaluating how much they would like to interact with peers they previously rated as low desirability. Moreover, greater positive connectivity related to increased social anxiety severity (Guyer, Lau, et al., 2008).

Default network connectivity. Unlike many other conditions, adults with social anxiety fail to show a difference in default network connectivity compared to controls (Pannekoek et al., 2013). However, no studies to date have examined default network connectivity during rest in socially anxious youths.

Genetic influences on brain and behavior

Mineralocorticoid receptor isoleucine/valine (iso/val). A common missense polymorphism (*rs5522*) within exon 2 of the human mineralocorticoid receptor gene (*NR3C2*) results in the substitution of an adenine nucleotide for guanine, thus changing the amino acid from valine to isoleucine. The valine allele is related to reduced cortisol binding, inhibiting hypothalamic–pituitary–adrenal axis function (DeRijk et al., 2006; van Leeuwen et al., 2010) as well as with heightened stress reactivity in adults (Bogdan, Fagerness, & Pizzagalli, 2010; DeRijk et al., 2006; van Leeuwen et al., 2010). Children and adolescents with a valine allele show greater amygdala reactivity regardless of whether they experienced previous emotional neglect, but children and adolescents with two copies of the isoleucine allele show greater amygdala reactivity only when they have a history of elevated emotional neglect. Moreover, at low levels of previous emotional neglect, youths with a valine allele show greater amygdala reactivity compared to youths with two copies of the isoleucine allele (Bogdan, Williamson, & Hariri, 2012).

Adverse environmental influences on the brain

To date, there have been no studies examining adverse environmental effects on the brain in children with social anxiety. However, child maltreatment can affect other anxiety-related brain and psychophysiological systems in youths (McCrory, De Brito, & Viding, 2011).

Pediatric Depression

Functional brain development

Amygdala. Adolescents with depression show greater amygdala activation in a variety of socioemotional tasks: when maintaining their emotional reaction to negatively valenced images (Perlman et al., 2012), when receiving the outcome of a reward task (Forbes et al., 2006), and when viewing emotional faces (Roberson-Nay et al., 2006). Moreover, children at high familial risk for depression (i.e., offspring of parents with major depression) show increased amygdala activation to fearful faces (Monk, Klein, et al., 2008). One study of children and adolescents with depression, however, found a decrease in amygdala activation to fearful faces compared to controls and to youths with anxiety (Thomas, Drevets, Dahl, et al., 2001).

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There is a well-documented increase in depression beginning in adolescence (Hankin et al., 1998), but earlier onset depression, such as in preschool age, occurs as well. Children aged 7–11 with preschool-onset depression do not show differences in amygdala activation to sad faces compared to controls (Barch, Gaffrey, Botteron, Belden, & Luby, 2012). However, in children with preschool-onset depression, worse depression symptoms measured in preschool relates to greater amygdala activation to sad faces at ages 4.5 (Gaffrey et al., 2011) and 7–11 years (Barch et al., 2012). More research is needed to determine whether adolescent and earlier onset depression are distinct in terms of etiology and treatment response. It is possible, for example, that preschool-onset depression is more influenced by genetic factors while adolescent-onset depression is influenced by environmental factors. The proposed framework allows researchers to link together multiple levels of analysis to determine how these developmental paths might be different in terms of brain and genetic etiology.

Brain connectivity. Youths with depression show differing patterns of connectivity in the amygdala–prefrontal circuit and the default network. Adolescents with depression show less connectivity between the amygdala and medial prefrontal cortex than do controls when asked to maintain their emotional reaction to negatively valenced emotional images (Perlman et al., 2012). However, within the depressed group alone, stronger connectivity is related to worse impairment (Perlman et al., 2012). Moreover, children with depression show weaker connectivity between the amygdala and prefrontal cortex than do healthy children (Luking et al., 2011).

Whereas the amygdala–prefrontal circuit is characterized by reduced connectivity in pediatric depression, within the default network, children with a history of preschool depression show increased posterior–anterior connectivity (between posterior cingulate and subgenual anterior cingulate cortices; Gaffrey et al., 2012). Stronger functional connection between posterior–anterior default network relates to worse emotional regulation and coping for both sadness and anger in children with preschool-onset depression but only sadness for controls (Gaffrey, Luby, Botteron, Repovs, & Barch, 2012). Whether this increased default network connectivity reflects an increased internal locus of attention or rumination that leads to poorer emotion regulation and coping could be a topic for future studies.

Genetic influences on brain and behavior

5-HTTLPR. 5-HTTLPR has been the subject of intense interest in depression, with many studies finding a link between the low-expressing genotypes and depression (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010). However, there has been some controversy over whether *5-HTTLPR* has an effect on depression. Two meta-analyses failed to find an association between *5-HTTLPR* and depression (Munafo, Durrant, Lewis, & Flint, 2009; Risch et al., 2009). However, a subsequent meta-analysis that included a more complete set of studies found a significant effect of *5-HTTLPR* on depression (Karg, Burmeister, Shedden, & Sen, 2011). In addition, it is worth noting that many of the studies that Risch (2009) and Munafo et al. (2009) included were of elderly populations. For example, one of the largest studies included in both meta-analyses (4,175 participants) had participants ranging in age from 41 to 80 years with a mean age of 60 years. This presents an intriguing possibility that the penetrance (i.e., degree of influence on phenotype) of *5-HTTLPR* varies over the life span, which is borne out in a child and adolescent sample (Wiggins et al., 2012). Future research could explore this possibility, which fits within the proposed framework emphasizing the differing relationships among the levels (genetics, brain, behavior) across the developmental timeline.

Another matter affecting these studies is that *5-HTTLPR* is thought to impact outcomes via a Gene × Environment interaction. A landmark study (Caspi et al., 2003) found a *5-HTTLPR* × Life Stress interaction such that, after experiencing several stressful life events, adults with the low-expressing *5-HTTLPR* genotypes exhibit greater depression symptoms than do adults with high-expressing genotypes. Similarly, in a prospective study with children, the low-expressing allele predicts increases in depressive symptoms 6 months later but only in children with chronic family stress (Jenness et al., 2011). These studies have suggested that individuals with the low-expressing *5-HTTLPR* genotypes are particularly vulnerable to stress. However, an alternative explanation is that *5-HTTLPR* acts not as a vulnerability gene but rather as a plasticity gene (Belsky et al., 2009). In this view, individuals with low-expressing *5-HTTLPR* genotypes are more sensitive to environmental influences, whether beneficial or adverse. Conversely, both beneficial and adverse environmental influences have less effect on socioemotional outcomes in individuals with the high-expressing genotypes. Belsky and colleagues (2009) point out that in many studies, individuals with the low-expressing genotypes have better socioemotional outcomes than do individuals with the high-expressing genotypes when in beneficial environments.

The *5-HTTLPR* genotype also impacts amygdala activation in youths with depression. Children and adolescents with depression (or depression comorbid with anxiety) show a significant Genotype × Diagnosis interaction during the viewing of happy and fearful faces (Lau et al., 2009). Specifically, controls with the low-expressing genotype activated the amygdala more to emotional faces relative to controls with the high-expressing genotype. However, the pattern was the opposite for youths with depression: depressed youths with the high-expressing genotypes show greater amygdala activation than do depressed youths with the low-expressing genotypes (Lau et al., 2009).

Brain-derived neurotrophic factor valine or methionine at codon 66 (BDNF/Val66Met). BDNF is involved in neuron survival, differentiation, and synaptic plasticity (Chen et al., 2006). A functional variant of the *BDNF* gene consists of a single nucleotide polymorphism with an adenine to guanine substitution (*rs6265*) in the 5′ prodomain region, which pro-

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duces Val66Met (Bath & Lee, 2006). The methionine allele, which results in a decrease in available *BDNF*, may confer vulnerability to affective dysregulation (Chen et al., 2006). The methionine allele is linked to depression symptoms in adults who experienced traumatic childhood events (Aguilera et al., 2009; Wichers et al., 2008). In addition, both adults and children with the methionine allele who experienced early adversity and have low-expressing *5-HTTLPR* genotypes show greater depression symptoms (Kaufman et al., 2006; Wichers et al., 2008).

BDNF impacts brain activation in adolescents with depression and/or anxiety as well. Adolescents with at least one methionine allele exhibit greater amygdala activation to emotional faces than do adolescents with two valine alleles within the depressed/anxious group only, not the healthy control group (Lau et al., 2010).

Adverse environmental influences on the brain

Examining adverse environmental influences on amygdala and default network function in depressed children and adolescents is an important direction for future research. One study demonstrated that a small sample ($N = 5$) of maltreated, depressed youths show greater amygdala activation to sad images compared to nonmaltreated healthy controls (De Bellis & Hooper, 2012). However, future research would need to tease apart the effects of maltreatment on amygdala activation in a larger sample of depressed youths with variation in childhood maltreatment histories.

ASDs

Functional brain development

Amygdala. ASD refers to a set of neurodevelopmental conditions characterized by impaired social and communicative functioning as well as repetitive and restrictive behaviors (American Psychiatric Association, 2013). A number of studies have focused on examining alterations in brain circuitry related to socioemotional functioning, including the amygdala, to understand the etiology and maintenance of social symptoms in ASD. One view regarding social symptoms is that individuals with ASD fail to develop social skills because they are disinterested in social stimuli, such as faces. Consistent with this view, many studies have shown that individuals with ASD show less amygdala activation to faces relative to controls (e.g., Ashwin, Baron-Cohen, Wheelwright, O'Riordan, & Bullmore, 2007; Critchley et al., 2000; Dapretto et al., 2006; Grelotti et al., 2005; Hadjikhani, Joseph, Snyder, & Tager-Flusberg, 2007; Pelphrey, Morris, McCarthy, & Labar, 2007; Pinkham et al., 2008). Because the amygdala is fundamentally involved in processing salient information in the information, such as social cues, reduced amygdala activation may indicate that people with ASD are less interested in social information.

An alternative view is that individuals with ASD are not disinterested in social stimuli; rather, they are distressed by social stimuli and find social stimuli aversive. This "distress" view is in line with observations that individuals with ASD avoid direct eye contact (Kliemann, Dziobek, Hatri, Steimke, & Heekeren, 2010). Moreover, children with ASD show greater autonomic arousal to faces (Joseph, Ehrman, McNally, & Keehn, 2008). Evidence from fMRI studies supports the "distress" view as well: when attention to the faces is constrained, adolescents with ASD (Dalton et al., 2005; Kliemann, Dziobek, Hatri, Baudewig, & Heekeren, 2012; Weng et al., 2011) as well as adults with ASD (Kleinhans et al., 2009; Monk et al., 2010) exhibit greater amygdala activation to faces compared to controls. Moreover, attention to the eyes of a face correlates with amygdala activation in youths with ASD (Dalton et al., 2005; Kliemann et al., 2012). Last, the studies that found reduced amygdala activation in ASD presented faces for relatively long periods of time (≥2 s) and did not monitor attention to the faces (e.g., Ashwin et al., 2007; Critchley et al., 2000; Dapretto et al., 2006; Grelotti et al., 2005; Hadjikhani et al., 2007; Pelphrey et al., 2007; Pinkham et al., 2008). Taken together, these fMRI studies suggest that reduced amygdala activation found in previous studies (e.g., Ashwin et al., 2007; Critchley et al., 2000; Dapretto et al., 2006; Grelotti et al., 2005; Hadjikhani et al., 2007; Pelphrey et al., 2007; Pinkham et al., 2008) may be because individuals with ASD attended away from the faces.

To more fully characterize amygdala activation in ASD, we recently examined amygdala habituation to faces in youths with ASD as well as controls. Habituation is the initial strong response and reduction in response over time. In contrast to typically developing youths who consistently habituate to repeatedly presented faces, youths with ASD not only fail to habituate but also increase their amygdala response over time to sad and neutral faces (Swartz, Wiggins, Carrasco, Lord, & Monk, 2013). As increased amygdala activation may index distress (Davis, 1999; Davis & Whalen, 2001; LeDoux, 1996; LeDoux, 2000), a failure to demonstrate amygdala habituation or an increase in response over time (e.g., sensitization) may indicate that individuals with ASD experience social stimuli as distressing.

Amygdala–prefrontal and default network connectivity. Initial studies of connectivity in ASD, largely with adults, generally reported decreased connectivity compared to controls (underconnectivity) in several brain systems (Hughes, 2007). Whereas underconnectivity appears to occur often in ASD, recent studies on adolescents and children suggest that abnormal connectivity in ASD can include both underconnectivity as well as overconnectivity, depending on the context and the brain regions. Adolescents and children with ASD have weaker connectivity between the amygdala and prefrontal cortex when viewing sad faces (Swartz et al., 2013). In another task with emotional faces, during interference trials, children with ASD show decreased left amygdala connectivity with the subgenual anterior cingulate cortex (a structure within the prefrontal cortex) but increased right amygdala connectivity with the pregenual anterior cingulate

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cortex (Murphy, Foss-Feig, Kenworthy, Gaillard, & Vaidya, 2012). In contrast, examining the default network in the context of rest reveals that children and adolescents with ASD have weaker posterior–anterior connectivity (Weng et al., 2010; Wiggins et al., 2011). Moreover, in a cross-sectional study, children and adolescents with ASD fail to develop posterior–anterior default network connectivity as strong as healthy children and adolescents (Wiggins et al., 2011).

Linking the brain to social symptoms

Relatively few studies have quantitatively linked brain function to variation in social symptom severity in ASD. One study found that decreased amygdala habituation to neutral faces is related to worse social symptoms in children and adolescents with ASD (Swartz et al., 2013). Another found that worse social impairment symptoms are associated with weaker posterior–anterior default network connectivity in youths with ASD (Weng et al., 2010). Future research that relates brain function to dimensional symptom domains in ASD, as opposed to seeking only group differences between people diagnosed with ASD and controls, may prove to be beneficial. This is because the symptom domains in ASD appear not to represent a single ASD concept but instead separate subdomains with potentially different genetic and brain etiologies that co-occur in ASD (Kuenssberg, McKenzie, & Jones, 2011). Considering different symptoms separately and quantitatively linking them to potential etiological mechanisms could reduce noise and heterogeneity in these types of studies.

Genetic influences on the brain and behavior

5-HTTLPR. Evidence indicates that the genetic variant *5-HTTLPR* plays a role in socioemotionally relevant brain activation and symptoms in ASD. Low-expressing *5-HTTLPR* genotypes are associated with greater social symptoms but not with a diagnosis of ASD as a whole (Brune et al., 2006; Tordjman et al., 2001). The *5-HTTLPR* genotype influences amygdala habituation to sad faces differently for individuals with ASD than for controls. Specifically, whereas controls of any genotype demonstrate amygdala habituation to the faces, youths with ASD fail to display amygdala habituation; moreover, youths with ASD and the low-expressing genotypes exhibit increased amygdala responses to the faces over time, a process known as sensitization (Wiggins, Swartz, Martin, Lord, & Monk, in press). In the default network, low-expressing *5-HTTLPR* genotypes are associated with increased posterior–anterior connectivity for youths with ASD, but the converse is true for controls (Wiggins et al., 2013). Moreover, youths with ASD and low-expressing genotypes have greater age-related increases in posterior–anterior default network connectivity compared to youths with ASD and high-expressing genotypes as well as controls with either genotype classification (Wiggins et al., 2013).

Methionine receptor tyrosine kinase (MET). MET is a gene that encodes proteins in the ERK/ PI3K signaling pathway and has been implicated in ASD (Levitt & Campbell, 2009). The C variant of a single nucleotide polymorphism (cytosine to guanine substitution, *rs1858830*) located in the promoter region of *MET* results in reduced *MET* expression and is associated with ASD (Campbell et al., 2007; Campbell, Li, Sutcliffe, Persico, & Levitt, 2008; Campbell et al., 2006; Jackson et al., 2009). *MET* variants moderate the severity of social symptoms in ASD such that individuals with ASD who carry the C variant have more severe social and communication phenotypes than those who do not (Campbell, Warren, Sutcliffe, Lee, & Levitt, 2010). Children and adolescents with the C variant show greater amygdala activation in response to faces, and this genotype effect is more pronounced in youths with ASD than in typically developing controls (Rudie et al., 2012). In addition, significantly weaker posterior–anterior default network connectivity is found in youths with ASD and C variant (but not the G variant) compared to typically developing youths with the C variant (Rudie et al., 2012). These studies show that genetic variation can help to tease apart potential subgroups based on brain function and behavior; subgroups may then represent different etiologies as well as prognoses.

Future Directions

As shown in this article, researchers are beginning to flesh out the links on the translational developmental neuroscience framework in terms of socioemotional functioning in both healthy and impaired development. However, much work remains to be done to fully understand the multiple etiologies and trajectories of these disorders as well as the multiple pathways to a healthy outcome. The translational developmental neuroscience framework is useful in guiding the research questions that we pose, and it shapes future directions in understanding the development of socioemotional functioning.

Genetics

Thus far, the majority of imaging genetics studies on socioemotional functioning link a single polymorphism to brain function. However, the single-gene approach is limited in that it leaves out the larger context, which likely involves the additive or interactive effects of multiple genes as well as Gene × Environment and Gene × Development interaction effects. One response to the limitations of single-gene association studies has been to use genomewide association studies in which brain activation or behavior can be tested against hundreds of thousands or even millions of single nucleotide polymorphisms simultaneously (Pearson & Manolio, 2008). For example, this exploratory, hypothesis-free approach was used to identify a single nucleotide polymorphism (*rs2023454*) in the gene *DOK5* that is significantly associated with amygdala activation, and penetrance of this genotype was greater in youths with bipolar disorder than in healthy

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youths (Liu et al., 2010). However, the frequent failure to replicate genomewide association findings (e.g., Hart, de Wit, & Palmer, 2013; Ousdal et al., 2012) has led to reticence to make the large expenditures for genomewide association studies. One of several issues that may be affecting the difficulty in replicating genomewide association studies is that multiple statistical tests (hundreds of thousands or more, one for each single nucleotide polymorphism) introduce the problem of finding a balance between alpha inflation and applying corrections for multiple comparisons that are too harsh, particularly because the tests may involve some degree of dependency (for a discussion of multiple comparison issues, see Moskvina & Schmidt, 2008). One way forward that takes into account multiple genes yet imposes some limits on the number of statistical tests is to examine only polymorphisms along a particular molecular signaling pathway that are related to a neural or behavioral phenotype of interest (Nikolova, Ferrell, Manuck, & Hariri, 2011). For example, building on the single-gene studies linking *5-HTTLPR* to socioemotionally relevant brain function in youths reviewed in this article, future research could expand the focus to include other polymorphisms in the serotonergic signaling pathway, such as *5-HT1A* and *5-HT1B* (serotonin receptor) genes, and consider the impact of all of these genes simultaneously. However, this approach, as well as genomewide or single-gene association studies, needs to be combined with other information, such as environment, development, or Gene × Gene interactions (Musani et al., 2007) to more fully capture the multiple and interacting influences on brain and behavior.

Epigenetics

Whereas functional polymorphisms have served as proxies for expression level of genetic products (e.g., *5-HTTLPR* variants can result in high or low expression of serotonin transporter), other factors can also affect the efficacy of gene expression without changing the underlying DNA sequence. One such epigenetic mechanism is methylation, in which a methyl group added to a cytosine nucleotide linearly adjacent to a guanine nucleotide in the promoter region of a gene can alter the degree of gene expression. Methylation can occur in response to psychosocial environmental influences such as stress. For example, adults with depression who experienced childhood stress and adversity have higher serotonin transporter promoter methylation (Kang et al., 2013). Methylation is also related to worse clinical presentation in the adults with depression (Kang et al., 2013). Methylation studies, however, involve challenging methodological issues (Aberg & van den Oord, 2011). Although methylation in response to environmental stress may affect some types of tissues equally (e.g., T cells and prefrontal cortex; Provencal et al., 2012), it is possible for methylation status to differ by tissue or location in the body (Grafodatskaya et al., 2010; Sun et al., 2010). Methylation of specific brain structures is of greatest interest in order to link functional significance of genes to brain activation and subsequently behavior. However, there is presently no ethical way to measure methylation status in the central nervous system of living humans. One possibility for at least correlating epigenetic data with brain function would be to combine neuroimaging information from living humans with methylation information obtained from postmortem brain tissue. Living subjects (e.g., a group of adolescents with major depressive disorder and controls) could be scanned and methylation status based on blood could be related to brain function (for an example of this approach applied to study working memory, see Ursini et al., 2011). To provide further support that there are group differences in methylation status in the central nervous system, postmortem brain tissue samples from existing brain banks could be analyzed. The fMRI findings could be used to identify the precise location to sample the tissue.

Combining multiple methods

Although functional neuroimaging and connectivity are the main brain measurement tools considered here, combining multiple methods of measuring the brain will be necessary to obtain converging evidence of brain alterations due to genetic and/or environmental effects in developmental socioemotional psychopathology. In particular, functional connectivity during different contexts, such as during a socioemotional task (in which brain structures are actively recruited in response to socioemotional stimuli) and during rest (when structures are allowed to operate without specific task demands), can reveal the extent to which symptom-related alterations are elicited or suppressed in response to specific stimuli or, alternatively, pervasive even in the absence of a task. Another complementary mode of measuring the brain is diffusion tensor imaging (DTI). DTI provides information about the structural connectivity of white matter tracts in vivo and, combined with functional connectivity measures, can tease apart whether functional alterations in a brain circuit are due to reduced structural integrity in a particular white matter pathway. Rudie and colleagues' (2012) study is one example that brings together these three types of evidence (connectivity during a task with socioemotional stimuli, connectivity during rest, structural connectivity via DTI) to look at genetic effects on ASD. In this study, all three of these measures were applied to the same sample of children and adolescents with ASD and typically developing controls. Rudie and colleagues (2012) found that the risk genotype of *MET* receptor tyrosine kinase predicts atypical amygdala activation and connectivity using all three measures and that the degree to which the genotype affects the brain phenotype in all three measures is greater for individuals with ASD than for controls.

Combining methodologies may also help to mitigate the problem of spurious connectivity due to head movement in the MRI scanner. In developmental studies of functional connectivity, particularly resting-state functional connectivity, movement is an issue because younger children and individuals with disorders move more than healthy adults (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; Van Dijk, Sabuncu, & Buckner, 2012). In addition to taking steps to re-

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duce movement, having converging evidence from multiple methods can help to evaluate whether connectivity differences are due to movement. If an alteration in connectivity persists across contexts in youths with a particular disorder, regardless of movement levels in any one scan, the alteration is less likely to be spurious.

Large samples

Sample sizes in the majority of current studies linking multiple levels of analysis (e.g., brain and genetics) are relatively modest due to the large expenditures required for both brain imaging and genetic assays. Moreover, sample sizes are often even smaller for clinical youth populations due to both the increased difficulty in recruiting these specialized populations and the cost of diagnosing participants. To increase sample sizes, there have been efforts to cooperate and share resting state MRI images among researchers for both ASD (via the Autism Brain Imaging Data Exchange; Di Martino et al., in press) and for typical development via the 1000 Connectome (http://fcon_1000.projects.nitrc.org/) and the National Institutes of Health MRI Study of Normal Brain Development (http://pediatricmri.nih.gov/nihpd/info/index.html), which includes longitudinal data. There have also been efforts to share genetic information and biological samples across multiple sites, such as the Simons Simplex Collection (http://sfari.org/sfari-initiatives/simons-simplex-collection) and the Autism Genetic Resource Exchange (http://research.agre.org/) for individuals with ASD. However, future databases that are the product of cooperation of many research sites and take multiple measures across several different levels (genetics, brain, behavior, etc.) delineated in the translational developmental neuroscience framework will be extremely valuable to tease apart multiple paths to health and psychopathology. Moreover, longitudinal studies will be necessary to examine individual developmental trajectories and identify the causes of the emergence of psychopathology. One example of a database that combines brain, behavior, and genetics in order to examine risk-taking behavior in a normative population is the IMAGEN study in Europe (http://www.imagen-info.com/). Future efforts for aggregation of data can follow a similar model for individuals with socioemotional developmental psychopathology.

Translational Implications for Intervention

The translational developmental neuroscience framework can guide future research that has implications for intervention. At the heart of this translational developmental neuroscience framework, the brain can be useful to measure responses to intervention. Future intervention studies may leverage the brain as a biomarker to test the efficacy of interventions with smaller samples. If the brain activation patterns of individuals with a disorder become more similar to typically developing participants after an intervention, this could indicate that the intervention may be effective (Bradstreet, Smith, Baral, & Rossignol, 2010). Moreover, the brain results could indicate that deploying more resources to subsequently do a randomized control trial with behavioral measures would be a prudent investment. However, in order to reliably use the brain as a biomarker, more research is needed to characterize both normal and impaired brain activation patterns associated with socioemotional impairment at every point in development.

Including the brain in intervention studies can also reveal information about brain plasticity. It is important to note that treatment can be considered an environmental influence as well (Cicchetti & Gunnar, 2008). In conjunction with brain imaging, treatment studies allow for the examination of brain plasticity in response to a beneficial environmental event (Maslowsky et al., 2010). This can be accomplished by examining brain function before and after treatment. Moreover, when treatment is done in the context of a randomized control trial, in which participants are randomly assigned to receive active treatment or placebo, changes in brain function can be more precisely attributed to the treatment (Cicchetti & Gunnar, 2008). Incorporating brain measures also can help to identify sensitive periods when brain plasticity is heightened and interventions may be more effective (Cicchetti & Gunnar, 2008; Zeanah et al., 2003).

Next, a multiple levels of analysis approach to trace the development of psychopathology may also yield targets for intervention, both as treatment (once the individuals already has a disorder) and as prevention (prior to developing clinical-level symptoms). Repetitive transcranial magnetic stimulation (rTMS) can be used as an intervention with a foundation in brain imaging research. In rTMS, fluctuating magnetic pulses are applied from the scalp surface to induce a current in the subjacent cortex, which then modulates cortical excitability (Kobayashi & Pascual-Leone, 2003). Strategic application of rTMS to portions of the neural circuitry involved in depression (such as the prefrontal cortex) appears to be an effective treatment for depression (Hovington, McGirr, Lepage, & Berlim, in press) as well as an array of other psychological and medical disorders (Lipton & Pearlman, 2010). This intervention also seems to have promise as a preventive measure (for example, with migraines; Lipton & Pearlman, 2010). As a preventive intervention for depression, research with a multiple levels of analysis approach across development will be needed to accurately identify individuals who are at the highest risk for a depressive episode and who would benefit the most from rTMS. Another promising intervention, attention bias modification treatment, grew out of work showing attention biases toward threatening faces (Eldar et al., 2012). In attention bias modification, clients with pediatric anxiety are trained to attend away from threatening stimuli (Eldar et al., 2012). Emerging evidence suggests that this hypothesis-driven treatment may be effective in reducing pediatric anxiety symptoms (Eldar et al., 2012). Combined with knowledge of the developmental time course of anxiety, this attention bias intervention could be used preventively in youths who are at risk for future anxiety disorders and selectively in youths who have the characteristics that make them most likely to be responsive to this particular intervention.

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Finally, characterizing heterogeneity that was previously opaque by using a multiple levels of analysis approach may reveal different etiologies and prognoses, and thus, ways to optimize treatments for each individual. Individuals with differing brain, genetic, and behavioral profiles across their developmental history may necessitate different treatment approaches. For example, depressed individuals with a history of trauma in early developmental periods are more responsive to psychotherapy alone (as opposed to psychotherapy in combination with pharmacotherapy or pharmacotherapy alone) than are depressed individuals without trauma in their early developmental histories (Nemeroff et al., 2003). As another example of how information gleaned from this framework can inform treatment decisions, a meta-analysis showed that Caucasian individuals with the high-expressing allele of *5-HTTLPR* have better responses to selective serotonin reuptake inhibitor treatment and higher rates of remission from depression after selective serotonin reuptake inhibitor treatment (Porcelli, Fabbri, & Serretti, 2012). Future research could aggregate information from multiple levels of analysis across development to better optimize treatments for individuals. Making more informed choices about the most effective front-line treatment for individuals instead of trying different treatments until the most effective one for a particular individual is identified will save considerable time and money. It will reduce the amount of suffering for individuals with psychological disorders seeking treatment.

In conclusion, the translational developmental neuroscience framework can provide guidance for a research program with the goal of fully understanding the complex process of socioemotional development. Understanding the multiple developmental pathways to health and disorder can inform the development of interventions to improve the well being of individuals with socioemotional impairment.

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