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Abnormal structure or function of the amygdala is a common component of neurodevelopmental disorders

Cynthia M. Schumann*, Melissa D. Bauman, David G. Amaral

Department of Psychiatry and Behavioral Sciences, The M.I.N.D. Institute and the California National Primate Research Center, University of California, Davis, Davis, CA 95618, United States

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ABSTRACT

The amygdala, perhaps more than any other brain region, has been implicated in numerous neuropsychiatric and neurodevelopmental disorders. It is part of a system initially evolved to detect dangers in the environment and modulate subsequent responses, which can profoundly influence human behavior. If its threshold is set too low, normally benign aspects of the environment are perceived as dangers, interactions are limited, and anxiety may arise. If set too high, risk taking increases and inappropriate sociality may occur. Given that many neurodevelopmental disorders involve too little or too much anxiety or too little of too much social interaction, it is not surprising that the amygdala has been implicated in many of them. In this chapter, we begin by providing a brief overview of the phylogeny, ontogeny, and function of the amygdala and then appraise data from neurodevelopmental disorders which suggest amygdala dysregulation. We focus on neurodevelopmental disorders where there is evidence of amygdala dysregulation from postmortem studies, structural MRI analyses or functional MRI. However, the results are often disparate and it is not totally clear whether this is due to inherent heterogeneity or differences in methodology. Nonetheless, the amygdala is a common site for neuropathology in neurodevelopmental disorders and is therefore a potential target for therapeutics to alleviate associated symptoms.

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1. Introduction

The amygdala is an almond-shaped brain region located in the anterior portion of the temporal lobe (Fig. 1). Occupying a volume of approximately 2.25 cm^3 on each side, it makes up barely 0.3% of the volume of the human brain. Yet, perhaps more than any other brain region, it has been implicated in a plethora of neuropsychiatric disorders. The amygdala is, in fact, a complex region made up of at least 13 nuclei and cortical areas in the nonhuman primate and human brains (Amaral, Price, Pitkänen, & Carmichael, 1992) (Fig. 2). The fact that the amygdala appears to interact with several functional systems of the brain (Johnston, 1923) has led some (Swanson & Petrovich, 1998) to question whether it should be considered an integrated entity at all. However, our own neuroanatomical data (Pitkänen & Amaral, 1998; Pitkänen, Kelly, & Amaral, 2002) indicate that the internal components of what we prefer to call the amydgaloid complex are linked together by powerful intrinsic connections. Moreover, others have demonstrated that the various nuclei of the amygdala have undergone a more coherent evolution than other brain regions suggesting a functional integrity (Barton, Aggleton, & Grenyer, 2003). Thus, despite its complexity and its interaction with systems that mediate functions ranging from olfaction, to sexual behavior, to detecting environmental dangers, there is every reason to believe that its components act in a coordinated fashion just as the various parts of the hippocampal formation act together to carry out episodic memory processing.

The evolution of the amygdala has not been entirely worked out. This is due to the fact that not all components of the amygdala are present in all classes of animals. There is substantial evidence that a homolog of the amygdala is found in amphibia (Laberge, Muhlenbrock-Lenter, Grunwald, & Roth, 2006). Here the portions of the amygdala associated with the olfactory and autonomic systems are apparent but nuclei that would constitute the "deep" nuclei of the amygdala are not. This would suggest that a prototype of the amygdala was established some 250 million years prior to the emergence of mammals. Even within the mammalian brain, there has been substantial evolution of the structure of the amygdaloid complex. In general, as one progresses from basal insectivores to primates, there is a diminution of the olfactory regions of the amygdala (particularly those involved with the vomeronasal organ and pheromone detection) and an increase in the size of the deep nuclei, such as the basal and lateral nuclei (Stephan, Frahm, & Baron, 1987). In fact, quantitative analyses have shown that there is a much larger lateral nucleus in the human amygdala than would be expected

* Corresponding author at: The M.I.N.D. Institute,UC Davis, 2805 50th Street, #1414, Sacramento, CA 95817, United States. Tel.: +1 916 703 0372; fax: +1 916 703 0287.
E-mail address: cschumann@ucdavis.edu (C.M. Schumann).

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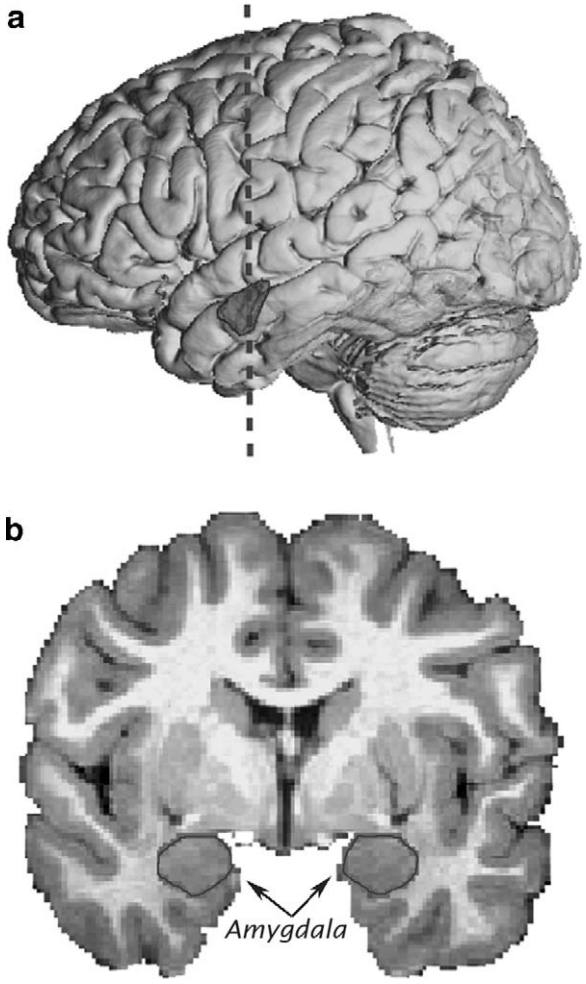

Fig. 1. Neuroanatomy of the human amygdala on MRI. (a) Lateral view of a three-dimensional reconstruction of an MRI of a human brain with amygdala outlined (dashed line represents location of coronal slide in panel b and (b) MRI coronal image with amygdala outlined.

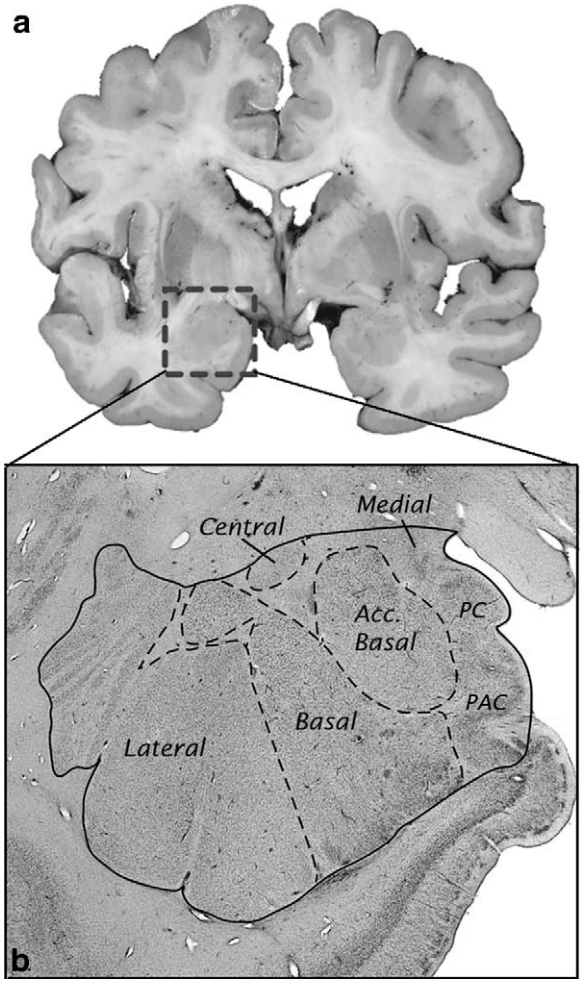

Fig. 2. Neuroanatomy of the human amygdala postmortem. (a) Coronal section of human brain tissue (box around amygdala) and (b) Nissl-stained section of amygdala nuclei.

for a nonhuman primate of comparable size (Barger, Stefanacci, & Semendeferi, 2007). Undoubtedly, this reflects the fact that the lateral nucleus receives input from the neocortex and that there has been a very large expansion of the neocortex in the human brain. But, this also makes the point that the amygdaloid complex cannot be thought of as a "primitive" or vestigial brain region since it is privy to the highest levels of sensory processing that has been afforded by the expansion of association cortex in the human brain.

In this chapter, we provide a brief overview of the development of the nonhuman primate and human amygdaloid complex. We then review data indicating the roles of the amygdala in primate development and function. We then provide an overview of data indicating that the structure and/or function of the human amygdala is compromised in a variety of neurodevelopmental disorders (Table 1). We conclude with some discussion concerning why pathology of the amygdala is such a common component of developmental neuropsychiatric disorders.

1.1. Structural development of the primate amygdala

Few studies have been carried out on the structural development of the human amygdala; however investigation of the nonhuman primate amygdala has provided preliminary information. There is evidence, for example, that the amygdaloid complex begins to develop early in gestation, derived from the ganglionic eminence, a thickening of the telencephalic and diencephalic proliferative zone, which protrudes into the ventricular cavity (Kordower, Piecinski, & Rakic, 1992; Muller & O'Rahilly, 2006). Neurogenesis of the macaque monkey amygdala occurs relatively early – in the first trimester of fetal development (Kordower et al., 1992). The first amygdaloid neurons are generated around embryonic day (ED) 33 in the ~165 day macaque gestation making them among the earliest postmitotic neurons in the telencephalon, beginning first in the superficial nuclei followed by the deep nuclei. Amygdala neurogenesis peaks around ED40 and ceases by ED56.

In the human around the fifth gestational month, there are cell dense columns in the inferior portion of the amygdala within the proliferative zone that serve as migrational routes for neurons (Nikolic & Kostovic, 1986; Ulfig, Setzer, & Bohl, 1998). These columns are thought to be formed by radial glia that provide a scaffold for migrating neurons (Rakic, 1995). Humphrey (1968) noted that the superficial, more medial, nuclei are identifiable in the human embryo earlier than the deep nuclei (lateral, basal, accessory basal). The superficial nuclei and central nucleus show evidence of synaptogenesis in the fifth month, potentially due to early connections with the brainstem, whereas the deep nuclei do not show evidence of synaptogenesis until the seventh month possibly due to the strong interconnectivity with association areas in the neocortex that also develop later (Ulfig, Setzer, & Bohl, 1999, 2003). In the sixth and seventh month of fetal development, the columns lose contact with the ganglionic eminence and cellular differentiation and reorganization takes place (Setzer & Ulfig, 1999). In the eighth month of human gestation, migration has essentially ended and

Table 1
MRI reports of amygdala volume differences in neurodevelopmental disorders by mean age of subject population.

Age group	Autism	Pediatric anxiety	Pediatric bipolar	Schizophrenia	William's syndrome	Fragile X
Young children	↑ Mosconi '09 ↑ Schumann '09 ↑ Sparks '02 ↑ Schumann '04	Unknown	Unknown	Unknown	Unknown	↓ Hazlett '09 – Kates '97 – Hoeft '08
Adolescents	– Schumann '04 – Palmen '05 ↓ Nacewicz '06	↑ De Bellis '00 ↓ Milham '05	– Frazier '05 ↓ Blumberg '03 ↓ Blumberg '05 ↓ Chang '05 – Chen '04 ↓ DelBello '04	↑ Welch '09[a] – Giedd '99[b] ↑ Levitt '01[b] – Frazier '08 – Jacobsen '98[b] ↑ Velakoulis '10[c]	– Campbell '09 ↑ Martens '09	↓ Gothelf '08
Adults	↓ Aylward '99 ↑ Howard '00 – Hazendar '00 ↓ Pierce '01	[e]	[e]	↓ Joyal '03[c] ↓ Witthaus '09[c] – Gibbs '08[c] ↓ Exner '04 – Velakoulis '10 – Tanskanen '05	↑ Reiss '04 – Chiang '07 – Meyer Lindenberg '04	↓ Moore '04[d] – Hessl '07[d]

[a] High-risk with psychotic and/or schizotypal symptoms.
[b] Early-onset or childhood schizophrenia.
[c] Following first-episode psychoses.
[d] Permutation carrier.
[e] Only the childhood-onset or pediatric form of the disorder was included in this review, with the exception of Schizophrenia.

the cytoarchitecture closely resembles that of the mature amygdala (Humphrey, 1972; Setzer & Ulfig, 1999; Ulfig et al., 1998, 2003).

During the early postnatal period, the macaque monkey amygdalocortical connections already closely resemble connections in the mature animals (Amaral & Bennett, 2003). Likewise, adult-like projections from inferior temporal areas to both amygdala and orbitofrontal areas have been observed in one-week-old macaques (Webster, Bachevalier, & Ungerleider, 1994; Webster, Ungerleider, & Bachevalier, 1991). Though little is known regarding development of specific neurochemical systems, it appears that the distribution of opiate receptors within the amygdala is comparable to adult patterns as early as one week of age (Bachevalier, Ungerleider, O'Neill, & Friedman, 1986) and that the pattern of serotonergic innervation of the amygdala resembles the adult pattern within the first postnatal month (Prather & Amaral, 2000). While these neurochemical systems appear to develop relatively early in the primate amygdala, other systems may undergo a more delayed maturational process. For example, androgen receptors that are identified immunohistochemically in the hypothalamus as early as the end of the first trimester in the male rhesus monkey are not observed in the amygdala until the postnatal period (Choate, Slayden, & Resko, 1998).

Taken together, these neuroanatomical studies indicate that the structure of the amygdala is well-developed at the time of birth. Interestingly, human MRI studies indicate that the typically developing amygdala continues to undergo substantial growth throughout development even into adolescence. The amygdala continues to increase in volume even at a time when the neocortex is decreasing in size. Three independent cross-sectional MRI studies have found that the amygdala increases in size from five years of age to adulthood by ~40% in typically developing males (Giedd, 1997; Giedd, Snell, & Lange, 1996; Ostby et al., 2009; Schumann et al., 2004). The underlying neurobiology that contributes to the protracted amygdala growth trajectory remains to be determined. Clearly much more work is needed to provide a comprehensive assessment of both prenatal and postnatal neuroanatomical development of the amygdala. There is evidence (discussed below) that in some neurodevelopmental disorders, such as autism, the amygdala undergoes an aberrant growth trajectory throughout development relative to typically developing children.

1.2. Functional development of the primate amygdala

In order to evaluate the role of the amygdala in neurodevelopmental disorders, it is necessary to understand the functional role of the amygdala in typical development. A widely held view is that the amygdala is essential for learning the emotional significance of a stimulus in the environment. This is particularly true for negative emotions such as fear and anger. Both human and animal studies demonstrate amygdala involvement in the acquisition, storage, and expression of conditioned fear learning (LeDoux, 2007; Phelps & LeDoux, 2005). As reviewed elsewhere in this issue, the amygdala, through its primary role of monitoring the environment for potential danger and adjusting levels of vigilance, also plays a modulatory role in social behavior. There is extensive literature from Adolphs and colleagues on the contribution of the amygdala to a network of brain structures involved in social cognition in adults, such as recognizing emotion in faces, judging the trustworthiness of a person, and generating a sense of personal space (Adolphs, 2009, 2010; Kennedy, Glascher, Tyszka, & Adolphs, 2009).

Although it is clear that the amygdala serves as an important structure for emotional learning and response, the precise function of the amygdala during *early* development is not well established. Children need to learn early in development to identify potential dangers by monitoring the responses of their caregivers and eventually making these determinations on their own. The amygdala is particularly recruited during the initial period of learning when associations are ambiguous (LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998), which is often the case early in development. Advances in functional neuroimaging techniques have allowed initial studies of the functional development of the human amygdala. These studies are still limited to late childhood due to methodological limitations. Some of these limitations can be circumvented by studying nonhuman primates and they thus provide a useful tool for understanding the early functional development of the amygdala. Below we discuss relevant functional imaging studies of the intact, typically developing human amygdala and lesion studies in the human and nonhuman primate in the context of development.

Amygdala lesions in humans early in life produce impairments in identifying the emotion in facial expressions, particularly

those depicting fear (Adolphs, Tranel, Damasio, & Damasio, 1994). However a lesion suffered in adulthood produces a less severe impairment (Hamann & Adolphs, 1999). These studies indicate that the amygdala may be critical for *learning* to judge emotions and determining the safety of a situation; this role may be diminished later in development once those associations have been made. Functional imaging studies in children and adolescents also support the notion that the amygdala is recruited early in development to form relationships of stimuli that may *or may not* be dangerous (Monk et al., 2003). As in adults, children and adolescents recruit the amygdala to interpret the emotion in facial expressions, albeit with a different pattern of activity (Baird et al., 1999; Killgore, Oki, & Yurgelun-Todd, 2001; Thomas, Drevets, Whalen, et al., 2001). Thomas, Drevets, Whalen, et al. (2001) found that in children, the amygdala is more active in response to neutral facial expressions than to those depicting fear. This suggests that the amygdala plays a dynamic role in learning to interpret emotions when the stimuli may be ambiguous in early development. Additional evidence that the amygdala may play an enhanced role in early development comes from studies of theory of mind, the ability to attribute mental states to others, in children and adults with amygdala lesions. Shaw et al. (2004) found that subjects who acquired damage either congenitally or early in development displayed deficits in understanding the emotional states and attributing the beliefs of others. Subjects who acquired damage to the amygdala in adulthood, by contrast, were not impaired on theory of mind tasks.

Nonhuman primate research has benefited from the ability to directly record from neurons in awake, behaving animals. Electrophysiological recordings from adult macaques indicate that neurons responding to faces, body movements, eye gaze, etc. are found throughout the amygdala (Brothers & Ring, 1993; Brothers, Ring, & Kling, 1990; Leonard, Rolls, Wilson, & Baylis, 1985; Rolls, 1984). What is not known is whether these response properties are already established at birth or if social experience plays a role in developing these highly selective response properties. Unfortunately, little is known regarding how and when the amygdala becomes specialized for processing facial information because of the many challenges of conducting this type of research in infant monkeys (Rodman, 1994).

At present, lesion research in nonhuman primates provides the most commonly utilized approach to evaluating the developmental role of the primate amygdala. The logic for these studies is that if a brain region plays an obligatory role in a particular function, then the loss of that brain region should substantially alter the expression of the function. The first studies of neonatal amygdala lesions in nonhuman primates reported few changes in behavior (Kling & Green, 1967) or changes in fear-related behaviors (Thompson, 1968, 1981; Thompson, Bergland, & Towfighi, 1977; Thompson, Schwartzbaum, & Harlow, 1969). More recently, Bachevalier and colleagues (Bachevalier, 1994) re-evaluated the effects of medial temporal lobe lesions in neonatal rhesus monkeys. These studies included a group of six neonates that received bilateral aspiration lesions of the amygdala, resulting in damage to the amygdala, piriform cortex, rostral portion of entorhinal cortex and inferior temporal cortical area TE (Bachevalier, Alvarado, & Malkova, 1999). When placed in social pairs at two and six months of age, the neonatal amygdala-lesioned infants showed less overall activity, exploration of the testing environment and initiation of social behavior as compared to age-matched controls. Although this finding was consistent with a proposed role of the amygdala in social development, it was possible that the behavioral changes in these monkeys may have been influenced by unintended collateral damage of neural tissue surrounding the amygdala and/or by the restricted rearing practices that were employed.

To address this question, we conducted a series of experiments to evaluate the effects of neurotoxic amygdala lesion in maternally and socially reared rhesus monkeys (Bauman, Lavenex, Mason, Capitanio, & Amaral, 2004a,b; Prather et al., 2001). We found that macaque monkeys that are reared by their mothers in a social environment and receive discrete, amygdala lesions at two weeks of age do not demonstrate profound impairments in social development within the first year of life. The amygdala-lesioned monkeys were able to produce and respond to a variety of species-typical social signals and did not differ from control monkeys in the amount of their social interactions (Bauman et al., 2004a,b). The amygdala-lesioned monkeys did, however, show abnormal fear responses to both social and nonsocial stimuli (e.g., heightened fear of conspecifics and absence of fear to normally aversive objects) (Bauman et al., 2004b; Prather et al., 2001). Thus, neonatal lesions of the macaque amygdala resulted in a sparing of species-typical social behavior, while profoundly impacting fear processing abilities. The collective results from the studies described above indicate that the amygdala is not essential for the early development of fundamental components of social behavior (i.e., the ability to produce and respond to species typical social behaviors and engage in social interactions with conspecifics). The current research does, however, suggest that the amygdala has a significant modulatory role on social behavior, especially in potentially threatening contexts. For humans and other group-living primates, the ability to rapidly and accurately evaluate social signals for signs of impending danger is an essential social skill that must be acquired early in development. If we assume that this ability is dependent upon a properly functioning amygdala, then it is reasonable to speculate that amygdala pathology may have a profound influence on aspects of social behavior. For further reading on the various theoretical perspectives of amygdala function, the reader is referred to the book, The Human Amygdala Ed. Whalen and Phelps (2009) which provides several excellent reviews.

1.3. The link of amygdala dysfunction to neurodevelopmental disorders

Given this short overview on the structure, development and function of the primate and human amygdaloid complex, we now turn to evidence that the amygdala is pathological in a variety of neurodevelopmental disorders. Interestingly, in autism where data are most extensive, it is the trajectory of amygdala development rather than the ultimate size that seems to be most perturbed. As we will review, it is not clear what leads to the altered developmental growth curve i.e. what are the neurobiological substrates? At this point, it is equally likely that this is accounted for by phenomena as diverse as abnormal development of connections or abnormal proliferation of glial cells. We will review data from structural magnetic resonance imaging (MRI) studies across several disorders. These were selected based on two criteria: (1) that the disorder was clearly developmental in origin and (2) that there is replicated evidence that the amygdala is pathological or dysfunctional. Though the results are often disparate and it is not totally clear whether this is due to the inherent heterogeneity in the conditions or differences is methodology. Nonetheless, the data highlight the point that the amygdala is very commonly associated with several neurodevelopmental disorders.

2. Alterations in amygdala development – neurodevelopmental disorders

2.1. Autism

Autism is a *behaviorally defined* severe disorder of neural development affecting one in 110 children and more likely to occur in males than females at a ratio of 4:1 (Rice, 2006). The etiol-

ogy(ies) of autism remains unknown and the neuropathology has not yet been clearly established. In toddlers, some of the first signs of autism are unusual affective behavior, reduced social interest, and poor eye contact (Dawson, Meltzoff, Osterling, & Rinaldi, 1998; Werner, Dawson, Osterling, & Dinno, 2000). By three years of age, a child may be given a diagnosis of autism if they display three core behavioral features: (i) impairments in reciprocal social interactions; (ii) abnormal development and use of language; and (iii) repetitive and ritualized behaviors and a narrow range of interests (American Psychiatric Association, 1994). In addition to the core features of autism, there are common co-morbid neurological disorders (Amaral, Schumann, & Nordahl, 2008), such as epilepsy and anxiety (Bishop, 2007; Pitkanen, Tuunanen, Kalviainen, Partanen, & Salmenpera, 1998).

The amygdala has long been a site of intense interest in the search for neuropathology in the brains of people with autism, given its role in modulating anxiety levels and social behavior. However, the heterogeneity and unknown etiologies of autism, as well as the varying methods employed across laboratories on subjects of different ages, has made it difficult to find consistent results across studies of amygdala volume. A recent pattern has emerged that the age of the subject population studied is a critical factor in determining outcome (Schumann et al., 2004). Four studies of toddlers and young children with autism have found the amygdala to be enlarged by ~15% relative to age-matched controls (Mosconi et al., 2009; Schumann, Barnes, Lord, & Courchesne, 2009; Schumann et al., 2004; Sparks et al., 2002). However, studies of older adolescents, adults, or a wide age range of subjects, have found either no difference in (Schumann et al., 2004; Haznedar et al., 2000) or even smaller (Aylward et al., 1999; Nacewicz et al., 2006; Pierce, Müller, Ambrose, Allen, & Courchesne, 2001) amygdala volumes in individuals with autism. In addition, the amygdala continues to grow in size throughout adolescence in typically developing male children (Giedd, 1997; Giedd et al., 1996), but this growth pattern does not seem to take place in male children with autism (Schumann et al., 2004). Recent evidence from children early in development suggests considerable heterogeneity in amygdala growth among children with autism and it is possible that subgroups may emerge as larger populations are studied (Nordahl, Scholz, Simon, Rogers, & Amaral, 2009). Therefore, on average, the amygdala appears to be initially larger than normal in children with autism, but does not undergo the same preadolescent increase in volume that takes place in typically developing children. This hypothesis parallels the general theory of early brain overgrowth (Courchesne et al., 2001, 2007), although the aberrant growth trajectory of the amygdala may extend to a later age (Schumann et al., 2004).

Sparks and colleagues were the first to suggest that the amygdala may be enlarged in young children with autism at 36–56 months of age (Sparks et al., 2002). In this same cohort of children, Munson et al. (2006) found that the amygdala enlargement in the children with autism was associated with more severe social and communication impairments (based on the ADI and Vineland) and poorer outcome at 6 years of age. In a recent longitudinal study of children at 2 and 4 years of age, bilateral amygdala enlargement was also observed in children with autism compared to a control group that consisted of typical and developmentally delayed children (Mosconi et al., 2009).

Schumann et al. (2009) recently carried out a prospective study to measure amygdala volume in toddlers at risk for autism at the age of first clinical detection compared to age-matched typically developing children. The children underwent an MRI around 2.5 years of age and returned at 4 years of age for clinical diagnosis and testing. They found further evidence that the amygdala is enlarged in young children with autism and that the overgrowth begins before 3 years of age at about the time symptoms become clinically evident. As found in the Sparks et al. (2002) and Mosconi et al. (2009) studies, the amygdala was disproportionately enlarged relative to total cerebral volume at 3 years of age. This study differed from previous studies on amygdala volume in that one of the primary goals was to characterize the neuropathological and behavioral profiles of males and females with autism independently. Strikingly, amygdala enlargement in females with autism was found to be more pronounced, compared to age- and gender-matched typically developing counterparts, than in males with autism. In male, but not female, toddlers who later received a diagnosis of autism, the degree of amygdala enlargement at 3 years of age was also associated with the severity of the child's social and communication impairments at final clinical evaluation at ~4 years of age. In contrast, in adolescents, Nacewicz et al. (2006) found that a smaller amygdala volume was associated with gaze avoidance and more severe behavioral impairments as measured with the ADI-R. This relationship is the opposite pattern of that observed in younger children in both the Munson et al. (2006) and Schumann et al. (2009) studies. One might speculate that individuals with autism that demonstrate early overgrowth and more severe behavioral impairments may ultimately demonstrate reduced amygdala size later in adulthood; this notion awaits validation from a longitudinal study on brain growth throughout development in people with autism.

No study to date has evaluated younger postmortem cases with autism to determine what cellular properties account for the early overgrowth in volume. But, there is some evidence that a decreased number of neurons may be contributing to the reduction in amygdala volume later in adulthood. We carried out a neuropathological study of the brain in individuals with autism using unbiased stereological methods to measure the number and size of neurons in the entire amygdaloid complex and in individual nuclei in nine male postmortem cases of autism, without seizure disorder, compared to 10 typically developing age-matched male controls ranging in age from 10 to 44 years at death (Schumann & Amaral, 2006). We found that the autism group had significantly fewer neurons in the total amygdala and in the lateral nucleus than the controls. Whereas the average number of neurons in the control amygdala was about 12.2 million, the average in the amygdala in the autism cases was about 10.8 million or about 85% of the total in the control brains.

Taken together with the findings from previous magnetic resonance imaging and postmortem studies, the autistic amygdala shows multiple signs of pathology. In general, it appears to undergo an abnormal pattern of postnatal development that includes precocious enlargement. In the adult, the overall volume of the amygdala may not be different in individuals with autism (although it may be smaller) but may contain fewer neurons. It will be important to determine whether decreased neuronal numbers is unique to the amygdala or occurs in other brain regions as well, as demonstrated in the fusiform gyrus (van Kooten et al., 2008).

How might pathology in the amygdala relate to specific behavioral abnormalities in autism? An emerging hypothesis is that the amygdala plays a role in mediating or directing visual attention (Adolphs et al., 2005; Grelotti, Gauthier, & Schultz, 2002; Pierce, Haist, Sedaghat, & Courchesne, 2004; Schultz, 2005). Dalton et al. (2005) carried out a series of studies utilizing functional imaging and eye-tracking technology simultaneously while showing subjects familiar and unfamiliar faces. They found that the amount of time persons with autism spent looking at the eye region of the face was strongly positively correlated with amygdala activation, but not in typically developing control subjects. Two possible theories may explain these findings. The first is that the normal function of the amygdala is to direct attention, based on motivation, to attend to the eye region of the face and that individuals with autism are simply less motivated to look at the eyes. Pierce et al. (2001) initially found reduced amygdala activation when individuals with

autism viewed faces depicting fear. However, when autistic subjects viewed familiar faces, they were able to activate the amygdala appropriately in response to familiar and unfamiliar faces (Pierce et al., 2004), suggesting that the familiar faces may have enhanced motivation or attention to all of the stimuli. A second emerging theory is that individuals with autism perceive social interactions as threatening, and therefore avoid socialization as a means of alleviating the fear that it triggers. Given the amygdala's role in fear and anxiety, one would predict heightened amygdala activation during eye contact in persons with autism, as found in the Dalton et al. (2005) study. This may be due to a heightened emotional, or even fearful, response when autistic individuals look at another person's eyes, regardless of whether they are familiar or a stranger. As mentioned earlier, Nacewicz et al. (2006) found that individuals with autism (8–25 years of age) who had a smaller amygdala also spent the least amount of time fixating on the eye region of the face. Spezio, Adolphs, Hurley, and Piven (2007) confirmed that individuals with autism show less fixation on the eyes and mouth, but also a greater tendency to saccade away from the eyes when information was present in those regions. Recently, Kleinhans et al. (2009) found evidence of reduced amygdala habituation to faces in their autism spectrum disorder group and the degree of reduction was related to the severity of their social impairments. This study lends further support to the theory that the amygdala is hyper-aroused in people with autism in response to socially relevant stimuli. These studies provide insight into the aberrant manner in which people with autism view faces, which is, in turn, is likely related to their heightened anxiety due to abnormal amygdala activation.

2.2. Anxiety/social phobia

Pediatric anxiety disorders, including social phobia, separation anxiety and generalized anxiety disorder (GAD) represent the most common forms of childhood psychopathology (Klein & Pine, 2002). Behavioral inhibition is an early identifiable temperament characterized by a tendency to withdraw in novel social situations (Kagan, Reznick, Snidman, Gibbons, & Johnson, 1988) that may predispose individuals to develop anxiety disorders (Kagan, Snidman, McManis, & Woodward, 2001; Perez-Edgar & Fox, 2005). Given the association between behavioral inhibition and the subsequent emergence of anxiety disorders, we will discuss amygdala pathology associated with both of these conditions.

The neurobiology of adult onset anxiety disorders is complex, and may not accurately reflect the pathophysiology of pediatric anxiety disorders (Charney & Deutch, 1996). Consequently, we will focus our discussion on studies from pediatric populations with anxiety. Using volumetric MRI analysis, De Bellis et al. demonstrated that children and adolescents with GAD (mean age 12.7 years) had larger right and total amygdala volume as compared to age-matched controls (De Bellis et al., 2000). A similar pattern of amygdala enlargement has recently been reported in adolescents (average age 14.7 years) who showed characteristics of behavioral inhibition earlier in childhood (Hill, Tessner, Wang, Carter, & McDermott, 2010). However, not all studies have reported increases in amygdala volume in individuals with pediatric anxiety or behavioral inhibition. For example, a voxel-based morphometry analysis that included children with separation anxiety, social phobia or GAD (mean age 12.9 years) reported a significant grey matter volume reduction within the left amygdala of children with a pediatric anxiety disorder compared to healthy controls (Milham et al., 2005). The authors highlighted the fact that pediatric anxiety disorders are heterogeneous conditions, and although changes in amygdala structure may be present, the changes depend on the specific diagnoses of the participants.

Research in animal models has established the amygdala to be a central component of fear processing in the brain and these findings have shaped our understanding of human disorders of fear (LeDoux, 2000). In human populations with anxiety, hyperactivation of the amygdala is thought to underlie fear responses to innocuous stimuli incorrectly perceived as threatening (Pine, 2007). Indeed, a number of studies have found that adult anxiety disorders are associated with atypical amygdala activation (Kilts et al., 2006; Phan, Fitzgerald, Nathan, & Tancer, 2006; Rauch et al., 2000; Stein, Goldin, Sareen, Zorrilla, & Brown, 2002; Straube, Mentzel, & Miltner, 2006; Yoon, Fitzgerald, Angstadt, McCarron, & Phan, 2007). However, as described above, the developing amygdala appears not to respond to threatening stimuli in the same way as in the adult (Monk et al., 2003; Thomas, Drevets, Whalen, et al., 2001). Thus, in order to understand the neurobiology of pediatric anxiety, it is essential to evaluate younger populations. Using functional imaging, Thomas et al. reported that anxious children show heightened amygdala activity in response to fearful faces compared with healthy children (Thomas, Drevets, Whalen, et al., 2001). McClure and colleagues further evaluated the issue of amygdala hyperactivation in pediatric generalized anxiety by controlling for attention states of the participants (McClure, Monk, et al., 2007). They found that anxious adolescents displayed right amygdala hyperactivity to fearful faces compared to happy faces, but only when attention was directed to an evaluation of fear (i.e., rating "how afraid are you?"), but not during other attention states (i.e., rating "how wide is the nose?"). The finding of hyperactivation of the amygdala during internal representation of fear was recently replicated in a study comparing depressive versus anxious adolescents (Beesdo et al., 2009). Reports of amygdala hyperactivation are also found in studies attempting to replicate more naturalistic social settings. Compared to controls, anxious adolescents are more likely to perceive unfamiliar peers as less likely to want to interact with them and show hyperactivation of the amygdala when viewing seemingly innocuous stimuli such as smiling peers (Guyer et al., 2008).

Amygdala hyperactivation has also been reported in experimental paradigms that do not require conscious perception of the stimuli. Monk and colleagues utilized "masked" emotional (angry, happy) or neutral faces presented for 17 ms and found that anxious adolescents showed greater right amygdala activation relative to controls (Monk et al., 2008). A functional connectivity analysis revealed that the heightened amygdala response in the GAD individuals occurred in the absence of compensatory activation in ventrolateral prefrontal cortex observed in control participants. Another fMRI study comparing anxious and healthy adolescents utilized a similar paradigm, but presented the images for 500 milliseconds (Monk et al., 2006). In this scenario, the anxious adolescents did not differ from controls in patterns of amygdala activation, but they did show hyperactivity in the ventrolateral prefrontal cortex. During the 500 ms presentation, the prefrontal cortex activity was negatively correlated with severity of anxiety. In contrast, during the 17 ms presentation paradigm, amygdala activity was positively correlated with severity of anxiety. Taken together, the authors suggest that in pediatric anxiety, amygdala activation reflects processes associated with the actual anxiety, while activation of the prefrontal cortex reflects modulation of the amygdala and the emotional response (Pine, Guyer, & Leibenluft, 2008).

A similar pattern of amygdala hyperactivation has been reported in studies of children identified as behaviorally inhibited. Schwartz et al. found greater amygdala activation to emotionally neutral faces in young adults who had been identified as having high levels of behavioral inhibition early in development (Schwartz, Wright, Shin, Kagan, & Rauch, 2003). Likewise, behaviorally inhibited adolescents show exaggerated amygdala activity when asked to rate subjective fear states (Perez-Edgar et al., 2007), though the behaviorally inhibited individuals show this response across all emotional stimuli, while adolescents with GAD showed heightened

amygdala activity in response to fearful and angry faces (McClure, Monk, et al., 2007).

Collectively, these studies indicate that the amygdala is structurally and functionally abnormal in cases of pediatric anxiety, and possibly in children who have not developed anxiety but do have a behaviorally inhibited temperament. Interestingly, the alteration of amygdala activity is similar to what has been seen in children with autism. This has prompted us to suggest that the amygdala pathology in autism may be more associated with the abnormal fear and anxiety that is a common co-morbid symptom of autism (Schumann & Amaral, 2009). In addition to serving as a possible biomarker for pediatric anxiety, heightened amygdala activity may also provide predictive information regarding treatment response (Maslowsky et al., 2010; McClure, Adler, et al., 2007). However, the relationship between amygdala activation and pediatric anxiety is likely to be complicated by the presence or absence of a number of other risk factors, including genetic influences such as the serotonin transporter (Lau et al., 2009).

2.3. Childhood bipolar

The hallmark of bipolar disorder is mood dysregulation, which typically includes manic episodes, marked by high energy and anxiety, and depressive episodes, marked by feelings of hopelessness and isolation, that severely interfere with daily function (American Psychiatric Association, 1994). Depression and mania can co-occur, or rapidly alternate, often resulting in paranoia; some severe manic episodes can lead to schizophrenia-like psychosis. The diagnosis of bipolar disorder in children is controversial. In fact, the APA's DSM-IV current criterion for diagnosis is limited to adult-onset (American Psychiatric Association, 1994). Nonetheless, population studies report that 1% of children may be considered bipolar (Hudziak, Althoff, Derks, Faraone, & Boomsma, 2005; Moreno et al., 2007), although the etiology and neurobiology of childhood versus adult onset may differ (Garrett & Chang, 2008; Kato, 2007).

Children given a diagnosis of bipolar disorder demonstrate impaired recognition of emotions in facial expressions and social function, which are often linked to amygdala dysfunction (Jacobsen et al., 1998; McClure, Pope, Hoberman, Pine, & Leibenluft, 2003; McClure et al., 2005). MRI studies in bipolar children consistently show a 10–16% *decrease* in amygdala volume compared to typically developing children (Blumberg et al., 2003; Chang et al., 2005; Chen et al., 2004; DelBello, Zimmerman, Mills, Getz, & Strakowski, 2004; Dickstein et al., 2005; Frazier et al., 2005; Garrett & Chang, 2008). There is some evidence that amygdala volume decreases further with age (Doty et al., 2008). One small longitudinal study found 10 adolescents with bipolar disorder had a decrease in amygdala volume over a 2-year period (Blumberg, Fredericks, et al., 2005) that did not occur in typically developing adolescents. However, it is difficult to determine whether the decrease in amygdala volume is a primary feature of bipolar disorder or is a consequence of the high level of stress associated with the disorder, which may have a neurotoxic effect (Post & Leverich, 2006). Postmortem studies of children with bipolar disorder are scarce. However there is some evidence that the smaller amygdala volume may be due to a reduction in glial cell density (Bowley, Drevets, Ongur, & Price, 2002).

The consistent finding of *reduced* amygdala volumes in *children* is in stark contrast to studies of *adult-onset* bipolar disorder, which typically report that the amygdala is *enlarged* (Arnone et al., 2009). Collectively, these studies suggest that child- and adult-onset bipolar disorders may have different etiologies. It is also difficult to interpret findings because the psychotropic medications that patients often take for bipolar disorder, such as lithium, may actually have neuroprotective effects that could alter amygdala size (Moore et al., 2000). Adults, following their first-episode of mania and no psychotropic exposure, had decreased amygdala volume compared to typical controls (Rosso et al., 2007). However, another study of bipolar adults with psychotropic exposure reported larger amygdala volumes relative to typical adults (Foland et al., 2008). Chang et al. (2005) found that children with bipolar disorder and *no psychotropic drug exposure* had decreased amygdala volumes compared to typically developing controls; however those *with psychotropic drug exposure* had amygdala volumes that did not differ from control. All of these findings (Table 1) are consistent with the notion that psychotropic drug administration over time leads to an increased size of the amygdala.

Among the few functional imaging studies that have been carried out in children with bipolar disorder, the amygdala seems to be hyperactive when the subject is asked to rate faces depicting fear and anger (Chang, Wagner, Garrett, Howe, & Reiss, 2008; Pavuluri, O'Connor, Harral, & Sweeney, 2007; Rich et al., 2006). Chang et al. (2008) reported that adolescents with bipolar disorder display increased amygdala activation while viewing negatively valenced pictures. Amygdala hyperactivation is also commonly seen in adults while performing a variety of emotional and face processing tasks (Altshuler et al., 2005; Blumberg, Donegan, et al., 2005; Pavuluri et al., 2007; Yurgelun-Todd et al., 2000), although mood stabilizing medications may suppress hyperactivity (Blumberg, Donegan, et al., 2005). Increased amygdala activity appears to be a consistent finding in patients with bipolar disorder regardless of age, duration of illness, or amygdala size (Garrett & Chang, 2008).

Collectively, structural and functional imaging studies in children with bipolar disorder suggest that the amygdala is pathological, but differs from the structural pathology found in adults with the disorder. It remains unclear whether the child- and adult-onset forms are in fact similar or different disorders. Future studies of children with bipolar disorder would benefit from a longitudinal design to determine if there is a relationship between amygdala size and either the age of onset or duration of psychotropic drug exposure.

2.4. Schizophrenia

Schizophrenia is characterized by disorganized thought and an abnormal perception of reality which results in severe social and occupational dysfunction (American Psychiatric Association, 1994). The diagnosis is based on the presence of "positive" symptoms including hallucinations and delusions and "negative" symptoms including flattened affect and disorganized speech. Patients also exhibit impairments in emotion perception and social cognition (Hooker & Park, 2002). There are behaviorally defined subtypes of schizophrenia in which some patients exhibit marked paranoia, catatonia, disorganized behavior, or some combination thereof (American Psychiatric Association, 1994).

Although typically not diagnosed until late adolescence or early adulthood, schizophrenia is increasingly considered a psychiatric disorder with neurodevelopmental origins (Lewis & Levitt, 2002; Murray et al., 2004; Weinberger, 1987). In addition to genetic risk (Walsh et al., 2008), obstetric events (Clarke, Harley, & Cannon, 2006) such as maternal malnourishment (Susser et al., 1996), stress (Huttunen & Niskanen, 1978), or infection (Davies, Welham, Chant, Torrey, & McGrath, 2003) in utero, may be contributory factors to developing the disease. Prospective studies have documented developmental delays and diagnoses of pervasive developmental disorder (PDD) in children prior to the onset of psychosis (Done, Crow, Johnstone, & Sacker, 1994; Isohanni et al., 2000; Jones, Rodgers, Murray, & Marmot, 1994) and a specific pattern of impairments in neuromotor, receptive language, and cognitive development are seen in children who later develop schizophrenia (Cannon et al., 2002).

To date, the extreme heterogeneity within the disorder and the often late-onset of *behavioral* symptoms has hampered the establishment of a consistent etiology or pathology for schizophrenia. There is good reason to suspect, from the behavioral perspective, that the amygdala may be pathological in schizophrenia given that patients are impaired in their ability to appropriately appraise and monitor emotional stimuli, including threatening or aversive stimuli, and anxiety is a common feature of the disorder. Patients show aberrant scan paths while viewing faces depicting strong emotion (Loughland, Williams, & Gordon, 2002) and tend to mislabel neutral or ambiguous stimuli as threatening (Holt & Phillips, 2009), suggesting that they have an increased sensitivity to threat (Green, Williams, & Davidson, 2003) which may be related to psychotic symptoms (Phillips, Senior, & David, 2000; Taylor, Liberzon, Decker, & Koeppe, 2002).

Recent evidence from longitudinal studies at the National Institute of Mental Health (NIMH) indicates that the etiology of childhood-onset schizophrenia may differ from the adolescent or adult-onset form (Addington & Rapoport, 2009). Children with schizophrenia who are diagnosed prior to 13 years of age show a progressive loss of cortical gray matter through the adolescent years that exceeds what is seen in typically developing adolescents (Arango & Kahn, 2008; Gogtay et al., 2004; Thompson et al., 2001, 2004). Reports of abnormalities in amygdala volume and function have been much less consistent but, similar to cortical abnormalities, seem to depend on time of onset of the disorder (see Table 1). As with autism, the amygdala in schizophrenic patients may undergo an abnormal growth trajectory rather than remain consistently larger or smaller than controls. There is a trend for patients at high-risk for childhood or early-onset schizophrenia to have an enlarged amygdala during adolescence (Levitt et al., 2001; Welch et al., 2009). However, adults with chronic schizophrenia tend to show a 5–10% reduction in amygdala volume relative to controls (Ellison-Wright, Glahn, Laird, Thelen, & Bullmore, 2008; Exner, Boucsein, Degner, Irle, & Weniger, 2004; Honea, Crow, Passingham, & Mackay, 2005; Joyal et al., 2003; Lawrie & Abukmeil, 1998; Nelson, Saykin, Flashman, & Riordan, 1998; Witthaus et al., 2009; Wright et al., 2000). Though, it is important to point out that almost half of the structural MRI studies carried out to date have not found a difference in amygdala volume at any age or stage of the disorder (Frazier et al., 2008; Gibbs et al., 2008; Giedd et al., 1999; Jacobsen et al., 1998; Tanskanen et al., 2005).

Velakoulis et al. (2006) reported amygdala enlargement in patients who recently experienced their first episode of psychosis, but not in those with chronic schizophrenia; the latter had been taking neuroleptic medications for several years. Two other studies reported a reduction in amygdala volume following an initial episode of psychosis (Joyal et al., 2003; Witthaus et al., 2009). These studies raise the possibility that the variability in findings may be due to *when* in development the onset of behavioral symptoms occur. In the study by Velakoulis et al. (2006), patients with schizophrenia experienced their first episode of psychosis in late adolescence, whereas in the study by Joyal et al. (2003) and by Witthaus et al. (2009), the first episode of psychosis occurred when subjects were, on average, in their late 20's (Steen, Mull, McClure, Hamer, & Lieberman, 2006 for review). Consistent evidence of amygdala pathology has not been found in childhood schizophrenia with onset prior to 13 years of age (Giedd et al., 1999; Jacobsen et al., 1998).

Postmortem studies on the amygdala in schizophrenia are scarce (Bogerts, 1984; Chance, Esiri, & Crow, 2002; Heckers, Heinsen, Heinsen, & Beckmann, 1990; Kreczmanski et al., 2007) and generally involve a wide age range of cases with mostly adult-onset. In early postmortem studies, reductions in GABAergic levels and increases in dopamine in the amygdala were linked to psychosis (see Reynolds, 1983; Benes, 2010 for review). Kreczmanski et al. (2007) carried out the only postmortem study of the amygdala employing modern stereological methods to measure the volume, neuron density and total neuron number in the lateral nucleus. In their study of 13 male patients with schizophrenia ranging in age from 22 to 64 years at death and 13 age-matched controls, they found a reduced mean volume and total neuron number of the lateral nucleus of the amygdala in cases of schizophrenia. One caveat to these findings is that most patients with schizophrenia also had seizure disorder and were subjected to long-term treatment with neuroleptics, which may or may not affect amygdala pathology. It is interesting, though, that the reduction in neuron number in the lateral nucleus of the amygdala in schizophrenia is similar to the reduced neuron numbers in the lateral nucleus reported in cases of autism (Schumann & Amaral, 2006).

Functional imaging studies to date suggest that there is no consistent pattern of amygdala dysfunction in patients with schizophrenia. Some studies have found *reduced* activation (Addington & Rapoport, 2009; Gur et al., 2007; Gur et al., 2002; Habel et al., 2004; Hempel, Hempel, Schonknecht, Stippich, & Schroder, 2003; Johnston, Stojanov, Devir, & Schall, 2005; Paradiso et al., 2003; Phillips et al., 1999; Schneider et al., 1998; Takahashi et al., 2004; Taylor, Liberzon, Decker, & Koeppe, 2002; Williams et al., 2004; Williams et al., 2007) and others *increased* activation (Gur et al., 2007; Hall et al., 2008; Holt et al., 2006; Kosaka et al., 2002) depending on the task, the stage of the disorder studied, and whether the patient population preferentially exhibited more positive or negative symptoms. Collectively, Holt and Phillips (2009) suggest that the pattern of amygdala dysfunction in schizophrenia is complex and results in an impairment in *appraising* the level of threat in the stimulus. They note that patients tend to show increased activation to neutral or ambiguous stimuli and judge them as more threatening than do controls. Interestingly, schizophrenic patients with prominent paranoia show a tendency to mislabel neutral or ambiguous stimuli as more threatening than controls and also exhibit increased amygdala activity during this task (Phillips, Drevets, Rauch, & Lane, 2003). However, the same patient population exhibits diminished amygdala response to faces clearly depicting fear (Phillips et al., 1999; Williams et al., 2004; Williams et al., 2007). Therefore it may be the uncertainty about the stimulus that leads to the elevated amygdala activation in patients with schizophrenia.

Another explanation for conflicting functional imaging findings is that, similar to autism and fragile X, people with schizophrenia avoid looking at the eye region of the face (Loughland et al., 2002) and therefore the reduced amygdala activation noted in several studies may be because they are not looking at the same features of the face that controls are. The eye region of the face is particularly important for recognizing fear; without information from the eyes, fear can be difficult to identify (Adolphs, 2008). Patients with schizophrenia are impaired in identifying fear (Schneider et al., 2006) and, in the majority of studies, exhibit decreased amygdala activation (Holt & Phillips, 2009). This paradox is also similar to studies of autism, in which increased amygdala activation compared to typical controls was found only when subjects were actually looking at the eye region of the face (Dalton et al., 2005). Morris, Weickert, and Loughland (2009) suggest that patients with schizophrenia avoid eye contact because they find all faces more threatening.

Collectively, structural and functional imaging, as well as postmortem studies, indicate that the amygdala is pathological in schizophrenia. However, the pattern of pathology is complicated by several factors including the patient's primary symptoms, degrees of illness severity, age of onset, illness duration, subtypes, comorbid diagnoses, and antipsychotic medications. As mentioned above, childhood schizophrenia may have an entirely different etiology than adolescent-onset schizophrenia (Arango & Kahn, 2008)

and thus potentially very different effects on brain morphology. Clearly more studies are needed of this population before firm conclusions can be drawn.

2.5. Williams syndrome

Williams syndrome (WS) is a rare neurodevelpmental disorder resulting from a hemizygous deletion of approximately 25 genes in chromosome band 7q11.23 (Ewart et al., 1993; Korenberg et al., 2000). Individuals with WS have a specific craniofacial dysmorphology, as well as a variety of connective or soft tissue disorders, including cardiac abnormalities (Tassabehji et al., 1999). In addition to these physical features, individuals with WS demonstrate a distinctive profile of cognitive, social and emotional abilities and impairments. While most individuals with WS have mild to moderate intellectual impairment (Bellugi, Lichtenberger, Jones, Lai, & St George, 2000), they demonstrate relative strengths in certain aspects of language and memory despite pronounced deficits in visuospatial skills (Mervis & John, 2010; Mervis & Klein-Tasman, 2000). Another defining feature of WS is hypersociability, characterized by uninhibited social interests and overly emotional and empathetic reasoning (Jones et al., 2000). In spite of this strong social drive to interact with others (Doyle, Bellugi, Korenberg, & Graham, 2004), individuals with WS often have difficulty maintaining peer relationships (Laws & Bishop, 2004). Interestingly, the majority of WS individuals present with at least one anxiety disorder (Dykens, 2003; Leyfer, Woodruff-Borden, & Mervis, 2009; Woodruff-Borden, Kistler, Henderson, Crawford, & Mervis, 2010), though anxious behaviors are typically manifested in nonsocial situations (Einfeld, Tonge, & Florio, 1997).

Williams syndrome provides a unique opportunity to study gene–brain–behavior relationships in a human condition with a known genetic basis paired with a well characterized and distinctive behavioral and cognitive profile (Meyer-Lindenberg, Mervis, & Berman, 2006). Neuroanatomical studies are a logical place to begin this endeavor. Unfortunately, there are very few comprehensive assessments of postmortem brain tissue available from individuals with WS and the cases that have been examined focus primarily on cortical neuropathology (Galaburda, Holinger, Bellugi, & Sherman, 2002; Galaburda, Wang, Bellugi, & Rossen, 1994). A single postmortem case study indicated that the overall volume of the amygdala was decreased in a WS patient compared to controls, with the most pronounced differences localized to the dorsal portion of the lateral nucleus (Galaburda & Bellugi, 2000). Additional postmortem analyses of the WS amygdala are clearly needed to interpret these findings.

Structural MRI studies of the WS brain have consistently reported an overall decrease in absolute brain volume of WS participants compared to controls, with the most pronounced reductions in occipital and parietal regions (reviewed by Eckert et al., 2006; Jarvinen-Pasley et al., 2008). However, in spite of this global decrease in brain volume, specific brain regions appear to show a relative sparing or even a disproportional increase relative to the overall brain volume. For example, using both volumetric analyses and voxel-based morphometry, Reiss et al. (2004) reported that amygdala volume was disproportionately increased in WS participants compared to age-matched controls. This study was based on a relatively large sample of 43 WS participants (mean age 28.9 years; range 12–50 years) and 40 age-matched controls. Manual tracing of the amygdala by Martens, Wilson, Dudgeon, and Reutens (2009) revealed a similar disproportionate enlargement of the amygdala in a younger population of WS participants (mean age 16.9; range 8–41) compared to 22 age-matched controls. However, not all volumetric studies have replicated these findings of disproportionately large amygdala volumes in individuals with WS. For example, Meyer-Lindenberg used voxel-based morphometry to examine amygdala volumes in individuals with WS who have normal IQ and found no differences in grey matter density within the WS amygdala compared to controls (Meyer-Lindenberg et al., 2004). Chiang et al. used tensor-based morphometry to automatically detect and quantify patterns of brain volume differences in adults with WS relative to control subjects (Chiang et al., 2007). They found a consistent 10–15% overall reduction in brain volume in individuals with WS compared to controls; however, the trend of larger right amygdala volume in WS compared to control participants was not significant. These inconsistencies are likely due to methodological and sample selection differences.

Given the paucity of studies involving children with WS, we know even less about the developmental trajectory of amygdala growth at earlier time points. While some structural abnormalities found in adults with WS have also been found in children with WS (i.e., changes in parieto-occipital grey matter) (Boddaert et al., 2006), disproportional increase in amygdala volumes have yet to be reported in younger WS samples. For example, manual tracing measures of amygdala volumes failed to reach statistical significance between WS children (mean age 13 years; range 8–16) and age- and gender-matched controls (Campbell et al., 2009).

In spite of the inconsistencies from structural imaging studies, associations have been made between amygdala volume and behaviors characteristic of WS. For example, Martens et al. reported that individuals with WS, but not controls, demonstrated a positive correlation between right amygdala volume and approachability ratings for pictures of negative faces (Martens et al., 2009). Interestingly, this study also reported that the WS individuals used a different strategy for evaluating approachability in faces. Unlike controls, the WS participants relied on features other than the eyes and mouth to determine approachability, a finding reminiscent of the unique face processing deficits observed in individuals with bilateral amygdala damage (reviewed in Adolphs, 2010).

Functional imaging studies have also provided evidence of amygdala dysfunction in WS. Meyer-Lindenberg and colleagues evaluated amygdala response to social and nonsocial threatening stimuli (i.e., faces or scenes) in adult individuals with WS (Meyer-Lindenberg et al., 2005). Compared to controls, the WS participants showed reduced amygdala activation to faces, but increased amygdala activity to threatening scenes. A subsequent study from this same sample of high functioning WS participants replicated the finding of amygdala hyperactivation in response to nonsocial fearful stimuli (Munoz et al., 2010). The findings of hypoactivation to fearful social stimuli have also been replicated. Hass et al. reported that adult WS participants demonstrate absent or attenuated amygdala reactivity to fearful faces, compared with control participants (Haas et al., 2009). When a subset of these individuals with WS participated in a subsequent study, they found that a greater tendency to approach strangers was associated with less left (but not right) amygdala activation in response to viewing fearful faces (Haas et al., 2010).

Collectively, the functional imaging studies suggest that individuals with WS show increased amygdala response to threatening nonsocial stimuli and decreased amygdala response to threatening social stimuli. These findings are opposite the pattern of amygdala activation observed in healthy controls, but are consistent with the behavioral profile of individuals with WS. It is not, however, known when changes in amygdala structure and function emerge and what consequence these changes have on other aspects of neural development. The structural and functional changes in the WS amygdala likely alter other aspects of brain circuitry, as evidenced by a reduction in functional connectivity of face processing centers of the brain (i.e., the fusiform face area) with the amygdala and prefrontal cortex in adults with WS (Sarpal et al., 2008). Additional studies of pediatric WS populations will play a critical role in deter-

mining the role of the amygdala in the unique behavioral profile of individuals with WS.

2.6. Fragile X

Fragile X (FXS) is the most commonly inherited form of intellectual disability, affecting approximately 1 in 4000 males and 1 in 8000 females (Crawford, Acuna, & Sherman, 2001). This disorder is caused by the disrupted expression of the fragile X mental retardation (*FMR1*) gene located on the long arm of the X chromosome (Verkerk et al., 1991). This region includes a trinucleotide CGG repeat expansion that results in ~30 copies of the trinucleotide repeat in typically developing individuals, 50–200 repeats in premutation carriers, and over 200 repeats in individuals with the full mutation. The full mutation result in hypermethylation of the *FMR1* gene promoter and the subsequent reduction of FMRP protein, which in turn has a profound impact on brain development. Individuals with FXS generally have intellectual disability, with other behavioral features including gaze aversion, social difficulties, impulsivity, anxiety and hyper arousal (Reiss & Freund, 1992).

Consistent changes in the brains of individuals with the full mutation include enlargement of the caudate nucleus, a decrease of the cerebellar vermis and superior temporal gyrus volume, with less consistent changes reported in amygdala volumes (reviewed in Hessl, Rivera, & Reiss, 2004; Lightbody & Reiss, 2009; Reiss & Dant, 2003). Using manual tracing protocols Kates et al. first reported a 10% reduction in amygdala volume in children with FXS (boys mean age 6.3 years; girls mean age 9 years); however, these volumes were not significantly different from matched controls (Kates, Abrams, Kaufmann, Breiter, & Reiss, 1997). Statistically significant decreases in amygdala volumes were, however, reported in a volumetric analysis of younger children with fragile X compared to matched controls (mean age 11.7; range 1.1–22.7) (Gothelf et al., 2008). Brain regions that best distinguished subjects with FXS from typically developing controls included an enlarged caudate, followed by decreased posterior vermis and decreased amygdala. Of the subjects that had all three of these characteristics, 91.5% were in the FXS group, indicating that the combination of these three neuroanatomical abnormities is highly characteristic of children with FXS. Decreased amygdala volumes were also reported in a recent study comparing very young boys (18–42 months) with FXS (with and without autism) to boys with idiopathic autism (without FXS) and controls (Hazlett et al., 2009). Manual tracing of the amygdala revealed that children with FXS had a smaller amygdala volume regardless of whether the child also met criteria for autistic disorder. However, not all studies in young children with FXS have found significant differences in amygdala volume. A recent study of 51 young boys with FXS (average age 35 months) failed to find significant differences in amygdala volumes with voxel-based or volumetric analyses (Hoeft et al., 2008). A pattern classification analysis of these data revealed that individuals with FXS demonstrate an unusual pattern of increased grey matter volumes in the medial portion of the amygdala paired with decreased grey matter volume in the lateral amygdala. These findings indicate that structural changes in the amygdala are a common feature of FXS.

Functional MRI has also been used to examine the neural basis of behaviors associated with FXS, focusing on the pronounced gaze aversion characteristic of subjects with this disorder. Studies in adults with FXS have linked gaze aversion with abnormal activity in face processing regions of the brain (Dalton, Holsen, Abbeduto, & Davidson, 2008; Garrett, Menon, MacKenzie, & Reiss, 2004; Holsen, Dalton, Johnstone, & Davidson, 2008), though specific differences in amygdala activation were not observed in these paradigms. Functional imaging studies in younger children with FXS have, however, found differences in amygdala function. When viewing stimuli of faces with direct eye gaze, young boys with FXS show greater amygdala activation than do typically developing controls (Watson, Hoeft, Garrett, Hall, & Reiss, 2008). When shown successive images of direct gaze, the boys with FXS responded with sustained left amygdala activation, indicating that unlike controls, the FXS participants were responding with increased rather than habituated amygdala activity. Moreover, a significant negative correlation between left amygdala sensitization and task accuracy suggests that repeated exposure to direct gaze stimuli may have increased anxiety and had a negative impact on test performance in children with FXS compared to controls. The authors suggest that this pattern of greater, sustained amygdala activation in response to direct gaze may underlie the striking gaze aversion observed in FXS populations.

Although many questions remain regarding the role of amygdala function in FXS, there is compelling evidence for a reduction in amygdala volume combined with reports of amygdala dysfunction in FXS. Interestingly, there is preliminary evidence suggesting that alterations in amygdala structure and function may even be present in individuals with the permutation (Hessl et al., 2007; Moore et al., 2004). Thus, future studies exploring the relationship between FMRP levels and specific profiles of amygdala dysfunction may provide insight into the mechanisms of the disorder.

3. Conclusions

The amygdaloid complex is a brain region that emerged early in phylogeny for the main purpose of detecting dangers in the environment. Through its myriad connections with other brain regions, it is capable, once having detected a potential danger, of coordinating an appropriate response leading to escape. The response is complex and includes influencing cortical sensory processing to focus attention on the environmental threat to mobilizing bodily resources to mount an effective escape. One end result of this process is the conscious appreciation of fear upon facing an imminent threat or of anxiety in contemplating a future, potential threat. This system, which is designed to detect dangers and modulate all subsequent behavior, can have a profound influence on human activities. If the threshold is to low, normally benign aspects of the environment are perceived as dangers and interactions are limited. If the set point for danger detection is too high, risk taking is increased and inappropriate sociality may occur. Given that many of the neurodevelopmental disorders that we have reviewed involve too little or too much fear or anxiety or too little of too much social interaction, it is not surprising that the amygdala has been implicated in the pathophysiology of many of them.

Much of the evidence for pathology of the amygdala in neurodevelopmental disorders comes from rather coarse levels of analysis. To find that the amygdala is smaller or larger in individuals with a neurodevelopmental disorder does not provide much insight into the underlying mechanism for potential dysfunction. As we have reviewed above, both enlarged and decreased size of the amygdala can be associated with increased anxiety! We have also learned from studies of autism, that *when* during development the measurements are made is critically important. There is now substantial evidence that, during early postnatal development, the amygdala grows larger faster in a sizable group of children with autism. But, the ultimate size of the amygdala is the same as typically developing children. Thus, if one studies a group of adolescents, the size of the amygdala in individuals with autism and age-matched controls is about the same and there is no indication of the abnormal trajectory of amygdala development in the autistic individuals. Given the paucity of postmortem data that are available from young individuals with autism, there is currently no information on the cellular basis for the precocious growth of the amygdala. On the one hand, normal progressive processes, such as dendritic growth and synap-

togenesis, could simply be happening at a more rapid pace. On the other hand, an abnormal process such as glial proliferation, perhaps as part of an inflammatory process, could underlie the precocious growth. Our inability to support or discount these possibilities belies the need for substantially greater effort at examining brains from individuals with autism and for developing high-resolution, noninvasive techniques for evaluating cellular and metabolic processes in the human brain.

In adults with autism, there are some data indicating that the amygdala is smaller. One can only speculate currently whether this is part of the evolving disease process or is a repercussion of earlier stages of abnormal development. If, for example, the early hypertrophy of the amygdala in autism leads to abnormal anxiety with concomitant activation of stress mechanisms, decreasing size of the amygdala could be a result of allostatic load and feedback degenerative processes as seen in long term depression (Frodl et al., 2008; McEwen, 2005).

Functional magnetic resonance imaging studies are an important validation of amygdala pathology in neurodevelopmenal disorders. Generally speaking, hyperactivity of the amygdala is associated with increased anxiety. But, the correlation between the size of the amygdala and increased activation is not particularly clear. Moreover, given that the amygdaloid complex comprises 13 different nuclei and cortical regions with a variety of different neuronal cell types, what if any implication does an increased bold signal have for understanding the neural systems of cellular dysregulation that underlies the behavioral alterations associated with neurodevelopmental disorders? Clearly, animal models will need to be developed to provide insight into potential targets of therapeutic interactions.

Finally, it has been known for many years that the amygdaloid complex is highly epileptogenic (Gloor, 1990; Goddard, McIntyre, & Leech, 1969). It is equally clear that the amygdala undergoes various pathological changes in individuals with epilepsy (Pitkanen et al., 1998). Co-morbid seizure disorders are common in autism and other neurodevelopmental disorders. At least some of the variability in reported findings that we reviewed above may be due to the inconsistent inclusion of subjects with or without seizure disorders in both structural and functional MRI studies and in postmortem analyses.

The amygdala is a common site for neuropathology in neurodevelopmental disorders and is therefore a potential target for the alleviation of core or co-morbid symptoms. The speed with which therapeutic interventions will be developed and applied may depend, in part, on the availability of much more intensive information on the normal development of the amygdala both in humans and in animal models. Knowledge of genes that are preferentially expressed in the amygdala (Zirlinger & Anderson, 2003; Zirlinger, Kreiman, & Anderson, 2001) and of physiological mechanisms underlying evaluation of environmental threat, will undoubtedly suggest targets for the alleviation of abnormal fears and anxiety. While treatment of these symptoms may not deal directly with the core features of neurodevelopmental disorders, it will nonetheless improve the quality of life of affected individuals and facilitate other therapies that are more targeted at the core symptoms.

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