Available online at www.sciencedirect.com
SCIENCE DIRECT
NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS
Neuroscience and Biobehavioral Reviews 30 (2006) 97–117
www.elsevier.com/locate/neubiorev

Review

The orbitofrontal–amygdala circuit and self-regulation of social–emotional behavior in autism

Jocelyne Bachevalier[a,*], Katherine A. Loveland[b]

[a]*Yerkes National Primate Research Center, Emory University, Atlanta, GA, USA*
[b]*Department of Psychiatry and Behavioral Sciences, University of Texas Medical School, University of Texas Health Science Center, Houston, TX, USA*

Received 13 June 2005; accepted 27 July 2005

Abstract

Individuals with an autistic spectrum disorder are impaired not only in understanding others' mental states, but also in self-regulation of social–emotional behavior. Therefore, a model of the brain in autism must encompass not only those brain systems that subserve social–cognitive and emotional functioning, but also those that subserve the self-regulation of behavior in response to a changing social environment. We present evidence to support the hypothesis that developmental dysfunction of the orbitofrontal–amygdala circuit of the brain is a critical factor in the development of autism and that some of the characteristic deficits of persons with autism in socio-emotional cognition and behavioral self-regulation are related to early dysfunction of different components of this circuit. A secondary hypothesis posits that the degree of intellectual impairment present in individuals with autism is directly related to the integrity of the dorsolateral prefrontal–hippocampal circuit of the brain. Together, these hypotheses have the potential to help explain the neurodevelopmental basis of some of the primary manifestations of autism as well as the heterogeneity of outcomes.

Keywords: Hippocampus; Prefrontal cortex; Cerebellum; Memory deficits

Contents

1. Autism, social understanding, and self-regulation . . . 98
2. Characteristics of a neurodevelopmental model for autism . . . 99
3. Neural networks involved in autism . . . 99
4. The anatomical organization of the orbitofrontal–amygdala circuit . . . 101
5. The orbitofrontal–amygdala circuit and self-regulation of socio-emotional behavior . . . 102
6. Maturation of the orbitofrontal-limbic circuit and severity of the autistic social deficits . . . 103
7. Heterogeneity of behavioral symptoms in autism . . . 106
8. Early medial temporal lobe dysfunction and heterogeneity of autistic symptoms . . . 106
9. Is the orbitofrontal–amygdala circuit dysfunctional in autism? . . . 108
10. Other possible neural components of social–emotional self-regulation . . . 109
11. Conclusion . . . 110
Acknowledgements . . . 111
References . . . 111

Despite the vast amount of research it has attracted in recent years, the autistic spectrum of disorder (including such diagnostic categories as Autistic Disorder, Asperger Disorder, and Pervasive Developmental Disorder—Not Otherwise Specified) is still in some respects poorly understood. The considerable behavioral and developmental heterogeneity of these disorders even among those

* Corresponding author. Tel.: +1 404 727 9765; fax: +1 404 727 8088.
E-mail address: jbachev@emory.edu (J. Bachevalier).

0149-7634/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neubiorev.2005.07.002

individuals who fully meet diagnostic criteria for autism, makes the search for causes and treatments extremely complex. At present, for example, we do not know why some children with autism develop language and others do not; why some have mental retardation and others do not; why some appear to progress normally from birth, only to suffer a 'regression' to autism in the second year of life; why individuals vary in the extent to which they manifest repetitive or obsessive–compulsive behaviors; or why the degree of autistic social deficits varies among individuals. The answers to such questions about phenotype are elusive in part because relationships between brain and behavior as the child with autism develops are incompletely understood. For example, apparent subtypes of the autistic spectrum may share a basis in impairment of overlapping areas of the brain, or may share impairments of the same structures but to differing degrees, or may differ in the developmental timing of brain dysfunction. Despite much research there is still no well-accepted account of an underlying brain dysfunction shared by all persons with the full syndrome of autism, to say nothing of the broader spectrum of autistic disorder. Indeed, it can be argued that the heterogeneity of autism is so great that a single neural substrate is unlikely (e.g. Reichler and Lee, 1987).

Moreover, it is clear that the manifestations of autism change with the development of the individual. This fact makes the task of explaining autism—whether on the neurobiological or the behavioral level—even more complex. A model of the neural substrates of autism and their relationship to behavior must include an accounting of the ways in which brain development, learning, the child's own self-organizing activity, and environmental factors work together over time to produce a particular developmental outcome. In this review, we present a model of neurobehavioral development in autism that addresses the central behavioral and cognitive manifestations of autism as they are currently understood, while taking account of the wide variability seen in the disorder, not only among individuals but also over the developmental course of an individual.

1. Autism, social understanding, and self-regulation

Autism is centrally characterized by developmental disruption in social–emotional behavior and communication. Numerous studies have documented that, across the spectrum of disability, individuals with autism have poor social and affective relatedness, difficulty developing and maintaining social relationships with peers, problems in the social use of language, unusual non-verbal behaviors including gesture, abnormalities of emotional awareness and expression, and in general, difficulty meeting cultural expectations for age-appropriate social behavior (see for reviews Loveland, 2005; Loveland and Tunali-Kotoski, 2005; Volkmar et al., 1997). The social- emotional manifestations of autism are among those that cause the most difficulty in the lives of persons with autism and their families.

Most recent explanations of autism on the psychological level have reflected the view that behavioral manifestations of the disorder are the result of underlying deficits in cognition, affect, or both. Research has provided clear evidence that, compared with persons without autism of similar verbal level, persons with autism are poorer at reasoning about what others think, know or believe, recognizing emotional expressions and gestures, and making social attributions and judgments (Adolphs et al., 2001, Baron-Cohen et al., 1985; Hobson and Lee, 1989; Hobson et al., 1988ab; Klin, 2000; Leslie and Frith, 1990; Loveland et al., 1995; 1997; Perner et al., 1989; Pierce et al., 1997; Snow et al., 1987; Weeks and Hobson, 1987). These findings have been interpreted to show that people with autism lack insight into the mental life of other people; that they do not appreciate others' points of view; and that they are impaired in recognizing other people's emotions and reactions in social situations. Thus, if they are in fact operating with incomplete or incorrect information about other people, it is not difficult to see how persons with autism might behave inappropriately in social situations.

However, there is an additional factor linking the person with autism's imperfect understanding of the social world with the resulting inappropriate behavior. Information about other persons, their mental states, emotions, attitudes, intentions, etc. as well as the larger context of their actions, is necessary for regulating one's own behavior. Self-regulation of social behavior—the ability to select and initiate complex behaviors in response to the specific conditions of the social environment—depends critically on detecting information about the social world but also on evaluating its functional significance for the self (Loveland, 2001). Because the conditions of the social environment continually change, behavioral self-regulation in response to the social world is an essential adaptive process for humans and for many non-human animals that begins very early in life (Cicchetti and Tucker, 1994). For example, studies of infants have illustrated the reciprocal sensitivity of parent–infant pairs to each other's variations in affect and responsiveness, and the effect of this sensitivity on the dialogic train of interactive behavior (Fogel et al., 1997; Trevarthen, 1979; Trevarthen and Hubley, 1978). Young children commonly rely on social referencing—identifying the adult's reaction to environmental events—to determine such things as the safety of a new situation and the best behavioral course to pursue. Older children and adults, too, are ordinarily quite sensitive to information about other individuals' mental states, attitudes, etc. and use this information to modify their own behavior accordingly.

The self-regulation of social behavior, then, depends first on the ability to perceive or infer relevant information about what others may think, feel or intend, because this information indicates what others are likely to do. It

depends secondly on the ability to evaluate and modify our own behavior in light of what believe to be true about others, so that our behavior toward them will be effective in achieving our social/communicative goals (e.g. recruiting help, being accepted, communicating a fact, attracting a mate, intimidating an enemy, etc.). This process of perception and action is continuous and cyclical, in that modifications to our own behavior affect the social environment that we perceive, which in turn leads us to modify our behavior further, and so forth (Loveland, 2001).

In autism, this cycle of social perception and action could break down in a number of ways. Failure to perceive or infer accurately what others know, feel or intend could lead to the expression of inappropriate behavior, but so also could a failure to modify one's own behavior appropriately in light of accurate information. Some studies have found that persons with autism may not modify their own behavior appropriately in response to the perceived distress of others, even when they seem to be aware of it (Loveland and Tunali, 1991; Sigman et al., 1992.) There is also recent evidence showing that some individuals with autism have the ability to 'mind-read', or predict others' mental states, but that they do not necessarily do so in their daily lives (Rieffe et al., 2000). Similarly, Serra et al. (1999) found that even though higher-functioning children with autism performed well on emotional role-taking tasks in the laboratory, they nonetheless were less likely than controls to describe inner states or psychological characteristics when talking spontaneously about others. Some findings suggest that individuals with autism may fail to perceive the behavioral consequences of other people's behavior for themselves; as a result, they may be poor at judging how to respond. Loveland and colleagues (2001) found that children and adolescents with autism were less accurate than controls to detect whether videotaped children were willing to share some candy. Likewise, persons with autism are poorer at judging whether a face looks 'trustworthy' (Adolphs et al., 2001). Such judgments are important to selecting the appropriate actions in a social context. Taken together these studies suggest that people with autism, though probably less able than others to understand mental states and other socially relevant information (social perception), may also be less able to use such information to guide their own behavior (emotional self-regulation). If so, then it is understandable that the social behavior of people with autism is inappropriate across a variety of situations.

2. Characteristics of a neurodevelopmental model for autism

If individuals with an autistic spectrum disorder have a central social–emotional impairment related not only to understanding of others' mental states, intentions, and emotions, but also to self-regulation of social behavior, then a model of brain dysfunction in autism must encompass not only those structures and systems that subserve social awareness and emotion recognition, but also those that subserve the regulation of behavior in response to a changing social environment (Damasio et al., 1991). If so, then, the neurodevelopmental basis of autism is likely to be more complex than can be captured by impairment of a single, discrete structure or region of the brain. In addition, because autism is a developmental disorder beginning very early in life, rather than the result of an acquired brain injury, early dysfunction of one specific structure of the brain could initiate a cascade of neural events leading to the emergence of aberrant neural circuits or structures, principally those with a protracted maturation. Hence, we should expect to find that dysfunction of brain systems or circuits, rather than of discrete structures, will underlie the development of autism (see also Lee et al., 2003).

Further, a model of the brain in autism must provide opportunities to account for heterogeneities across the spectrum. It must help to explain the ways in which individuals across the autistic spectrum are known to differ, in terms of brain systems that may be impaired to varying extents in different individuals. Although it can be argued that one should focus exclusively on commonalities among persons with autism, rather than their differences, we believe that differences across the autistic spectrum are important and may help illuminate the basis of the disorder. In any case, autism will not be completely understood until the sources of these differences in outcome can be identified.

Finally, a neurodevelopmental model of autism must necessarily reflect the fact that persons with autism change as they develop. Manifestations of autism change as the individual matures, resulting in different needs and skills at different ages in the same individual. Behavioral changes in the manifestations of autism over development reflect the effects of experience, but also the maturation of a brain that may be impaired from very early in life. Such a person may be developing and organizing in ways very different from the usual pattern of development and may differently react to environmental stressors early in life. A model for the development of the brain in autism must, for example, take into consideration the adverse impact that the dysfunction of early-developing brain structures will have on later developing structures with which they are interconnected as well as the additional adverse effects of abnormal early transactions with the child's environment, which can affect both subsequent brain development and the child's learned ability to self-regulate behavior.

3. Neural networks involved in autism

Although a number of areas of the brain, including the brainstem, cerebellum, frontal lobe, and limbic structures, have been implicated as abnormal in persons with autism

(Bachevalier, 1991, 1994, 2000; Bachevalier and Merjanian, 1994; Bauman and Kemper, 2004; Courchesne, 1989, Courchesne, 1997; Damasio and Maurer, 1978; Fein et al., 1987; McEvoy et al., 1993; Ornitz, 1983; Rumsey and Hamburger, 1988), there is as yet no single, well-accepted neurodevelopmental model for autism. For example, viewing autism as a disorder of sensory modulation affecting cortical mechanisms of selective attention, Ornitz (1983) and Courchesne et al. (1994) have hypothesized involvement of the cerebellum, parietal cortex, brainstem, thalamus, and striatum. Alternatively, DeLong (1978) and Heltzer and Griffin (1981) have hypothesized bilateral dysfunction in medial temporal lobe structures (hippocampus and amygdala) and have drawn parallels between the amnesic and Klüver–Bucy syndromes and autism. By analogy to adult behavioral neurology, Damasio and Maurer (1978) have speculated that there is dysfunction in bilateral neural structures that include mesolimbic cortex in the mesial frontal and temporal lobes, neostriatum, and anterior and medial nuclear groups of the thalamus, structures that are targets of dopaminergic mesencephalic neurons. This fronto-limbic dysfunction in autism was also posited by Bishop (1993). The functional abnormalities revealed by recent electroencephalographic and metabolic studies (EEG, PET, and NMR) in the association areas of the cortex have led Minshew and colleagues (Minshew et al., 1997) to view autism as a disorder of information processing. Baron-Cohen et al. (1999, 2000) based on a fMRI study, identified dysfunction within a neural network important for social cognition in autism and comprising the superior temporal gyrus, the amygdala, and the orbitofrontal cortex. Finally, based on neuroimaging studies indicating activation of the anterior cingulate area when normal subjects have to take into account others' mental states, Frith and Frith (2001) speculated that the social deficit in autism may also be linked to a dysfunction of this neural system.

One of the underlying problems with the studies described above is that they lack a specific hypothesis that explains not only the symptoms associated with autism, but their heterogeneity, and their developmental time course. A major challenge for any model of brain development in autism is to address the neural substrate for the central characteristics of the disorder, while at the same time giving an account of how variations in its expression might arise. Clearly a simple and static unidirectional model in which a defective brain structure results in a specific behavioral deficit is not adequate for this purpose. In our model we present the basis for a more comprehensive approach, one that provides some insights into possible sources of variability linked to differences in neural development. Given that the core symptoms of autism relate to difficulties not only in understanding others' mental states, intentions, and emotions, but also in self-regulation of social and emotional behavior, a neurodevelopmental model of autism must involve neural structures or networks maturing relatively early in infancy and subserving emotion, social cognition, and self-regulation of behavior. We thus propose that a dysfunction of a neural circuit involving the amygdala, the orbitofrontal cortex, and their interconnections with the cingulate cortex, temporal pole area, and superior temporal gyrus (STS) are at the origin of the social deficits in autism. At the same time, given the heterogeneity of the symptoms, our general framework or hypothesis takes into account additional considerations:

A number of recent experimental neurobiological and clinical studies have identified the amygdala, and orbitofrontal, cingulate and temporopolar cortex as being particularly important for the regulation of emotional states and the development of well-adapted social skills. Thus, we speculate as have others (Baron-Cohen et al., 1999, 2000; Dawson et al., 1998; Schultz et al., 2000b) that early dysfunction of this neural circuit might be the substrate for the severe socio-emotional deficits seen in autism. This proposal is consistent with evidence suggesting that the amygdala and orbitofrontal cortex mature relatively early in the first years of life in humans, so that an early impairment of these brain structures could result in behavioral changes that will appear in infancy.

The second consideration is based on differences in the time periods in which these neural structures arrive at maturity. Thus, given that the amygdala is almost fully mature at birth (Humphrey, 1968; Nikolic and Kostovic, 1986) whereas the orbitofrontal cortex begins to mature slightly later, i.e. around the second year of life (Happaney et al., 2004; Overman, 2004), we postulate that the severity of the emotional and social changes as well as their developmental time course may vary, depending on which of these two structures, or both, are affected earlier in life. Although relatively little is known about the maturation of other neural structures within the neural network subserving social cognition, it is likely that they will also play a significant role in the timing, nature and severity of the behavioral deficits.

Developmental behavioral studies in both rodents (Daenen et al., 2002; Diergaarde et al., 2004; Wolterink et al., 2001) and non-human primates (Bachevalier, 1994; Bauman et al., 2004; Prather et al., 2001; Thompson, 1981) have shown that early damage to the amygdala produces behavioral changes that share similarities with some of the symptoms described in people with autism. Further, if the damage extends to the hippocampus and adjacent cortical areas, intellectual deficits are associated with the behavioral changes (Bachevalier, 1994). We thus hypothesize that mental retardation in the majority of people with autism may likewise be associated with extent of dysfunction within the medial temporal lobe.

Finally, animal studies have also shown that neonatal focal lesions of structures within the medial temporal region may have widespread effects on the maturing brain, propagating to and affecting structures and functions of other neural systems distant from the site of the lesions, such

as striatal-prefrontal dopamine regulation (Bertolino et al., 1997; Lipska et al., 1992; Saunders et al., 1998; Wood et al., 2003). We thus speculate that in autism, perturbations of the dynamic processes associated with brain maturation across development could trigger a cascade of structural and functional changes, which leads to the formation of aberrant neural circuits. These aberrant circuits could manifest themselves as behavioral abnormalities associated with the primary social deficit of autism. These neurobehavioral abnormalities, rather than remaining static throughout life, can further evolve as the subject matures, leading to greater developmental differences over time. This process could thus help to explain the heterogeneity of cognitive and behavioral deficits found in people with autism.

In the remainder of this paper, we review the clinical and experimental evidence that substantiates our general framework. Following a brief overview of the anatomical organization of the orbitofrontal–amygdala circuit and its role in the self-regulation of socio-emotional behavior, we review data on the development of this neural system and on the behavioral consequences of its dysfunction early in development. Evidence is provided to support the idea that heterogeneity of autistic symptoms may rest upon the extent to which the orbitofrontal–amygdala circuit is impaired and on the influence of this early dysfunction on the developing brain overall. Finally, growing evidence for a dysfunction of the orbitofrontal cortex and amygdala in autism is considered.

4. The anatomical organization of the orbitofrontal–amygdala circuit

Social cognition is realized through a complex neural network of interconnected structures, which includes the ventromedial portion of the prefrontal cortex, the amygdala within the temporal lobe, and their interconnections with the hypothalamus and brain stem (MacLean, 1949; Papez, 1937). Anatomical studies have further demonstrated that two major subsystems appear to feed into this limbic system (for review see Barbas, 1995; Goldman-Rakic and Goldman-Rakic, 1987). One is a system centered around the hippocampus, which comprises the posterior cingulate cortex and parahippocampal gyri, anterior thalamic nuclei, and the parietal and dorsolateral prefrontal cortex. This dorsal circuit appears to monitor the online-processing of sensory events and current actions in the service of the visuospatial domain and memory. The second is a ventral circuit centered around the amygdala, which includes the anterior cingulate and orbital frontal cortex and the mediodorsal nucleus of the thalamus. This ventral circuit has been implicated in the monitoring of emotional states and social cognition as well as in the self-regulation of behavior through knowledge of emotional responses and intentions of others (Barbas, 1995; Brothers, 1989, Brothers, 1995).

The amygdala, located in the anterior portion of the medial temporal lobe, comprises a set of thirteen interconnected nuclei with different connectional features (for reviews see Amaral, 1992; Emery and Amaral, 1999; Rolls, 1999). Its cytological components and interconnections have been extensively studied in monkeys and share strong similarity with those of humans (Gloor, 1997). Briefly, the lateral nucleus receives an enormous array of highly processed sensory information, including visual information from faces and facial expressions, gaze direction, body postures and movements, as well as auditory information from specific vocal sounds and intonations. Reciprocally, via the basal nucleus, it provides a route by which affective states can modulate the cortical processing of sensory stimuli. Interestingly, because these feedback projections from the amygdala to the cortical sensory areas are widespread, reaching not only the association cortical areas but also the primary sensory cortical areas, emotional states could influence sensory inputs at very early stages in their processing, by weighting the emotional significance of sensory information. The central nucleus provides a relay to the brainstem and hypothalamus through which the amygdala is thought to influence the autonomic and endocrine manifestations of emotion, respectively. Via this pathway, sensory stimuli could influence and activate emotional reactions. The basal and accessory basal nuclei project substantially to the ventral striatum, thereby offering a way by which affective states could provide access to subcortical elements of the motor system and so affect actions, including the modulation of facial and vocal expressions, body postures and movements. In addition, the amygdala significantly interacts with the hippocampal formation, and can thus act upon and modulate stored information in cortical areas (e.g. past experience with an individual).

The orbital region of the prefrontal cortex is a mesiocortical area that occupies the ventral surface of the frontal lobe. Comparative anatomical studies have indicated that the orbitofrontal cortex shares great similarities among primates, including humans, and that it can be subdivided into distinct cortical areas (for review see Barbas, 1995; Carmichael and Price, 1994; Cavada et al., 2000; Öngür and Price, 2000; Petrides and Pandya, 2002; Semendeferi et al., 1998). Like the amygdala, it receives highly-processed information from all sensory modalities (visual, somatosensory, visceral, olfactory, and gustatory) and, based on the pattern of its connectivity, it has been divided into medial and lateral networks. The medial network of the orbital frontal cortex, e.g. area 14, has strong connections with the hippocampus and associated areas of the cingulate, retrosplenial, and entorhinal cortices. The lateral network has been further subdivided into a caudal sector, e.g. areas 12 and 13, that is mainly interconnected with the amygdala, midline thalamus, and temporal pole, and a rostral sector, e.g. areas 12 and 11, that has more pronounced connections with the insula, mediodorsal nucleus of the thalamus, inferior parietal lobule and dorsolateral prefrontal

cortex. Interestingly, the orbital frontal cortex differs in many ways from the most dorsolateral prefrontal region. For example, unlike the dorsolateral prefrontal area, which receives projections primarily from the mediodorsal nucleus of the thalamus, the orbital frontal area receives projections primarily from midline and intralaminar nuclei (Barbas, 1995). In addition, the orbital frontal cortex receives robust projections from both the amygdala and the temporopolar area, whereas the rest of the prefrontal cortex appears to have few, if any, links with the amygdala and temporal pole (Ghashghaei and Barbas, 2002). Thus, unlike the dorsolateral aspect of the prefrontal cortex, the orbital frontal area receives information about all aspects of the external and internal environment, from thalamic nuclei involved in associative aspects of memory, and from the amygdala and temporal pole that are thought to regulate emotional states. Thus, the connections between the amygdala and orbital frontal cortex may permit the modulation and self-regulation of emotional behavior in relation to rapid changes in a social situation or context (e.g. dominance relationships, situational features). Finally, the orbital frontal cortex also sends inputs to brain regions, such as the preoptic region of the lateral hypothalamus, that are critical for hormonal modulation of emotions, and to motor centers, such as the head of the caudate and the ventral tegmental area, that are critical for motor control of emotional behaviors (Selemon and Goldman-Rakic, 1985).

In sum, the anatomical organization and reciprocal relationship between the amygdala and orbitofrontal cortex implies that these brain regions may share a close functional relationship within a system essential for the maintenance of intra-specific social bonding and the self-regulation of emotional states. Converging evidence from rodents, humans, and non-human primates indicates that the interconnections between the basolateral complex of the amygdala and the orbital frontal cortex are crucial to the formation and use of expectancies for reinforcers in the guidance of goal-directed behavior (Gottfried et al., 2003; Holland and Gallagher, 2004). Yet, the mechanisms by which these neural structures participate in social cognition are still poorly understood and it is unknown whether the specific mechanisms related to each structure can be distinguished or whether these neural structures function as a unitary 'system'. Nevertheless, as reviewed below, there exists some evidence to suggest that each component of this neural network may contribute differently to the control of social cognition.

5. The orbitofrontal–amygdala circuit and self-regulation of socio-emotional behavior

Recent studies of humans with restricted amygdala damage have reported inappropriate and irrational social behavior and social disinhibition (for review see Adolphs, 2003; Bechara et al., 2003). In addition, when presented with pictures of unfamiliar people, these patients abnormally rated as trustworthy faces of people who were judged as untrustworthy by control subjects. Interestingly, the deficit appeared to be greatest with the faces that controls had rated the most negatively. Thus, the human amygdala appears critical for the retrieval of socially relevant knowledge on the basis of facial information (Adolphs et al., 2005). For example, damage to the amygdala impaired judgments of fear and sadness but not of happiness (Adolphs et al., 1995; Adolph and Tranel, 2004). This view is supported by growing evidence indicating that the amygdala is implicated in the detection and interpretation of visual information from faces (for review see Zald, 2003). Electrophysiological recordings in epileptic patients have shown that neural activity in the amygdala can be evoked by neutral faces and faces of family members and friends. Further, the amygdala is activated in response to overt or masked emotionally expressive faces, to arousal, threatening or fear-provoking stimuli, or during gaze monitoring. There is still some debate on whether the amygdala is preferentially activated by negative emotions. Thus, greater activation of the amygdala has been found to occur with fearful than happy faces and, perhaps, with sad rather than angry faces, although both pleasant and aversive tastes activate the amygdala. Nevertheless, it is likely that the recognition of different emotional states involves separable neural circuits (Harmer et al., 2001; Liotti et al., 2000). Evidence for the involvement of the amygdala in the regulation of emotions in humans has also come from studies involving patients' reports of their subjective experiences upon stimulation of temporal lobe structures, including the amygdala (Gloor, 1997). These reports frequently touch on some aspects of the patients' relationship with other people, and they tend to involve actions, attitudes or intentions of others, perceived by the patients to be directed at them. More recently, case report studies have also shown that damage to the amygdala acquired either in infancy or in adulthood impairs 'Theory of Mind' (ToM) tasks, leading to the view that the amygdala plays a critical role in 'on-line' theory of mind (Fine et al., 2001; Stone et al., 2003).

Like lesions of the amygdala, prefrontal lesions that include the orbital sector result in dramatic emotional changes in humans, including euphoria, irresponsibility, and lack of affect (for review see Damasio, 1994; Rolls, 1999). Patients with damage to the orbitofrontal region manifest impairment in real-life decision making, associated with changes in their autonomic responses (Bechara et al., 1994) and failed to monitor changes in the reward value of stimuli and to use this information to guide their behavior (Hornak et al., 1996). They also show impaired ability to generate expectations about others' negative emotional reactions (Blair and Cipolotti, 2000) and are impaired both in the production of facial expressions of emotion and recognition of emotional expression from the face, voice, or gesture (Damasio et al., 1990; Hornak et al., 1996; Kolb and Taylor, 1981, 1990; Ross and Mesulam, 1979; Ross et al., 1981).

Neural activation of the orbitofrontal cortex has also been found to reflect the magnitude of abstract reward and punishment (O'Doherty et al., 2001b), and the processing of unpleasant auditory information (Frey et al., 2000), as well as to occur in the presence of pleasant and aversive tastes (O'Doherty et al., 2001a) and uncertainty about outcome (Critchley et al., 2001). More generally, the human orbital frontal cortex appears to monitor outcomes even when no reward is provided (Schnider et al., 2005).

The data indicate that, although the amygdala and orbital frontal cortex are critical for understanding the emotional and social significance of stimuli, their specific roles in the regulation of emotional and social behavior most likely differ (for review see Bachevalier and Meunier, 2005). Thus, the amygdala does not seem to be the generator of specific emotional responses, such as fear, rather it appears to code and process facial movements, eye-gaze directions, body postures, and gestures that are potent signals for the production and modulation of appropriate social and emotional responses towards other individuals. In addition, the amygdala appears to be implicated in a specific class of stimulus-reward associations: that is, associations between discrete stimuli and their intrinsic reward value. Examples include discovering the relationship between the way a particular food item appears and how pleasant it tastes, or the link between a specific animal in a social troop and its level of agonistic behavior (for review see Baxter and Murray, 2000). By contrast, the orbitofrontal cortex appears to be less important for identifying the reward value (significance or valence) of stimuli, but rather contributes to the anticipation of reward and adjusts behavioral responses when the reward values of stimuli have changed. For example, both monkeys and humans with damage to the orbitofrontal cortex are impaired on go/no-go task performance, in that they go on the no-go trials (Iversen and Mishkin, 1970), and on object reversal and extinction tasks in that they continue to respond to an object that is no longer rewarded (Butter and Snyder, 1972; Dias et al., 1996; Jones and Mishkin, 1972; Meunier et al., 1997; Rolls et al., 1983). This role of the orbitofrontal cortex in modulating goal-directed behavior when changes in reward value have occurred has also been demonstrated by electrophysiological recording during similar behavioral tasks (Schultz et al., 2000; Thorpe et al., 1983). Thus, the failure to respond normally after damage to the orbitofrontal cortex by adapting behavior when reinforcers have changed may be a fundamental deficit that underlies impulsiveness, disinhibition, inappropriate responses to other people's moods, and inadequate self-regulation of social–emotional behavior.

In sum, while the amygdala appears to be a neural system that acts to detect the significance of objects or events for the individual, the orbitofrontal cortex makes use of this information to guide goal-directed behaviors and to adjust behavior appropriately in accordance with changing conditions (Bechara et al., 1999; for review see Holland and Gallagher, 2004). This process of self-regulation is of particular interest as it applies to the social and emotional cognition and behavior of persons with autism. Given the specific roles of the amygdala and orbitofrontal cortex in the self-regulation of social–emotional behaviors, a dysfunction of the amygdala might result in difficulty detecting information relevant to the mental states, emotions, attitudes and intentions of others and their significance for the self. By contrast, a dysfunction of the orbitofrontal cortex would result in difficulty in modifying one's own behavior appropriately in response to changes in the behavior of others. Like individuals with partial damage to the amygdala who show impaired recognition of facial emotions, but intact visual discrimination (Young et al., 1996), people with autism are impaired in face recognition, identification of facial expressions, discrimination of faces, and memory for faces (for review see Grelotti et al., 2002) and lack insight into the mental life of other individuals. Further, people with autism are less able to use such information to guide their own behavior. Thus, they also resemble individuals with damage to the orbitofrontal cortex, who have difficulty modulating goal-directed behaviors in response to changes.

Even though a dysfunction of the orbitofrontal–amygdala circuit could be related to many, if not all, the *social* symptoms seen in autism, it does not by itself explain the heterogeneous expression of the disorder. As we have mentioned earlier, a simple and static unidirectional model in which a defective brain system results in specific behavioral deficits is inadequate to explain the complexity of a developmental disorder such as autism. We thus present below the basis for a more comprehensive developmental approach that provides some insights into possible source of variability linked to differences in neural development.

6. Maturation of the orbitofrontal-limbic circuit and severity of the autistic social deficits

A critical factor that must be taken into consideration in a neurodevelopmental model of autism is that the orbitofrontal cortex and amygdala not only play different roles in the control and modulation of socio-emotional cognition but they also appear to develop at different time periods during postnatal life. As a result, dysfunction in either or both of these two brain areas can result in different behavioral outcomes that could be of great significance in explaining the varying severity and nature of the social deficits seen in people with autistic spectrum disorders.

For example, Bechara and colleagues (1999) showed that patients with damage to the orbitofrontal cortex and those with damage to the amygdala are both impaired in decision-making, although the nature of the deficits seen after each lesion is different, and each lesion yields a different pattern of behavioral outcomes in the real-life activities of these patients. The decision-making deficits of patients with

amygdala damage appear to be related to a failure to appropriately perceive the affective significance (valence) of things they experience and to evoke the corresponding affective somatic states (i.e. experience the corresponding emotional feelings and the consequent motivational states). By contrast, the deficits of patients with damage to the orbitofrontal cortex involve failure to modify behavior appropriately and continuously in response to the varying significance of things they experience.

Impairment of the amygdala usually results in inappropriate behavioral and emotional reactions that eventually lead to physical harm to the patient and others. In fact, most such patients need to be under supervised care and cannot function alone in society (Lee et al., 1988, Lee et al., 1995). For example, such a patient might come to harm in a situation where other persons are provoked to anger, because he or she does not understand the significance of others' angry or aggressive behavior and does not experience an appropriate emotional/motivational reaction to it. By contrast, the decision-making deficit in a patient with orbitofrontal damage is less related to a failure to experience appropriate emotional states associated with social situations, than to a failure of the patient to modify or modulate these states and their behavior when the social situations change. Such an impairment usually has less immediate consequences than does amygdala impairment, resulting mostly in financial losses or problems in peer relationships (Eslinger and Damasio, 1985), but in some cases, it could lead to involvement in inappropriate or dangerous activity. This distinction between the role of the orbitofrontal cortex and that of the amygdala in decision-making, together with their specific roles in goal-oriented behaviors, suggests that early dysfunction of the orbitofrontal cortex may result in less debilitating socio-emotional disturbances than early damage to the amygdala. In fact, we could envision that early dysfunction of the amygdala results in a severe impairment of the recognition of faces, facial expressions, and other meaningful gestures, together with profound deficits in awareness of the social and emotional significance of things and situations experienced. By contrast, early dysfunction of the orbitofrontal cortex could result in a relatively spared ability to recognize simple emotional expressions (at least the easier ones, such as happiness and sadness), although recognition of more difficult or complex emotions, such as disgust and surprise, could still be impaired. A relative sparing of emotion recognition could be combined with difficulty recognizing other people's thoughts, beliefs, intentions, etc. and their significance for the self, together with difficulty regulating one's own behavioral responses in the context of a continuously changing social world.

The emergence of these different behavioral outcomes may also follow different time courses (for review see Machado and Bachevalier, 2003). Both the amygdala and the orbitofrontal cortex develop relatively early in infancy. However, the amygdala appears functional at birth (Humphrey, 1968; Kling, 1966; Kordower et al., 1992; Nikolić and Kostović, 1986), whereas, the orbitofrontal cortex develops gradually over the postnatal period. Thus, the ability to perform the object reversal task, a measure of orbital frontal cortex functioning, reaches adult proficiency around 30 months of age in children (Diamond and Doar, 1989; Overman, 2004). Prior to 30 months of age, males outperformed females in the object reversal task, suggesting a more rapid functional maturation of this prefrontal cortical region in male children than in females. Yet, functional maturation of the orbital frontal cortex continues until adulthood, as revealed by another measure of orbital frontal cortex function, i.e. the Iowa Gambling Task (Overman, 2004). In this task, performance improved with age, from 12 years of age until adulthood. Interestingly, it has been hypothesized that the beginning of the maturational process of the orbitofrontal cortex constitutes a critical period for socio-emotional development in humans (Schore, 1994, 1996). Thus, while an early dysfunction of the amygdala could be associated with behavioral changes present at birth, the behavioral changes associated with an early dysfunction of the orbitofrontal cortex may not become apparent until around the second year of life, when this neural structure begins to function. That is, prior to the age at which the orbitofrontal cortex begins to show functional maturity, both normally developing children and children with autism should perform equally on skills mediated by the orbitofrontal cortex. However, after this age, as these skills continue to develop and are used in the monitoring of more complex social situations, a dysfunction of the orbital frontal cortex, which was functionally silent at an early age, may in fact yield more debilitating functional outcomes as the brain progressively continues to develop.

There is relatively little information available on the long-term behavioral effects of early dysfunction of the orbitofrontal–amygdala circuit in humans. However, a few case reports have recently appeared in the literature. One patient with bilateral damage to the amygdala that occurred in childhood or early adolescence from Urbach–Wiethe disease displayed significant deficits in the interpretation of moving geometric displays that most normal participants interpret as social agents pursuing goals and having feelings (Adolphs et al., 2002). Fine et al. (2001) report a patient with early left amygdala damage and a diagnosis of Asperger's syndrome and schizophrenia who was impaired on second-order false belief tasks, comprehension of mental state cartoons, and advanced theory of mind stories requiring participants to understand non-literal utterances, such as white lies, bluffing or sarcasm. Further, two other cases with early damage to the frontal pole and ventromedial prefrontal cortex (before 16 months of age) were shown to have severely impaired social behavior despite normal basic cognitive abilities (Anderson et al., 1999). These two patients had also defective social and moral reasoning, abilities that are usually spared in patients with acquired frontal lobe damage. Finally, a recent review of

cases with early prefrontal damage by Eslinger et al. (2004) indicate that early injury to the orbitofrontal cortex is associated with intractable deficits in the regulation of emotions and social functioning.

There exists also several experimental findings that support the view that the orbitofrontal–amygdala circuit is operating relatively early in life to subserve the modulation of socio-emotional behaviors. For example, neonatal amygdala lesions in rodents have been shown to result in severe changes in social behavior (Daenen et al., 2002; Hanlon and Sutherland, 2000). In primates, Thompson and colleagues (Thompson and Towfighi, 1976; Thompson et al., 1968, Thompson et al., 1969) showed that bilateral amygdala lesions (created by aspiration) made during the third postnatal month leave subjects affectively and socially impaired. After surgery, operated monkeys displayed more fear responses during social encounters than did control monkeys with whom they were paired, and the fear responses made by the operated monkeys were most profound whenever control animals became more active. These enhanced fear reactions first appeared between three and five months following surgery and intensified significantly thereafter. By contrast, responses to novel objects in the absence of other monkeys revealed an opposite pattern of results, with operated monkeys displaying fewer fear responses than controls. These results have recently been replicated (Bauman et al., 2004; Prather et al., 2001) using similar testing paradigms but using more selective damage to the amygdala that spared the surrounding cortical areas at approximately two weeks of age and more naturalistic rearing conditions. Thus, early amygdala lesions do not abolish the normal emergence of fear responses at around three months of age, but do affect the *magnitude* of the fear responses displayed in the presence of peers and novel objects. This finding suggests that the operated animals have difficulty in evaluating the significance of social and non-social situations and implementing behaviors that will keep them from harm. When monkeys who received amygdala lesions during infancy were re-tested during adulthood (Thompson, 1981; Thompson et al., 1977), they showed transient hyperactivity, subordination and decreased fear during social interactions, suggesting that the amygdala lesions may have affected the normal development of aggressive responses. These changes in social and emotional behavior seen after early damage to the amygdala were also found by Bachevalier (1994), who investigated the development of social interactions in infant monkeys that were amygdalectomized during the first post-natal month. In addition to the socio-emotional changes, the operated subjects displayed drastically altered vocal responses to social separations (Newman and Bachevalier, 1997). Thus, the amygdala appears to be operating early in life to regulate affective responses and to establish and maintain social relationships.

At the current time, there is only one study on the effects of early damage to the orbital frontal cortex on social and emotional behavior in non-human primates. Bowden et al. (1971) investigated the behavioral effects of damaging the orbitofrontal or dorsolateral prefrontal cortex at approximately two months of age in monkeys during free interactions between the operated and unoperated control monkeys. The monkeys with early lesions of the orbitofrontal and dorsolateral prefrontal cortex showed higher frequencies of huddling alone than controls during social encounters, and orbitofrontal cortex lesion subjects also initiated fewer behaviors overall than controls and monkeys with dorsolateral prefrontal cortex lesions. However, there was no indication of significant changes in fear reactions in either group. Thus, unlike early damage to the amygdala, which appears to dysregulate both fear *and* social behavior, early damage to the orbitofrontal and dorsolateral prefrontal cortices only impairs the initiation of social interactions. Furthermore, although the long-term effects of neonatal orbitofrontal and dorsolateral prefrontal cortex damage on social and emotional behaviors is still unknown, tests of behavioral inhibition, extinction and working memory indicate that orbital frontal and dorsolateral prefrontal cortex lesions produced after eight months of age result in greater impairment that when the same lesions are inflicted just after birth (Goldman et al., 1974; Jones and Mishkin, 1972; Lewis, 1997). These results contrast with findings on early lesions of the amygdala, as discussed earlier. The message emerging from these developmental studies is that if a lesion affects a brain structure or region that has yet to mature functionally, the effects of the lesion may remain silent until a time in development when that structure or system becomes functionally mature.

The behaviours exhibited by non-human primates with neonatal lesions of the amygdala parallel in some ways those seen in children with autism (cf Loveland, 2005 for more discussion; Amaral, 2002). Like amygdalectomized monkeys, young children with autism often display excessive fear in response to situations that would not ordinarily evoke such a degree of fear in typically developing young children (e.g. the sound of a vacuum cleaner, the presence of a large group of people, a toilet flushing). At the same time, they sometimes do not display sufficient fear or caution in response to situations where fear or caution would ordinarily be expected (e.g. fearlessly approaching strangers or climbing in high places). The form and degree of fearfulness/fearlessness in autism varies from individual to individual, reflecting that child's history of experiences, and it results in idiosyncratic patterns of affective responding to specific stimuli. However, as a group, individuals with autism have a high degree of anxiety relative to typically developing persons (Bradley et al., 2004; Kim et al., 2000; Loveland et al., unpublished work). Like the amygdalectomized non-human primates, they can be described as having difficulty evaluating the significance for themselves of both social and non-social stimuli and difficulty regulating their affective and behavioral responses to them. Furthermore, like the animals with

early damage to the orbital frontal cortex, individuals with autism have difficulty in the initiation of social interactions (see for review Loveland, 2005).

The foregoing discussion suggests that the time of emergence, nature, and severity of autistic behavioral symptoms may relate to the extent of damage to the orbitofrontal–amygdala circuit, i.e. whether both, or only one, of these two structures is dysfunctional but also when, during the maturation of this neural circuit, the dysfunction occurs. This conjecture could help to explain why the severity of autistic social deficits varies from one individual to the next, as well as why some individuals have clear autistic behavioral deficits from birth, while others develop normally but suffer a regression to autism in the second year of life.

7. Heterogeneity of behavioral symptoms in autism

Yet another important issue that must be addressed in a neurobiological model of autism is the heterogeneity of behavioral symptoms. For example, such a model should explain why some individuals with autism have mental retardation, but others do not, and why individuals vary in the extent to which they manifest repetitive or obsessive–compulsive behaviors. Behavioral heterogeneity in autism has already received several possible explanations. One is that the primary social deficits of autism may in turn affect the development of other intellectual abilities including language and may be directly related to the emergence of repetitive behaviors.

Another possibility is that other neural systems, known to mediate executive functions and memory, could also be primarily affected in autism. In a number of studies, persons with autism have been found to have neurobiological and functional abnormalities in the frontal lobe of the brain (Carper and Courchesne, 2000; Harrison et al., 1998; Kawasaki et al., 1997; Minshew et al., 1999). There have also been a number of recent studies that support a role for prefrontal deficits in the behavioral and cognitive manifestations of autism. In particular, deficits in executive functioning have been found in many studies of people with autism (Ciesielski and Harris, 1997; Ciesielski et al., 1997; Coldren and Halloran, 2003; Craig and Baron-Cohen, 1999; Dawson et al., 1995, Dawson et al., 1998; Gilotty et al., 2002; McEvoy et al., 1993; Ozonoff, 1995; Ozonoff and McEvoy, 1994; Ozonoff et al., 1991; Planche et al., 2002; Rinehart et al., 2002; Rumsey and Hamburger, 1988; Russell et al., 1999). Some of these studies have suggested not only that executive functioning is deficient in persons with autistic spectrum disorders or their near relatives (Hughes et al., 1997, Hughes et al., 1999; Piven and Palmer, 1997), but also that such deficits are associated with, and may account for, deficits in performance on ToM tasks. However, there is also evidence that executive function deficits are not specific to autism (e.g. Baron-Cohen and Robertson, 1995; Griffith et al., 1999; Ozonoff, 1997; Pennington et al., 1997; Sergeant et al., 2002) and that they may be reduced or absent in the highest functioning individuals, especially those with Asperger syndrome (Liss et al., 2001; Rinehart et al., 2001). Thus, even though executive function deficits are present in persons with autism, they are, by themselves, probably insufficient to account for the behavioral manifestations of autism, apart from performance on ToM and some other cognitive tasks. On the other hand, the presence of these deficits in individuals with autism supports the hypothesis that frontal lobe impairments are associated with autism, and suggests that cognitive deficits originating in the frontal lobe most likely play a role in the manifestations of autism.

Yet another possible explanation for the heterogeneity of symptoms in autism rests more specifically on a primary dysfunction of the subcortical temporal lobe structures. Indeed, experimental evidence not only suggests that early damage to the amygdala and hippocampus yields severe deficits in socio-emotional behaviors and memory, respectively, but also that early damage to these structures has widespread secondary impact on other developing neural systems. Among these are the dorsolateral prefrontal cortex and striatum, both of which have been implicated in executive functions and stereotyped behaviors, respectively, in autism.

8. Early medial temporal lobe dysfunction and heterogeneity of autistic symptoms

The developmental studies in non-human primates reported above (Bachevalier, 1994) have also indicated that the behavioral deficits observed after early damage to the amygdala are substantially exacerbated when the lesions were extended more caudally to include the hippocampal formation and the adjacent temporal cortex (Bachevalier, 1991, Bachevalier, 1994; Bachevalier and Merjanian, 1994; Bachevalier et al., 2001; Málková et al., 1997). Although the operated monkeys were able to initiate social signals (threat, fear grimaces, etc…), they show numerous abnormalities in the use and regulation of these social signals as they matured, including withdrawal from social interactions and lack of or reduced initiation of social interactions. In addition, they displayed profound and persistent loss of certain types of memory functions as well as stereotypies. Thus, the extent to which the medial temporal lobe structures were affected constitutes another significant factor for the nature and severity of the long-term behavioral and cognitive changes observed (Bachevalier, 1994, Bachevalier, 2000).

All together these experimental data led us to speculate that the extent of damage to the medial temporal lobe region could have the potential to explain some of the heterogeneity of behavioral deficits found in autism. That is, the severe learning and memory deficits shown in

people with autism and severe mental retardation might result from involvement of large portions of the medial temporal lobe, including the amygdala, hippocampus, and adjacent cortex. However, in the case of subjects with relatively preserved cognitive abilities, the amygdala may be more affected than the hippocampus and adjacent cortical areas, resulting in social abnormalities but more intact learning and memory abilities. Interestingly, human studies have already shown that lower-functioning persons with autism show impairment in medial temporal lobe memory functions (for review see Shalom, 2003). By contrast, high-functioning people with autism performed remarkably well on two versions of a delayed-matching task (Barth et al., 1995), which is a memory task commonly used to measure medial temporal lobe memory functioning in humans and monkeys. These findings led to our secondary hypothesis, that the degree of intellectual impairment present in individuals with autism could be directly related to the integrity of a second neural circuit, which includes the hippocampus and its relationship to the medial temporal, parietal and dorsolateral prefrontal cortex (see above). There is, as yet, no consistent report of changes in hippocampal volumes in autism (for review see Cody et al., 2002): some studies found decreased hippocampal volumes (Aylward et al., 1999; Saitoh et al., 2001), others reported enlarged volumes (Schumann et al., 2004; Sparks et al., 2002), and still others found no changes (Haznedar et al., 2000; Howard et al., 2000; Piven et al., 1998). Nevertheless, postmortem investigations of the brain of autistic people (Bauman and Kemper, 2004) reported reduced neuronal cell size and increased cell-packing density bilaterally in the hippocampus.

Finally, the developmental studies in monkeys also revealed that the early insult to the medial temporal lobe led to widespread repercussions for other brain structures with which they are interconnected. Thus, adult monkeys with early damage to the medial temporal lobe not only showed impairment in tasks measuring functions of the medial temporal lobe structures, but also in tasks measuring dorsolateral prefrontal functions; i.e. these operated animals showed clear deficits on a working memory task, such as spatial delayed alternation (J. Bachevalier, unpublished data). Furthermore, as compared to normal control and monkeys that had received the same lesions in adulthood, those with medial temporal lobe lesions in infancy showed a delayed maturation of the dorsolateral prefrontal cortex (Bertolino et al., 1997; Chlan-Fourney et al., 2000), associated with a dysregulation of striatal dopaminergic neurotransmission (Heinz et al., 1999; Saunders et al., 1998) and increased volume of the caudate nucleus (Málková and Bachevalier, unpublished observations). Such dysregulation of prefrontal-striatal dopamine transmission could have an interesting relationship with the ritualistic and stereotyped behaviors seen in some people with autism (Sears et al., 1999). These newest findings suggest that the lack of functional inputs from the medial temporal structures prevents the prefrontal cortex from undergoing proper neuronal development. The data also imply that a fixed dysfunction localized to one of the nodes of a neural circuit can influence other areas of the circuit, especially if this dysfunction occurs early in development. Interestingly, a recent neuroimaging study investigating the basal ganglia in autism has reported increased volume of the caudate nucleus which correlated significantly with stereotyped repetitive behaviors, but not with social or communication deficits (Sears et al., 1999).

In sum, the experimental findings lead to several provocative hypotheses concerning potential configurations of underlying brain dysfunction that may be related to differing outcomes in autism. For example, one could speculate that an early dysfunction of both the amygdala and hippocampus (in the perinatal period) would yield not only early impairment of functions normally served by the amygdala and hippocampus, but would also lead to dysregulation of the prefrontal areas (orbitofrontal and dorsolateral prefrontal cortices) to which the amygdala and hippocampus are interconnected. Such a child might manifest both a severe disorder of socio-emotional development and a deficit in intellectual development (e.g. Wing's Aloof category) (Wing and Attwood, 1987; Wing and Gould, 1979), associated with stereotypies.

By contrast, a child with a dysfunction restricted to the amygdala, which could further affect the maturation of the orbitofrontal cortex with which the amygdala is strongly interconnected, might show severe social impairments together with relatively unimpaired intellectual abilities. Finally, a child with dysfunction of the orbitofrontal cortex might not manifest social skills impairment until the second year of life, leading to an observed loss of skills at the time when the dysfunctional orbitofrontal cortex begins to mature (differences in behavioral outcomes among regressors might be related to the presence/absence of impairments in other structures, such as the dorsolateral prefrontal cortex).

As these examples illustrate, our neurodevelopmental model has the potential to illuminate some of the most persistent issues in the field of autism research. Among these are the origins of the developmental differences observed in persons with autism with and without mental retardation, those who do or do not exhibit early regression, and those with differing severity of autism. Such a model may also provide important information about relationships between the development of neuropsychological deficits and clinical and laboratory measures of socio-emotional functioning. As might be expected, there is growing evidence in recent years to suggest that the orbitofrontal–amygdala circuit is dysfunctional in people with autism.

9. Is the orbitofrontal–amygdala circuit dysfunctional in autism?

Recent clinical and experimental studies lend support to the view that medial temporal lobe structures are involved in the genesis of ASD (for review see Baron-Cohen et al., 2000; Dawson, 1996). Within the medial temporal lobe, the amygdala in particular has been linked to manifestations of autism. Fein and colleagues (1987) have argued that dysfunction of the amygdala in autism results in disruption of the ability to assign meaning to social stimuli. Similarly, Fotheringham (1991) suggested that dysfunction of the amygdala in autism brings about a failure to appreciate the normal motivational and emotional significance of stimuli. These formulations are compatible with the theoretical positions of Hobson (1992) and Loveland (1991, 2001), both of whom have argued that for people with autism the world is not meaningful in the same ways as for other people.

Clinically, children and adults with autism or another ASD have been reported to have abnormalities affecting the medial temporal lobe structures, such as enlargement of the temporal horn of the lateral ventricles (Campbell et al., 1982; Damasio et al., 1980; Hauser et al., 1975; Jacobson et al., 1988), and temporal lobe epilepsy or temporal EEG abnormalities (DeLong, 1978; Deonna et al., 1993; Deykin and MacMahon, 1979; Hauser et al., 1975; Payton and Minshew, 1987). In addition, Hoon and Reiss (1992) described a young male child with a left temporal oligodendroglioma, who demonstrated a constellation of autistic behaviors meeting the DSM-III-R criteria for pervasive developmental disorder. Finally, White and Rosenbloom (1992) described a child with infantile autism who was found on CT scanning to have a partial absence of the left temporal lobe.

There are only few postmortem investigations of brains of persons with autism. Neuropathological studies (Bauman and Kemper, 2004; Hof et al., 1991) have shown that, while the brains of people with autism appear of normal weight, gyral configuration, and myelination, microscopic cytoarchitectonic abnormalities (increased cell densities, small cell sizes) occur in limbic structures, such as the hippocampus, amygdala, entorhinal cortex, septal nuclei, and mammillary bodies along with a loss of Purkinje cells in the cerebellum. The overall size of the hippocampus is reduced and, in the amygdala, there is an indication that the more severe cases of autism have larger portions of the amygdala affected by abnormal cell-packing densities.

Recently, a growing number of both structural and functional neuroimaging studies have reported increased head size and brain volume (Bailey et al., 1998; Courchesne and Pierce, 2005; Hardan et al., 2001; Piven et al., 1996) as well as abnormalities in medial temporal lobe structures, such as the amygdala, hippocampus, and ventral temporal cortex, which suggest that these structures are indeed dysfunctional in people with ASD (for review see Cody et al., 2002). Interestingly, Howard et al. (2000) reported that high-functioning subjects with autism showed impairment in the recognition of facial expressions that was associated with enlarged amygdala volume, and Schultz and colleagues (Schultz et al., 2000a,b) showed an abnormal activation of the ventral temporal cortex during face discrimination in individuals with Autism and Asperger syndrome. More recently, Sparks et al. (2002) observed that a subset of 31 children with autistic disorder had larger amygdala volumes than 14 children with PDD-NOS, suggesting that increased volume of the amygdala may be related to the severity of symptoms present in autism. Furthermore, Schumann et al. (2004) indicated an early abnormal development of the amygdala in autism, as well as an abnormal development of the hippocampus. Using a single-case voxel-based morphometric analyses, Salmond et al. (2003) found abnormality in the amygdala in half of the children (7 out of 14) with autism. Increases and/or decreases in grey matter volume were found in several brain regions related to social cognition (see below), including the amygdala, right fusiform gyrus, the anterior cingulate and superior temporal sulcus, the superior temporal gyrus, and the cerebellum (Abell et al., 1999; Waiter et al., 2004).

Using fMRI, Critchley et al. (2000) showed facial expressions of emotion to high-functioning adults with autism and control subjects. Subjects with autism differed from controls in the activity of cerebellar, mesolimbic and temporal lobe cortical brain regions. For example, when asked to explicitly judge emotional expressions, they did not activate the fusiform gyrus (e.g. the cortical 'face area'), and when asked to make implicit judgments about emotional expressions, they did not activate the left amygdala region and left cerebellum as the control subjects did. Finally, people with autism spectrum disorders have been found to show metabolic decreases in the anterior and posterior cingulate areas (Haznedar et al., 2000) and in the temporal and frontal areas (Hashimoto et al., 2000).

Similarly, a number of recent studies have found abnormalities in the frontal lobe, particularly the ventral prefrontal portion (Carper and Courchesne, 2000; George et al., 1992; Harrison et al., 1998; Kawasaki et al., 1997; Minshew et al., 1999; Salmond et al., 2003; Siegel et al., 1995; Zilbovicius et al., 1995), suggesting that the orbitofrontal cortex is likely to be dysfunctional in autism (Dawson et al., 1998; Schultz et al., 2000). Thus, all evidence points towards a dysfunction of a neural network in autism that includes not only the amygdala and orbital frontal cortex, but also interconnected brain structures, such as the anterior cingulate, ventral temporal cortex, superior temporal gyrus, and cerebellum (see below).

Additional evidence for a dysfunction of this neural network in autism is provided by recent findings on abnormalities in the development of the brain serotonin system in autism (Chugani, 2004; Scott and Deneris, 2005; Whitaker-Azmitia, 2005). During normal development in humans, brain serotonin levels increase throughout the first

two to five years and then decline of more than 50% to reach the adult levels (Chugani et al., 1999; Hedner et al., 1986). Functional imaging studies indicate that, unlike non-autistic children who show serotonin synthesis capacity greater than 200% of adult values until the age of 5 years, autistic children had lower levels of serotonin synthesis (Chugani et al., 1997, Chugani et al., 1999). These reduced levels of brain serotonin early in development affected the development of several cortical territories including the frontal, temporal, parietal, and occipital lobes asymmetrically (Chandana et al., 2005) and the formation of intracortical and thalamocortical circuitry (Chugani, 2004). As recently reviewed (Chugani, 2002; Whitaker-Azmitia, 2001; Whitaker-Azmitia, 2005), beside its role as a neurotransmitter, serotonin plays a critical role during development in dendritic elaboration, synaptogenesis, neurogenesis as well as cortical organization (Janusonis et al., 2004). In addition, a recent rodent model of autism produced by prenatal treatment with a serotonin agonist, 5-methoxytryptamine (5-MT), has shown behavioral changes that share some similarities with the symptoms observed in autism, and that are accompanied with metabolic abnormalities in the cortex suggestive of a delayed or arrested maturation of the cortex (Kahne et al., 2002) as well as cellular changes in the amygdala and the hypothalamus (Whitaker-Azmitia, 2005). Furthermore, treatment with 5-MT during fetal development led to alterations of presubicular cortical column development, a finding consistent with the recent observation of abnormalities in cortical columns in the brain of autistic individuals (Casanova et al., 2002a,b).

10. Other possible neural components of social–emotional self-regulation

Although the present review has focused on the amygdala and orbitofrontal cortex as major players in the development of autism, there are several other brain structures that are known to be implicated in the regulation of socio-emotional behaviors in both humans and animals. They include the temporopolar region, the anterior cingulate, cortical areas within the superior temporal structures and the cerebellum. Interestingly, all have direct or indirect connections with the amygdala and orbitofrontal cortex and have been associated to some of the symptoms observed in autism.

The anterior cingulate cortex is an agranular cortical area which lies on the medial surface of the frontal lobe, around the genu of the corpus callosum. This cortical area is interconnected with the amygdala and receives dense projections from the midline and intralaminar nuclei of the thalamus but few direct cortical projections from the frontal pole and lateral prefrontal cortex, from the temporopolar, parahippocampal and entorhinal cortices, or from the posterior parietal cortex (Bachevalier et al., 1997; Baleydier and Mauguière, 1980; Vogt et al., 1979). The anterior cingulate cortex has been implicated in the production of vocalizations in monkeys (Jürgens and Ploog, 1970; Ploog, 1986; Robinson, 1967) and in the initiation of speech in humans (Barris and Schuman, 1953; Jürgens and von Cramon, 1982). Thus, the pathway connecting the amygdala to the anterior cingulate cortex may be crucial for the emotional modulation of vocalizations and speech. In addition, because the anterior cingulate cortex is involved in effector and executive functions, i.e. in controlling visceromotor, endocrine, or skeletomotor outputs, it is likely that this area controls emotional outputs not only for speech but for all body postures and movements, and for internal emotional changes (Devinsky et al., 1995; Vogt et al., 1992). That is, as the organism evaluates the affective significance of something experienced, the anterior cingulate may be involved in selecting specific responses that are consistent with the situation as evaluated (e.g. fight or flight?). Another function attributed to the anterior cingulate cortex is the control of the mechanisms underlying exploratory behavior and attention toward sensory stimuli. Thus, this cortical area may be important to direct the subject's vigilance towards events that are of emotional or motivational significance. In addition, a rostral anterior cingulate cortex activation have generally been found when human subjects viewed emotionally arousing images (Blair et al., 1999; Lane et al., 1999; Whalen et al., 1998), or in self-regulation of emotional responses (Beauregard et al., 2001), appraised and evaluated emotional stimuli (Nakamura et al., 1999; Narumoto et al., 2000), or made attributions about the thoughts and beliefs of others (Frith and Frith, 1999; Gallagher et al., 2000). As reviewed by Frith (2001), the anterior cingulate cortex is activated during the attribution of mental states to others and during the monitoring of inner states of self, and damage to this cortical area have been associated with difficulty in attributing mental states to others. Finally, a recent study assessing the effects of bilateral anterior cingulate cortex lesions (Hadland et al., 2003) showed a decreased in social interactions and in vocalizations indicating that the cingulate cortex clearly has a role in the regulation of affiliative behavior.

The temporopolar cortex covers the rostral tip of the temporal pole and consists of a mesiocortical area that corresponds to a great extent to Brodmann's area 38 (Chabardès et al., 2002). It provides a site for convergence of highly processed sensory inputs arising from sensory cortical areas and limbic inputs from amygdala and orbitofrontal cortex (Gloor, 1997; Moran et al., 1987). This cortical region represents a discrete temporal area where integration of both internal and external inputs could occur and that has been associated with the regulation of autonomic functions and emotions (Chabardès et al., 2002). The temporopolar region has also been linked to social–emotional behavior in humans (for review see Dupont, 2002). For example, activation of the left temporopolar region has been found in healthy volunteers performing face

recognition tasks, and activation of the right temporopolar region has been reported when normal volunteers processed stories with emotional and affective content (Beauregard et al., 1997). In addition, direct electrical stimulation of the temporal pole in patients with drug-resistant temporal lobe epilepsy elicits psychic, viscero-sensitive, autonomic and viscero-motor responses (Ostrowsky et al., 2002). To date there are no observations on socioaffective changes after lesions involving exclusively the temporopolar cortex. Nevertheless, in few non-human primate studies in which this area was damaged together with more lateral temporal cortical areas, but in which the amygdala was left intact, changes in social behavior and affect were noted (Akert et al., 1961; Myers, 1958, Myers, 1975; Myers and Swett, 1970). The monkeys with such lesions showed abnormal social interactions as well as a lack of vocal and facial communications. Those operated animals that were released in the field never rejoined their social group, though there was no evidence that they were rejected by their peers. When attacked by strangers, they displayed no aggressive responses. Conversely, bilateral lesions of temporal visual areas located more posteriorly, but which spared the temporopolar area, resulted in no changes in social behavior. Thus, this pattern of results indicates that the behavioral deficits in socioaffective behavior following anterior temporal lesions are dependent on rostral temporal cortical removal and can occur without incidental damage to the medial temporal lobe structures, such as the amygdala.

Cortical areas within the superior temporal sulcus (STS) appear to be critical for the processing of faces and voices during social communication. For example, the direction of eye gaze, one of the most important cues for determining the direction of another's attention (for review see Emery, 2000), appears to occur in the STS. A small population of neurons in these cortical areas responds selectively to face stimuli, and more specifically to eye gaze directions (Gross and Sergent, 1992; Perrett et al., 1982). In addition, recent fMRI studies have identified voice-selective areas in normal adults, located along the upper bank of STS bilaterally (Belin et al., 2000). Individuals with autism have difficulties in voice perception, such as a lack of preference for their mother's voice and impairment in the extraction of mental states from voices (Klin, 1991; Loveland et al., 1995; Rutherford et al., 2002) and failed to activate the STS voice-selective regions in response to vocal sounds, although they showed normal activation pattern in response to non-vocal sounds (Gervais et al., 2004). There exist no reports on the effects of lesions of this cortical area on social behavior.

Interestingly a circuit involving the medial prefrontal cortex, superior temporal sulcus at the temporo-parietal junction, and temporal poles is activated in normal subjects while attributing mental states to animated shapes. By contrast, less activation in these brain regions was found in people with autism or Asperger syndrome (Castelli et al., 2002), indicating a functional connectivity between these brain structures in mental state attributions.

Finally, there exists increasing evidence for a role of the cerebellum in the modulation of higher-cognitive functions in addition to its well-recognized role in the coordination of equilibrium, posture, and gait (Kandel and Jessell, 1991). For example, the cerebellum is important for sensory acquisition, discrimination, and modulation for the purpose of aiding sensory systems in exploring and understanding the environment. The cerebellum is also critical for the coordination of attention, perception and thought in a manner analogous to its role in motor control. Socio-emotional disturbances, and autistic-like behaviors, as well as cognitive impairments have also been noted in children with surgical removals of posterior fossa tumors, which include portions of the cerebellum (Levisohn et al., 2000; Riva and Giorgi, 2000). Many studies have now shown neuropathological changes within the cerebellum of people with autism. This finding has led Courchesne et al. (1994) to propose that impairment in specific attention processes could contribute to the deficit in joint attention described in people with autism and that, in turn, this deficit in joint attention may impede development of higher social, language, and cognitive skills. Furthermore, Lee et al. (2003), based on similar evidence, suggested that autism is a disorder of a circuit involving the cerebellum and limbic structures such as the amygdala, hippocampus, orbital frontal cortex and cingulate cortices.

11. Conclusion

We emphasize that the theoretical approach presented in this article is not reductionistic, in that it does not seek to *replace* formulations based on behavioral development with formulations based on brain development. Rather, we assume that descriptions and theories based on *relationships among cognition, behavior, and brain over the course of development* are necessary to explain how and why autism is manifested in children and adolescents (cf Bachevalier and Loveland, 2003; Happé and Frith, 1996; Loveland, 2001). The neurodevelopmental model discussed in the present paper reflects an integrated view of current ideas about the social deficits in autism, the accumulating knowledge on the neurobiology of social cognition and emotion, as well as a description of disordered patterns of behavior resulting from experimental damage to the frontolimbic system. Because of the complexity of the clinical disorder and our incomplete knowledge of the neural network that controls and guides complex social behavior in our daily life, the model is at the present time over-simplified. For example, even though the amygdala and the orbitofrontal cortex are central to our neurodevelopmental model of autism, we believe that other brain structures, such as the temporal pole areas, the cingulate cortex, cerebellum, etc. will also likely be involved in

specific ways in this disorder. Thus, this neural model is offered not as a complete explanatory theory, but rather as an heuristic approach that will permit the generation of testable hypotheses about the possible outcomes that might result from early dysfunction of different portions of this neural network. We believe that a vertically integrated approach to the study of autism—one that combines multifaceted human investigations and experimental studies with animal models—has the potential not only to revise our current understanding of brain development and its relation to the maturation of basic processes such as social cognition and self-regulation of social–emotional behavior, but also to offer a new foundation for determining the neuropathological bases of several developmental disorders in humans.

Acknowledgements

Research described in this paper was supported in part by grants to the authors MH58846 (NIMH), RR00165 (NIH), DC00357 (NIDCD), HD35471 (NICHD), the National Alliance for Autism Research and the John and Catherine MacArthur Foundation: Research Network on Early Experience and Brain Development.

References

Abell, F., Krams, M., Ashburner, J., Passingham, R., Friston, K., Frackowiak, R., Happé, F., Frith, C., Frith, U., 1999. The neuroanatomy of autism: a voxel-based whole brain analysis of structural scans. NeuroReport 10, 1647.

Adolphs, R., 2003. Is the human amygdala specialized for processing social information? Ann. N.Y. Acad. Sci. 985, 326.

Adolph, R., Tranel, D., 2004. Impaired judgments of sadness but not happiness following bilateral amygdala damage. J. Cogn. Neurosci. 16, 453.

Adolphs, R., Gosselin, F., Buchanan, T.W., Tranel, D., Schyns, P., Damasio, A.R., 2005. A mechanism for impaired fear recognition after amygdala damage. Nature 433, 68.

Adolphs, R., Sears, L., Piven, J., 2001. Abnormal processing of social information from faces in autism. J. Cogn. Neurosci. 13, 232.

Adolphs, R., Tranel, D., Baron-Cohen, S., 2002. Amygdala damage impairs recognition of social emotions from facial expressions. J. Cogn. Neurosci. 14, 1.

Adolphs, R., Tranel, D., Damasio, H., Damasio, A.R., 1995. Fear and the human amygdala. J. Neurosci. 15, 5879.

Akert, K., Gruesen, R.A., Woolsey, C.N., Meyer, D.R., 1961. Klüver-Bucy syndrome in monkeys with neocortical ablations of temporal lobe. Brain 84, 480.

Amaral, D.G., 1992. Anatomical organization of the primate amygdaloid complex. In: Aggleton, J.P. (Ed.), The Amygdala: Neurobiological Aspects of Emotion, Memory, and Dysfunction. Wiley-Liss, New York, pp. 1–66.

Amaral, D.G., 2002. The primate amygdala and the neurobiology of social behavior: implications for understanding social anxiety. Biol. Psychiatry 51, 11.

Anderson, S.W., Bechara, A., Damasio, H., Tranel, D., Damasio, A.R., 1999. Impairment of social and moral behavior related to early damage in human prefrontal cortex. Nat. Neurosci. 2, 1032.

Aylward, E.H., Minshew, N.J., Goldstein, G., Honeycutt, N.A., Augustine, A.M., Yates, K.O., Barta, P.E., Pearlson, G.D., 1999. MRI volumes of amygdala and hippocampus in non-mentally retarded autistic adolescents and adults. Neurology 53, 2145.

Bachevalier, J., 1991. An animal model for childhood autism: memory loss and socioemotional disturbances following neonatal damage to the limbic system in monkeys. In: Tamminga, C.A., Schulz, S.C. (Eds.), Advances in Neuropsychiatry and Psychoparmacology, Volume 1: Schizophrenia Research. Raven Press, New York, pp. 129–140.

Bachevalier, J., 1994. Medial temporal lobe structures and autism: a review of clinical and experimental findings. Neuropsychologia 32, 627.

Bachevalier, J., 2000. The amygdala, social behaviour, and autism. In: Aggleton, J.P. (Ed.), The Amygdala: A Functional Analysis, second ed. Oxford University Press, New York, pp. 509–544.

Bachevalier, J., Loveland, K., 2003. Early orbitofrontal-limbic dysfunction and autism. In: Cicchetti, D., Wlaker, E. (Eds.), Neurodevelopmental Mechanisms in Genesis and Epigenesis of Psychopathology: Future Research Directions. Cambridge University Press, New York, pp. 215–236.

Bachevalier, J., Málková, L., Mishkin, M., 2001. Effects of selective neonatal medial temporal lobe lesions on socioemotional behaviors in monkeys. Behav. Neurosci. 115, 545.

Bachevalier, J., Merjanian, P.M., 1994. The contribution of medial temporal lobe structures in infantile autism: a neurobehavioral study in primates. In: Bauman, M.L., Kemper, T.L. (Eds.), The Neurobiology of Autism. The Johns Hopkins University Press, Baltimore, MD, pp. 146–169.

Bachevalier, J., Meunier, M., 2005. Neurobiology of socio-emotional cognition in primates. In: Eaton, A., Emery, N. (Eds.), Cognitive Neuroscience of social behaviour. Psychology Press, UK, pp. 19–58.

Bachevalier, J., Meunier, M., Lu, M., Ungerleider, L.G., 1997. Thalamic and temporal cortex input to medial prefrontal cortex in rhesus monkeys. Exp. Brain Res. 115, 430.

Bailey, A., Luthert, P., Dean, A., Harding, B., Janota, I., Montgomery, M., Rutter, M., Lantos, P., 1998. A clinicopathological study of autism. Brain 121, 889.

Baleydier, C., Mauguière, F., 1980. The duality of the cingulate cortex in monkey: neuroanatomical study and functional hypothesis. Brain 103, 525.

Barbas, H., 1995. Anatomic basis of cognitive-emotional interactions in the primate prefrontal cortex. Neurosci. Biobehav. Rev. 19, 499.

Baron-Cohen, S., Leslie, A., Frith, U., 1985. Does the autistic child have a 'theory of mind'? Cognition 21, 37.

Baron-Cohen, S., Ring, H.A., Bullmore, E.T., Wheelwright, S., Ashwin, C., Williams, S.C., 2000. The amygdala theory of autism. Neurosci. Biobehav. Rev. 24, 355.

Baron-Cohen, S., Ring, H.A., Wheelwright, S., Bullmore, E.T., Brammer, M.J., Simmons, A., Williams, S.C.R., 1999. Social intelligence in the normal and autistic brain: an fMRI study. Eur. J. Neurosci. 11, 1891.

Baron-Cohen, S., Robertson, M.M., 1995. Children with either autism, Gilles de la Tourette syndrome or both: mapping cognition to specific syndromes. Neurocase Case Stud. Neuropsychol. Neuropsychiatry Behav. Neurol. 1, 101.

Barris, R.W., Schuman, H.R., 1953. Bilateral anterior cingulate gyrus lesions: syndrome of the anterior cingulate gyri. Neurology 3, 44.

Barth, C., Fein, D., Waterhouse, L., 1995. Delayed match-to-sample in autistic children. Dev. Neuropsychol. 11, 53.

Bauman, M.L., Kemper, T.L., 2004. Structural brain anatomy in autism: what is the evidence?. In: Bauman, M.L., Kemper, T.L. (Eds.), The Neurobiology of Autism, second ed. Johns Hopkins Press, Baltimore, MD, pp. 119–145.

Bauman, M.D., Lavenex, P., Mason, W.A., Capitanio, J.P., Amaral, D.G., 2004. The development of social behavior following neonatal amygdala lesions in rhesus monkeys. J. Cogn. Neurosci. 16, 1388.

Baxter, M.G., Murray, E.A., 2000. Reinterpreting the Behavioural Effects of Amygdala Lesions in Non-human Primates. Oxford University Press, New York pp. 545–568.

Beauregard, M., Chertkow, H., Gold, D., Karama, S., Benhamou, J., Babins, L., Faucher, A., 1997. Word priming with brief multiple presentation technique: preservation in amnesia. Neuropsychologia 35, 611.

Beauregard, M., Levesque, J., Bourgouin, P., 2001. Neural correlates of conscious self-regulation of emotion. J. Neurosci. 21, RC165.

Bechara, A., Damasio, A.R., Damasio, H., Anderson, S.W., 1994. Insensitivity to future consequences following damage to human prefrontal cortex. Cognition 50, 7.

Bechara, A., Damasio, H., Damasio, A.R., Lee, G.P., 1999. Different contirbutions of the human amygdala and ventromedial prefrontal cortex to decision-making. J. Neurosci. 19, 5473.

Bechara, A., Damasio, A.R., Damasio, H., 2003. Role of the amygdala in decision-making. Ann. N.Y. Acad. Sci. 985, 356.

Belin, P., Zatorre, R.J., Lafaille, P., Ahad, P., Pike, B., 2000. Voice-selective areas in human auditory cortex. Nature 403, 309.

Bertolino, A., Saunders, R.C., Mattay, V.S., Bachevalier, J., Frank, J.A., Weinberger, D.R., 1997. Altered development of prefrontal neurons in rhesus monkeys with neonatal mesial temporo-limbic lesions: a proton magnetic resonance spectroscopic imaging study. Cereb. Cortex 7, 740.

Bishop, D.V.M., 1993. Annotation: autism, executive functions, and theory of mind: a neuropsychological perspective. J. Child Psychol. Psychiatry 54, 279.

Blair, R.J.R., Cipolotti, L., 2000. Impaired social response reversal: a case of acquired sociopathy. Brain 123, 1122.

Blair, R.J.R., Morris, J.S., Frith, C.D., Perrett, D.I., Dolan, R.J., 1999. Dissociable neural responses to facial expressions of sadness and anger. Brain 122, 883.

Bowden, D.M., Goldman, P.S., Rosvold, H.E., Greenstreet, R.L., 1971. Free behavior of rhesus monkeys following lesions of the dorsolateral or orbital prefrontal cortex in infancy. Exp. Brain Res. 12, 265.

Bradley, E., Summers, J., Wood, H., Bryson, S., 2004. Comparing rates of psychiatric and behavior disorders in adolescents and young adults with severe intellectual disability with and without autism. J. Autism Dev. Disord. 34, 151.

Brothers, L., 1989. A biological perspective on empathy. Am. J. Psychiatry 146, 10.

Brothers, L., 1995. Neurophysiology of the perception of intention by primates. In: Gazzaniga, M.S. (Ed.), The Cognitive Neurosciences. The MIT Press, Cambridge, MA, pp. 1107–1117.

Butter, C.M., Snyder, D.R., 1972. Alternations in aversive and aggressive behaviors following orbital frontal lesions in rhesus monkeys. Acta Neurobiol. Exp. 32, 525.

Campbell, M., Rosenbloom, S., Perry, R., George, A.E., Kricheff, I.I., Anderson, L., Small, A.M., Jennings, S.J., 1982. Computerized axial tomography in young autistic children. Am. J. Psychiatry 139, 510.

Carmichael, S.T., Price, J.L., 1994. Architectonic subdivision of the orbital and medial prefrontal cortex in the macaque monkey. J. Comp. Neurol. 15, 366.

Carper, R.A., Courchesne, E., 2000. Inverse correlation between frontal lobe and cerebellum sizes in children with autism. Brain 123, 836.

Casanova, M.F., Buxhoeveden, D.P., Brown, C., 2002. Clinical and macroscopic correlates of minicolumnar pathology in autism. J. Child Neurol. 17, 692.

Casanova, M.F., Buxhoeveden, D.P., Switala, A.E., Roy, E., 2002. Minicolumnar pathology in autism. Neurology 58, 428.

Castelli, F., Frith, C., Happé, F., Frith, U., 2002. Autism, asperger syndrome and brain mechanisms for the attribution of mental states to animated shapes. Brain 125, 1839.

Cavada, C., Company, T., Tejedor, J., Cruz-Rizzolo, R.J., Reinoso-Suarez, F., 2000. The anatomical connections of the macaque monkey orbitofrontal cortex. A review. Cereb. Cortex 10, 220.

Chabardès, S., Kahane, P., Minotti, L., Hoffman, D., Benabid, A.-L., 2002. Anatomy of the temporal pole region. Epileptic Disord. 4, 9.

Chandana, S.R., Behen, M.E., Juhasz, C., Muzik, O., Rothermel, R.D., Mangner, T.J., Chakraborty, P.K., Chugani, H.T., Chugani, D.C., 2005. Significance of abnormalities in developmental trajectory and asymmetry of cortical serotonin synthesis in autism. Int. J. Dev. Neurosci. 23, 171.

Chlan-Fourney, J., Webster, M.J., Felleman, D.J., Bachevalier, J., 2000. Neonatal medial temporal lobe lesions alter the distribution of tyrosine hydroxylase immunoreactive varicosities in the macaque prefrontal cortex. Soc. Neurosci. Abstr. 26, 609.

Chugani, D.C., 2002. Role of altered brain serotonin mechanisms in autism. Mol. Psychiatry 7, S16.

Chugani, D.C., 2004. Serotonin in autism and pediatric epilepsies. Ment. Retard. Dev. Disabil. Res. Rev. 10, 112.

Chugani, D.C., Muzik, O., Behen, M., Rothermel, R., Janisse, J.J., Lee, J., Chugani, H.T., 1999. Developmental changes in brain serotonin synthesis capacity in autistic and nonautistic children. Ann. Neurol. 45, 287.

Chugani, D.C., Muzik, O., Rothermel, R., Behen, M., Chakraborty, P., Mangner, T., da Silva, E.A., Chugani, H.T., 1997. Altered serotonin synthesis in the dentatothalamocortical pathway in autistic boys. Ann. Neurol. 42, 666.

Cicchetti, D., Tucker, D., 1994. Development and self-regulatory structures of the mind. Dev. Psychopathol. 6, 533.

Ciesielski, K.T., Harris, R.J., 1997. Factors related to performance failure on executive tasks in autism. Child Neuropsychol. 3, 1.

Ciesielski, K.T., Harris, R.J., Hart, B.L., Pabst, H.F., 1997. Cerebellar hypoplasia and frontal lobe cognitive deficits in disorders of early childhood. Neuropsychologia 35, 643.

Cody, H., Pelphrey, K., Piven, J., 2002. Structural and functional magnetic resonance imaging of autism. Int. J. Dev. Neurosci. 766, 1.

Coldren, J.T., Halloran, C., 2003. Spatial reversal as a measure of executive functioning in children with autism. J. Genet. Psychol. 164, 29.

Courchesne, E., 1989. Neuroanatomical systems involved in infantile autism: the implications of cerebellar abnormalities. In: Dawson, G. (Ed.), Autism: Nature, Diagnosis, and Treatment. Guilford Press, New York, pp. 119–143.

Courchesne, E., 1997. Brainstem, cerebellar, limbic neuroanatomical abnormalities in autism. Curr. Opin. Neurobiol. 7, 269.

Courchesne, E., Chisum, H., Townsend, J., 1994. Neural activity-dependent brain changes in development: implications for psychopathology. Dev. Psychopathol. 6, 697.

Courchesne, E., Pierce, K., 2005. Why the frontal cortex in autism might be talking only to itself: local over-connectivity by long-distance disconnection. Curr. Opin. Neurobiol. 15, 225.

Craig, J., Baron-Cohen, S., 1999. Creativity and imagination in autism and Asperger syndrome. J. Autism Dev. Disord. 29, 319.

Critchley, H.D., Daly, E.M., Bullmore, E.T., Williams, S.C., Van Amelsvoort, T., Robertson, D.M., Rowe, A., Phillips, M., McAlonan, G., Howlin, P., Murphy, D.G., 2000. The functional neuroanatomy of social behaviour: changes in cerebral blood flow when people with autistic disorder process facial expressions. Brain 123, 2203.

Critchley, H.D., Mathias, C.J., Dolan, R.J., 2001. Neural activity in the human brain relating to uncertainty and arousal during anticipation. Neuron 29, 537.

Daenen, E.W., Wolterink, G., Gerrits, M.A., van Ree, J.M., 2002. The effects of neonatal lesions in the amygdala and ventral hippocampus on social behaviour later in life. Behav. Brain Res. 136, 571.

Damasio, A.R., 1994. Descartes' Error. Avon Press, New York.

Damasio, A.R., Maurer, R.G., 1978. A neurological model for childhood autism. Arch. Neurol. 35, 777.

Damasio, A.R., Maurer, R.G., Damasio, A.R., Chui, H., 1980. Computerized tomographic scan findings in patients with autistic behavior. Arch. Neurol. 37, 504.

Damasio, A.R., Tranel, D., Damasio, H., 1990. Individuals with sociopathic behavior caused by frontal damage fail to respond autonomically to social stimuli. Behav. Brain Res. 41, 81.

Damasio, A.R., Tranel, D., Damasio, H., 1991. Somatic markers and the guidance of behavior: theory and preliminary testing. In: Levin, H.S.,

Eisenberg, H.M., Benton, A.L. (Eds.), Frontal Lobe Function and Dysfunction. Oxford University Press, New York, pp. 217–229.
Dawson, G., 1996. Brief report: neuropsychology of autism: a report on the state of the science. J. Autism Dev. Disord. 26, 179.
Dawson, G., Klinger, L.G., Panagiotides, H., Lewy, A., Castelloe, P., 1995. Subgroups of autistic children based on social behavior display distinct patterns of brain activity. J. Abnorm. Child Psychol. 23, 569.
Dawson, G., Meltzoff, A.N., Osterling, J., Rinaldi, J., 1998. Neuropsychological correlates of early symptoms of autism. Child Dev. 69, 1276.
DeLong, G.R., 1978. A neuropsychological interpretation of infantile autism. In: Schopler, E., Mesibov, G.B. (Eds.), Autism. Plenum Press, New York, pp. 207–218.
Deonna, T., Ziegler, A.-L., Moura-Serra, J., Innocenti, G., 1993. Autistic regression in relation to limbic pathology and epilepsy: Report of two cases. Dev. Med. Child Neurol. 35, 166.
Devinsky, O., Morrell, M.J., Vogt, B.A., 1995. Contributions of anterior cingulate cortex to behaviour. Brain 118, 279.
Deykin, E.Y., MacMahon, B., 1979. The incidence of seizures among children with autistic symptoms. Am. J. Psychiatry 136, 860.
Diamond, A., Doar, B., 1989. The performance of human infants on a measure of frontal cortex function, the delayed response task. Dev. Psychobiol. 22, 271.
Dias, R., Robbins, T.W., Roberts, A.C., 1996. Dissociation in prefrontal cortex of affective and attentional shifts. Nature 380, 69.
Diergaarde, L., Gerrits, M.A., Stuy, A., Spruijt, B.M., van Ree, J.M., 2004. Neonatal amygdala lesions and juvenile isolation in the rat: differential effects on locomotor and social behaviour later in life. Behav. Neurosci. 118, 298.
Dupont, S., 2002. Investigating temporal pole function by functional imaging. Epileptic Disord. 4, 17.
Emery, N.J., 2000. The eyes have it: the neuroethology, function and evolution of social gaze. Neurosci. Biobehav. Rev. 24, 581.
Emery, N.J., Amaral, D.G., 1999. The role of the amygdala in primate social cognition. In: Lane, R.D., Nadel, L. (Eds.), Cognitive Neuroscience of Emotion. Oxford University Press, Oxford, England, pp. 156–191.
Eslinger, P.J., Damasio, H., 1985. Severe disturbance of higher cognition after bilateral frontal lobe ablation. Patient EVR. Neurology 35, 1731.
Eslinger, P.J., Flaherty-Craig, C.V., Benton, A.L., 2004. Cognitive, social and moral development after early prefrontal cortex damage: review of available clinical cases. Brain Cogn. 55, 84.
Fein, D., Pennington, B., Waterhouse, L., 1987. Implications of social deficits in autism for neurological dysfunction. In: Schopler, E., Mesibov, G.B. (Eds.), Neurobiological Issues in Autism. Plenum Press, New York, pp. 127–144.
Fine, C., Lumsden, J., Blair, R.J.R., 2001. Dissociation between 'theory of mind' and executive functions in a patient with early left amygdala damage. Brain 124, 287.
Fogel, A., Dickson, K.L., Hsu, H., Messinger, D., Nelson-Goens, G.C., Nwokah, E., 1997. Communication of smiling and laughter in mother-infant play: research on emotion from a dynamic systems perspective. In: Barret, C., Caplovitz, K. (Eds.), The Communication of Emotion: Current Research from Diverse Perspectives New Directions for Child Development, No. 77. Jossey-Bass Inc., San Francisco, CA, pp. 5–24.
Fotheringham, J.B., 1991. Autism and its primary psychosocial and neurological deficit. Can. J. Psychiatry 36, 686.
Frey, S., Kostopoulos, P., Petrides, M., 2000. Orbitofrontal involvement in the processing of unpleasant auditory information. Eur. J. Neurosci. 12, 3709.
Frith, C., Frith, U., 1999. Interacting mind—a biological basis. Science 286, 1692.
Frith, U., 2001. Mind blindness and the brain in autism. Neuron 32, 969.
Frith, U., Frith, C., 2001. The biological basis of social interaction. Curr. Dir. Psychol. Sci. 10, 151.
Gallagher, H.L., Happé, F., Brunswick, N., Fletcher, P.C., Frith, U., Frith, C., 2000. Reading the mind in cartoons and stories: an fMRI study of 'theory of mind' in verbal and nonverbal tasks. Neuropsychologia 38, 11.
George, M.S., Costa, D.C., Kouris, K., Ring, H.A., Ell, P.J., 1992. Cerebral blood flow abnormalities in adults with infantile autism. J. Nerv. Ment. Dis. 180, 413.
Gervais, H., Belin, P., Boddaert, N., Leboyer, M., Coez, A., Sfaello, I., Barthelemy, C., Brunelle, F., Samson, Y., Zilbovicius, M., 2004. Abnormal cortical voice processing in autism. Nat. Neurosci. 7, 801.
Ghashghaei, H.T., Barbas, H., 2002. Pathways for emotion: interactions of prefrontal and anterior temporal pathways in the amygdala of the rhesus monkey. Neuroscience 115, 1261.
Gilotty, L., Kenworthy, L., Sirian, L., Black, D.O., Wagner, A.E., 2002. Adaptive skills and executive function in autism spectrum disorders. Child Neuropsychol. 8, 241.
Gloor, P., 1997. The Temporal Lobe and Limbic System. Oxford University Press, Oxford, UK.
Goldman, P.S., Crawford, H.T., Stokes, L.P., Galkin, T.W., Rosvold, H.E., 1974. Sex-dependent behavioral effects of cerebral cortical lesions in the developing rhesus monkeys. Science 186, 540.
Goldman-Rakic, P.S., Goldman-Rakic, P.S., 1987. Circuitry in primate prefrontal cortex and regulation of behavior by representational memory. In: Halgren, V.B., Baudena, E., Heit, G. (Eds.), The Nervous System: Handbook of Physiology. American Physiological Society, Bethesda, MD, pp. 272–417.
Gottfried, J.A., O'Doherty, J., Dolan, R.J., 2003. Encoding predictive reward value in human amygdala and orbitofrontal cortex. Science 301, 1104.
Grelotti, D.J., Gauthier, I., Schultz, R.T., 2002. Social interest and the development of cortical face specialization: what autism teaches us about face processing. Dev. Psychobiol. 40, 213.
Griffith, E.M., Pennington, B.F., Wehner, E.A., Rogers, S.J., 1999. Executive functions in young children with autism. Child Dev. 70, 817.
Gross, C.G., Sergent, J., 1992. Face recognition. Curr. Opin. Neurobiol. 2, 156.
Hadland, K.A., Rushworth, M.F.S., Gaffan, D., Passingham, R.E., 2003. The effect of cingulate lesions on social behaviour and emotion. Neuropsychologia 41, 919.
Hanlon, F.M., Sutherland, R.J., 2000. Changes in adult brain and behavior caused by neonatal limbic damage: implications for the etiology of schizophrenia. Behav. Brain Res. 107, 71.
Happaney, K., Zelazo, P.D., Stuss, D.T., 2004. Development of orbitofrontal function: current themes and future directions. Brain Cogn. 55, 1.
Happé, F., Frith, U., 1996. The neuropsychology of autism. Brain 119, 377.
Hardan, A.Y., Minshew, N.J., Mallikarjuhn, M., Keshavan, M.S., 2001. Brain volume in autism. J. Child Neurol. 16, 421.
Harmer, C.J., Thilo, K.V., Rothwell, J.C., Goodwin, G.M., 2001. Transcranial magnetic stimulation of medial-frontal cortex impairs the processing of angry facial expressions. Nat. Neurosci. 4, 17.
Harrison, D.W., Demaree, H.A., Shenal, B.V., Everhart, D.E., 1998. EEG assisted neuropsychological evaluation of autism. Int. J. Neurosci. 93, 133.
Hashimoto, T., Sasaki, M., Fukumizu, M., Hanaoka, S., Sugai, K., Matsuda, H., 2000. Single-photon emission computed tomography of the brain in autism: effect of the developmental level. Pediatr. Neurol. 23, 416.
Hauser, S.L., DeLong, G.R., Rosman, N.P., 1975. Pneumoencephalographic finding in the infantile autism syndrome: a correlation with temporal lobe disease. Brain 98, 667.
Haznedar, M.M., Buchsbaum, M.S., Wei, T.-C., Hof, P.R., Cartwright, C., Bienstock, C.A., Hollander, E., 2000. Limbic circuitry in patients with autism spectrum disorders studied with positron emission tomography and magnetic resonance imaging. Am. J. Psychiatry 157, 1994.
Hedner, J., Lundell, K.H., Breese, G.R., Mueller, R.A., Hedner, T., 1986. Developmental variations in CSF monoamine metabolites during childhood. Biol. Neonate 49, 190.

Heinz, A., Saunders, R.C., Kolachana, B.S., Jones, D.W., Gorey, J.G., Bachevalier, J., Weinberger, D.R., 1999. Striatal dopamine receptors and transporters in monkeys with neonatal temporal limbic damage. Synapse 32, 71.

Hetzler, B.E., Griffin, J.L., 1981. Infantile autism and the temporal lobe of the brain. J. Autism Dev. Disord. 9, 153.

Hobson, R.P., 1992. Social perception in high level autism. In: Schopler, E., Mesibov, G.B. (Eds.), High Functioning Individuals with Autism. Plenum Press, New York, pp. 157–186.

Hobson, R.P., Lee, A., 1989. Recognition of emotion in mentally retarded adolescents and young adults. Am. J. Ment. Retard. 93, 434.

Hobson, R.P., Ouston, J., Lee, A., 1988. What's in a face? The case of autism. Br. J. Psychol. 79, 441.

Hobson, R.P., Ouston, J., Lee, A., 1988. Emotion recognition in autism: coordinating faces and voices. Psychol. Med. 18, 911.

Hof, P.R., Knabe, R., Bovier, P., Bouras, C., 1991. Neuropathological observations in a case of autism presenting with self-injury behavior. Acta Neuropathol. 82, 321.

Holland, P.C., Gallagher, M., 2004. Amygdala-frontal interactions and reward expectancy. Curr. Opin. Neurobiol. 14, 148.

Hoon, A.H., Reiss, A.L., 1992. The mesial-temporal lobe and autism: case report and review. Dev. Med. Child Neurol. 34, 252.

Hornak, J., Rolls, E.T., Wade, D., 1996. Face and voice expression identification in patients with emotional and behavioural changes following ventral frontal lobe damage. Neuropsychologia 34, 247.

Howard, M.A., Cowell, P.E., Boucher, J., Broks, P., Mayes, A., Farrant, A., Roberts, N., 2000. Convergent neuroanatomical and behavioural evidence of an amygdala hypothesis of autism. NeuroReport 11, 2931.

Hughes, C., Leboyer, M., Bouvard, M., 1997. Executive function in parents of children with autism. Psychol. Med. 27, 209.

Hughes, C., Plumet, M., Leboyer, M., 1999. Towards a cognitive phenotype for autism: Increased prevalence of executive dysfunction and superior spatial span amongst siblings of children with autism. J. Child Psychol. Psychiatry Allied Disc. 40, 705.

Humphrey, T., 1968. The development of the human amygdala during early embryonic life. J. Comp. Neurol. 132, 135.

Iversen, S., Mishkin, M., 1970. Perseverative interference in monkeys following selective lesions of the inferior prefrontal convexity. Exp. Brain Res. 11, 376.

Jacobson, R., Le Couteur, A., Howlin, P., Rutter, M., 1988. Selective subcortical abnormalities in autism. Psychol. Med. 18, 39.

Janusonis, S., Gluncic, V., Rakic, P., 2004. Early serotonergic projections to Cajal–Retzius cells: relevance for cortical development. J. Neurosci. 24, 1652.

Jones, B., Mishkin, M., 1972. Limbic lesions and the problem of stimulus—reinforcement associations. Exp. Neurol. 36, 362.

Jürgens, U., Ploog, D., 1970. Cerebral representation of vocalization in the squirrel monkey. Exp. Brain Res. 10, 532.

Jürgens, U., von Cramon, D., 1982. On the role of the anterior cingulate cortex in phonation: a case report. Brain Lang. 15, 234.

Kahne, D., Tudorica, A., Borella, A., Shapiro, L., Johnstone, F., Huang, W., Whitaker-Azmitia, P.M., 2002. Behavioral and magnetic resonance spectroscopic studies in the rat hyperserotonemic model of autism. Physiol. Behav. 75, 403.

Kandel, E.R., Jessell, T., 1991. Early experience and the fine structure of synaptic connections. In: Kandel, E.R., Swartz, J.H., Jessell, T.M. (Eds.), Principles of Neural Sciences. Elsevier, New York, pp. 945–958.

Kawasaki, Y., Yokota, K., Shinomiya, M., Shimizu, Y., Niwa, S., 1997. Electroencephalographic paroxysmal activities in the frontal area emerged in middle childhood and during adolescence in a follow-up study of autism. J. Autism Dev. Disord. 27, 605.

Kim, J., Szatmari, P., Bryson, S., Streiner, D., Wilson, F., 2000. The prevalence of anxiety and mood problems among children with autism and Asperger syndrome. Autism 4, 117.

Klin, A.S., 1991. Young autistic children's listening preferences in regard to speech: a possible characterization of the symptom of social withdrawal. J. Autism Dev. Disord. 21, 29.

Klin, A.S., 2000. Attributing social meaning to ambiguous visual stimuli in higher-functioning autism and Asperger syndrome: The Social Attribution Task. Child Psychol. Psychiatry 41, 831.

Kling, A.S., 1966. Ontogenetic and phylogenetic studies on the amygdaloid nuclei. Psychosom. Med. 28, 155.

Kolb, B., Taylor, L., 1981. Effective behaviour in patients with localised cortical excisions: role of lesion site and side. Science 214, 89.

Kolb, B., Taylor, L., 1990. Neocortical substrate of emotional behaviour. In: Stein, N.L., Leventhal, B., Trabasso, T. (Eds.), Psychological and Biological Approaches to Emotion. Erlbaum, Hilsdale, NJ, pp. 115–144.

Kordower, J.H., Piecinski, P., Rakic, P., 1992. Neurogenesis of the amygdaloid nuclear complex in the rhesus monkey. Dev. Brain Res. 68, 9.

Lane, R.D., Chua, P.M., Dolan, R.J., 1999. Common effects of emotional valence, arousal and attention on neural activation during visual processing of pictures. Neuropsychologia 37, 989.

Lee, D.A., Lopez-Alberola, R., Bhattachrjee, M., 2003. Childhood autism: a circuit syndrome? Neurologist 9, 99.

Lee, G.P., Meador, K.J., Smith, J.R., Loring, D.W., Flanigin, H.F., 1988. Preserved cross-modal association following bilateral amygdalotomy in man. Int. J. Neurosci. 40, 47.

Lee, G.P., Reed, M.F., Meador, K.J., Smith, J.R., Loring, D.W., 1995. Is the amygdala crucial for cross-modal associations in humans? Neuropsychology 9, 236.

Leslie, A., Frith, U., 1990. Autistic children's understanding of seeing, knowing, and believing. Br. J. Dev. Psychol. 6, 315.

Levisohn, L., Cronin-Golomb, A., Schmahmann, J.D., 2000. Neuropsychological consequences of cerebellar tumor resection in children: cerebellar cognitive affective syndrome in a paediatric population. Brain 123, 1041.

Lewis, D.A., 1997. Development of the primate prefrontal cortex. In: Keshanan, M.S., Murray, R.M. (Eds.), Neurodevelopmental and Adult Psychopathology. Cambridge University Press, Cambridge, MA, pp. 12–30.

Liotti, M., Mayberg, H.S., Brannan, S.K., McGinnis, S., Jerabek, P., Fox, P.T., 2000. Differential limbic-cortical correlates of sadness and anxiety in healthy subjects: implications for affective disorders. Biol. Psychiatry 48, 30.

Lipska, B.K., Jaskiw, G.E., Chrapusta, S., Karoum, F., Weinberger, D.R., 1992. Ibotenic acid lesion of the ventral hippocampus differentially affects dopamine and its metabolites in the nucleus accumbens and prefrontal cortex in the rat. Dev. Brain Res. 585, 1.

Liss, M., Fein, D., Allen, D., Dunn, M., Feinstein, C., Morris, R., Waterhouse, L., Rapin, I., 2001. Executive functioning in high-functioning children with autism. J. Child Psychol. Psychiatry Allied Disc. 42, 261.

Loveland, K., 2001. Toward an ecological theory of autism. In: Burack, J.A., Charman, T., Yirmiya, N., Zelazo, P.R. (Eds.), The Development of Autism: Perspectives from Theory and Research. Erlbaum Press, New Jersey, pp. 17–37.

Loveland, K., 2005. Social-emotional impairment and self-regulation in Autism spectrum disorders. In: Nadel, J., Muir, D. (Eds.), Typical and Impaired Emotional Development. Oxford University Press, Oxford, pp. 365–382.

Loveland, K., Tunali, B., 1991. Social scripts for conversational interactions in Autism and Down syndrome. J. Autism Dev. Disord. 21, 177.

Loveland, K., Tunali-Kotoski, B., 2005. The school-aged child with autism. In: Volkmar, F., Klin, A., Paul, R. (Eds.), The Handbook of Autism and Pervasive Developmental Disorders, third ed. Wiley, New York.

Loveland, K., Tunali-Kotoski, B., Chen, R., Ortegon, J., Pearson, D.A., Brelsford, K., Gibbs, M.C., 1997. Affect recognition in autism: verbal and non-verbal information. Dev. Psychopathol. 9, 579.

Loveland, K., Tunali-Kotoski, B., Pearson, D., Chen, R., Brelsford, K., Ortegon, J., 1995. Intermodal perception of affect by persons with Autism or Down syndrome. Dev. Psychopathol. 7, 409.

Loveland, K., Pearson, D.A., Tunali-Kotoski, B., Ortegon, J., Gibbs, M.C., 2001. Judgments of social appropriateness by children and adolescents with autism. J. Autism Dev. Disord. 31, 367.

Machado, C.J., Bachevalier, J., 2003. Non-human primate models of childhood psychopathology: the promise and the limitations. J.Child Psychol. Psychiatry 44, 1.

MacLean, P.D., 1949. Psychosomatic disease and the 'visceral brain': recent developments bearing on the Papez theory of emotion. Psychosom. Med. 11, 338.

Málková, L., Mishkin, M., Suomi, S.J., Bachevalier, J., 1997. Socio-emotional behavior in adult rhesus monkeys after early versus late lesions of the medial temporal lobe. Ann. N.Y. Acad. Sci. 807, 538.

McEvoy, R.E., Rogers, S.J., Pennington, B.F., 1993. Executive function and social communication deficits in young autistic children. J. Child Psychol. Psychiatry 34, 563.

Meunier, M., Bachevalier, J., Mishkin, M., 1997. Effects of orbital frontal and anterior cingulate lesions on object and spatial memory in rhesus monkeys. Neuropsychologia 35, 999.

Minshew, N.J., Goldstein, G., Siegel, D.J., 1997. Neuropsychologic functioning in autism: profile of a complex information processing disorder. J. Int. Neuropsychol. Soc. 3, 303.

Minshew, N.J., Luna, B., Sweeney, J.A., 1999. Oculomotor evidence for neocortical systems but not cerebellar dysfunction in autism. Neurology 52, 917.

Moran, M.A., Mufson, E.J., Mesulam, M.M., 1987. Neural inputs into the temporopolar cortex of the rhesus monkey. J. Comp. Neurol. 256, 88.

Myers, D.P., 1958. Some psychological determinants of sparing and loss following damage to the brain. In: Harlow, H.F., Woolsey, C.N. (Eds.), Biological & Biochemical Bases of Behavior. University of Wisconsin Press, Madison, WI, pp. 173–192.

Myers, R.E., 1975. Neurology of social behavior and affect in primates: a study of prefrontal and anterior temporal cortex. In: Zulch, K.J. et al. (Ed.), Cerebral Localization. Springer, New York, pp. 161–170.

Myers, R.E., Swett, C., 1970. Social behavior deficits of free-ranging monkeys after anterior temporal cortex removal: a preliminary report. Brain Res. 1, 551.

Nakamura, S., Sadato, N., Oohashi, T., Nishina, E., Fuwamoto, Y., Yonekura, Y., 1999. Analysis of music-brain interaction with simultaneous measurement of regional cerebral blood flow and electroencephalogram beta rhythm in human subjects. Neurosci. Let. 275, 222.

Narumoto, J., Yamada, H., Iidaka, T., Sadato, N., Fukui, K., Itoh, H., Yonekura, Y., 2000. Brain regions involved in verbal or non-verbal aspects of facial emotion recognition. Neuroreport 11, 2571.

Newman, J.D., Bachevalier, J., 1997. Neonatal ablations of the amygdala and inferior temporal cortex alter the vocal response to social separation in rhesus macaques. Brain Res. 758, 180.

Nikolić, I., Kostović, I., 1986. Development of the lateral amygdaloid nucleus of the human fetus: transient presence of discrete cytoarchitectonic units. Anat. Embryol. 174, 355.

O'Doherty, J., Kringelbach, M.L., Rolls, E.T., Hornak, J., Andrews, C., 2001. Abstract reward and punishment representations in the human orbitofrontal cortex. Nat. Neurosci. 4, 95.

O'Doherty, J., Rolls, E.T., Francis, S., Bowtell, R., McGlone, F., 2001. Representation of pleasant and aversive taste in the human brain. J. Neurophysiol. 85, 1315.

Öngür, D., Price, J.L., 2000. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. Cereb. Cortex 10, 206.

Ornitz, E.M., 1983. The functional neuroanatomy of infantile autism. Int. J. Neurosci. 19, 85.

Ostrowsky, K., Desestret, V., Ryvlin, P., Coste, S., Mauguière, F., 2002. Direct electrical stimulations of the temporal pole in human. Epileptic Disord. 4 (Suppl. 1), 23.

Overman, W.H., 2004. Sex differences in early childhood, adolescence, and adulthood on cognitive tasks that rely on orbital prefrontal cortex. Brain Cogn. 55, 134.

Ozonoff, S., 1995. Executive functions in autism. In: Schopler, E., Mesibov, G.B. (Eds.), Learning and Cognition in Autism. Plenum Press, New York, pp. 199–215.

Ozonoff, S., 1997. Components of executive function in autism and other disorders. In: Russell, J. (Ed.), Autism as an Executive Disorder. Oxford University Press, New York, pp. 179–211.

Ozonoff, S., McEvoy, R.A., 1994. Longitudinal study of executive function and theory of mind development in autism. Dev. Psychophysiol. 6, 415.

Ozonoff, S., Pennington, B.F., Rogers, S.J., 1991. Executive function deficits in high-functioning autistic individuals: relationship to theory of mind. J. Child Psychol. Psychiatry 32, 1081.

Papez, J.W., 1937. A proposed mechanism of emotion. Arch. Neurol. Psychiatry 38, 725.

Payton, J.B., Minshew, N.J., 1987. Early appearance of partial complex seizures in children with infantile autism. Ann. Neurol. 22, 408.

Pennington, B., Rogers, S., Bennetto, L., Griffith, E., Reed, D.T., Shyu, V., 1997. Validity tests of the executive dysfunction hypothesis of autism. In: Russell, J. (Ed.), Autism as an Executive Disorder. Oxford University Press, New York, pp. 143–178.

Perner, J., Frith, U., Leslie, A., Leekham, S., 1989. Exploration of the autistic child's theory of moind: Knowledge, belief, and communication. Child Dev. 60, 689.

Perrett, D.L., Rolls, E.T., Caan, W., 1982. Visual neurons responsive to faces in the monkey temporal cortex. Exp. Brain Res. 47, 329.

Petrides, M., Pandya, D.N., 2002. Comparative cytoarchitectonic analysis of the human and the macaque ventrolateral prefrontal cortex and corticocortical connection patterns in the monkey. Eur. J. Neurosci. 16, 291.

Pierce, K., Glad, K.S., Schreibman, L., 1997. Social perception in children with autism: an attentional deficit? J. Autism Dev. Disord. 27, 265.

Piven, J., Arndt, S., Bailey, J., Andreasen, N., 1996. Regional brain enlargement in autism: a magnetic resonance imaging study. J. Am. Acad. Child. Adolesc. Psychiatry 35, 530.

Piven, J., Bailey, J., Ransom, B., Arndt, S., 1998. No difference in hippocampus volume detected on magnetic resonance imaging in autistic individuals. J. Autism Dev. Disord. 28, 105.

Piven, J., Palmer, P., 1997. Cognitive deficits in parents from multiple-incidence autism families. J. Child Psychol. Psychiatry Allied Disc. 38, 1011.

Planche, P., Lemonnier, E., Moalic, K., Labous, C., Lazartigues, A., 2002. Modalities of information processing in autistic children [French]. Les modalites du traitement de l'information chez les enfants autistes. Ann. Med. Psychol. 160, 559.

Ploog, D., 1986. Biological foundations of the vocal expressions of emotions. In: Plutchik, R., Kellerman, H. (Eds.), Emotion: Theory, Research, and Experience, vol. 3. Academic Press, New York, pp. 173–197.

Prather, M.D., Lavenex, P., Mauldin-Jourdain, M.L., Mason, W.A., Capitanio, J.P., Mendoza, S.P., Amaral, D.G., 2001. Increased social fear and decreased fear of objects in monkeys with neonatal amygdala lesions. Neuroscience 106, 653.

Reichler, R.J., Lee, E.M.C., 1987. Overview of biomedical issues in autism. In: Schopler, E., Mesibov, B. (Eds.), Neurobiological Issues in Autism. Plenum Press, New York, pp. 13–43.

Rieffe, C., Meerum Terwogt, M., Stockmann, L., 2000. Understanding atypical emotions among children with autism. J. Autism Dev. Disord. 30, 195.

Rinehart, N.J., Bradshaw, J.L., Moss, S.A., Brereton, A.V., Tonge, B.J., 2001. A deficit in shifting attention present in high-functioning autism but not Asperger's disorder. Autism 5, 67.

Rinehart, N.J., Bradshaw, J.L., Tonge, B.J., Brereton, A.V., Bellgrove, M.A., 2002. A neurobehavioral examination of individuals with high-functioning autism and Asperger disorder using a fronto-striatal model of dysfunction. Behav. Cogn. Neurosci. Rev. 1, 164.

Riva, D., Giorgi, C., 2000. The cerebellum contributes to higher functions during development: Evidence from a series of children surgically treated for posterior fossa tumors. Brain 123, 1051.

Robinson, B.W., 1967. Vocalization evoked from forebrain in *Macaca mulatta*. Physiol. Behav. 2, 345.

Rolls, E.T., 1999. The Brain and Emotion. Oxford University Press, Oxford.

Rolls, E.T., Rolls, B.J., Rowe, E.A., 1983. Sensory-specific and motivation-specific satiety for the sight and taste of food and water in man. Physiol Behav. 30, 185.

Ross, E.D., Harney, J.H., Delacoste-Utsamsing, C., Ourdy, P.D., 1981. How the brain integrates affective and propositional language into a unified behavioral function. Arch. Neurol. 38, 745.

Ross, E.D., Mesulam, M.M., 1979. Dominant language functions in the right hemisphere. Arch. Neurol. 36, 144.

Rumsey, J.M., Hamburger, S.D., 1988. Neuropsychological findings in high-functioning men with infantile autism, residual state. J. Clin. Exp. Neuropsychol. 10, 201.

Russell, J., Saltmarsh, R., Hill, E., 1999. What do executive factors contribute to the failure on false belief tasks by children with autism? J. Child Psychol. Psychiat. Allied Disc. 40, 859.

Rutherford, M.D., Baron-Cohen, S., Wheelwright, S., 2002. Reading the mind in the voice: a study with normal adults and adults with Asperger syndrome and high functioning autism. J. Aut. Develop. Disord. 32, 189.

Saitoh, O., Karns, C., Courchesne, E., 2001. Development of the hippocampal formation from 2 to 42 years: MRI evidence of smaller area. Brain 124, 1317.

Salmond, C.H., de Haan, M., Friston, K.J., Gadian, D.G., Vargha-Khadem, F., 2003. Investigating individual differences in brain abnormalities in autism. Phil. Trans. Roy. Soc. Lond.: Biol. Sci. 358, 405.

Saunders, R.C., Kolachana, B.S., Bachevalier, J., Weinberger, D.R., 1998. Neonatal lesions of the medial temporal lobe disrupt prefrontal cortical regulation of striatal dopamine. Nature 393, 169.

Schnider, A., Treyer, V., Buck, A., 2005. The human orbitofrontal cortex monitors outcomes even when no reward is at stake. Neuropsychologia 43, 316.

Schore, A.N., 1994. Affect Regulation and the Origin of the Self: The Neurobiology of Emotional Development. Lawrence Erlbaum, Hillsdale, NJ.

Schore, A.N., 1996. The experience-dependent maturation of a regulatory system in the orbital prefrontal cortex and the origin of developmental psychopathology. Develop. Psychopathol. 8, 59.

Schultz, R.T., Gauthier, I., Klin, A., Fulbright, R.K., Anderson, A.W., Volkmar, F., Skudlarski, P., Lacadie, C., Cohen, D.J., Gore, J.C., 2000. Abnormal ventral temporal cortical activity during face discrimination among individuals with autism and Asperger syndrome. Arch. Gen. Psychiat. 57, 331.

Schultz, R.T., Romanski, L.M., Tsatsanis, K.D., 2000a. Neurofunctional models of autistic disorder and Asperger syndrome: clues from neuroimaging. In: Klin, A., Volkmar, F.R., Sparrow, S. (Eds.), Asperger Syndrome. The Guilford Press, New York, pp. 172–209.

Schultz, W., Tremblay, L., Hollerman, J.R., 2000b. Reward processing in primate orbitofrontal cortex and basal ganglia. Cer. Cort. 10, 272.

Schumann, C.M., Hamstra, J., Goodlin-Jones, B.L., Lotspeich, L.J., Kwon, H., Buonocore, M.H., Lammers, C.R., Reiss, A.L., Amaral, D.G., 2004. The amygdala is enlarged in children but not adolescents with autism; the hippocampus is enlarged at all ages. J. Neurosci. 24, 6392.

Scott, M.M., Deneris, E.S., 2005. Making and breaking serotonin neurons and autism. Int. J. Develop. Neurosci. 23, 277.

Sears, L.L., Vest, C., Mohamed, S., Bailey, J., Ranson, B.J., Piven, J., 1999. An MRI study of the basal ganglia in autism. Prog. Neuropsychopharmacol. Biol. Psychol. 23, 613.

Selemon, L.D., Goldman-Rakic, P.S., 1985. Longitudinal topography and interdigitation of corticostriatal projections in the rhesus monkey. J. Neurosci. 5, 776.

Semendeferi, K., Armstrong, E., Schleicher, A., Zilles, K., Van Hoesen, G.W., 1998. Limbic frontal cortex in hominoids: a comparative study of area 13. Am. J. Physiol. Anthropol. 106, 129.

Sergeant, J.A., Geurts, H., Oosterlaan, J., 2002. How specific is a deficit of executive functioning for attention-deficit/hyperactivity disorder? Behav. Brain Res. 130, 3.

Serra, M., Minderaa, R.B., van Geert, P.L., Jackson, A.E., 1999. Social-cognitive abilities in children with lesser variants of autism: skill deficits or failure to apply skills? Eur. Child Adol. Psychiat. 8, 301.

Shalom, D.B., 2003. Memory in autism: review and synthesis. Cortex 39, 1129.

Siegel, B.V., Nuechterlein, K.H., Abel, L., Wu, J.C., Buchsbaum, M.S., 1995. Glucose metabolic correlates of continuous performance test performance in adults with a history of infantile autism, schizophrenics, and controls. Schizophrenia Res. 17, 85.

Sigman, M.D., Kasari, C., Kwon, J.H., Yirmiya, N., 1992. Responses to the negative emotions of others by autistic, mentally retarded, and normal children. Child Develop. 63, 796.

Snow, M.E., Hertzig, M.E., Shapiro, T., 1987. Expression of emotion in young autistic children. J. Am. Acad. Child Adol. Psychol. 26, 836.

Sparks, B.F., Friedman, S.D., Shaw, D.W., Aylward, E.H., Echelard, D., Artru, A.A., Maravilla, K.R., Giedd, J.N., Munson, J., Dawson, G., Dager, S.R., 2002. Brain structural abnormalities in young children with autism spectrum disorder. Neurology 59, 184.

Stone, V.E., Baron-Cohen, S., Calder, A., Keane, J., Young, A., 2003. Acquired theory of mind impairments in individuals with bilateral amygdala lesions. Neuropsychologia 41, 209.

Thompson, C.I., 1981. Long-term behavioral development of rhesus monkeys after amygdalectomy in infancy. In: Ben-Ari, Y. (Ed.), The Amygdaloid Complex. Elsevier, Amsterdam, pp. 259–270.

Thompson, C.I., Bergland, R.M., Towfighi, J.T., 1977. Social and nonsocial behaviors of adult rhesus monkeys after amygdalectomy in infancy or adulthood. J. Comp. Physiol. Psychol. 91, 533.

Thompson, C.I., Schwartzbaum, J.S., Harlow, H.F., 1968. Development of social fear after amygdalectomy in infant rhesus monkeys. Physiol. Behav. 4, 249.

Thompson, C.I., Schwartzbaum, J.S., Harlow, H.F., 1969. Development of social fear after amygdalectomy in infant rhesus monkeys. Physiol. Behav. 4, 249.

Thompson, C.I., Towfighi, J.T., 1976. Social behavior of juvenile rhesus monkeys after amygdalectomy in infancy. Physiol. Behav. 17, 831.

Thorpe, S.J., Rolls, E.T., Maddison, S., 1983. The orbitofrontal cortex: neuronal activity in the behaving monkey. Exp. Brain Res. 49, 93.

Trevarthen, C., 1979. Communication and cooperation in early infancy. A description of primary intersubjectivity. In: Bullowa, M. (Ed.), Before Speech: The Beginning of Human Communication. Cambridge University press, London, pp. 321–347.

Trevarthen, C., Hubley, P., 1978. Secondary intersubjectivity: confidence, confining and acts of meaning in the first year. In: Lock, A. (Ed.), Action Gesture and Symbol. Academic Press, London, pp. 183–229.

Vogt, B.A., Finch, D.M., Olson, C.R., 1992. Functional heterogeneity in cingulate cortex: The anterior executive and posterior evaluative regions. Cer. Cort. 2, 435.

Vogt, B.A., Rosene, D.L., Pandya, D.N., 1979. Thalamic and cortical afferents differentiate anterior from posterior cingulate cortex in the monkey. Science 204, 205.

Volkmar, F.R., Carter, A., Grossman, J., Klin, A., 1997. Social development in autism. In: Cohen, D.J., Volkmar, F.R. (Eds.), Handbook of Autism and Pervasive Developmental Disorders, second ed. Wiley, New York, pp. 173–194.

Waiter, G.D., Williams, J.H.G., Murray, A.D., Gilchrist, A., Perrett, D.I., Whiten, A., 2004. A voxel-based investigation of brain structure in male adolescents with autism spectrum disorder. NeuroImage 22, 619.

Weeks, S., Hobson, R.P., 1987. The salience of facial expression for autistic children. J. Child Psychol. Psychiat. 28, 137.

Whalen, P.J., Rauch, S.L., Etcoff, N.L., McInerney, S.C., Lee, M.B., Jenike, M.A., 1998. Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. J. Neurosci. 18, 411.

Whitaker-Azmitia, P.M., 2001. Serotonin and brain development: Role in human developmental diseases. Brain Res. Bull. 56, 479.

Whitaker-Azmitia, P.M., 2005. Behavioral and cellular consequences of increasing serotonergic activity during brain development: a role in autism? Int. J. Develop. Neurosci. 23, 75.

White, C., Rosenbloom, L., 1992. Temporal-lobe structures and autism. Develop. Med. Child Neurol. 34, 558.

Wing, L., Attwood, A., 1987. Syndromes of autism and atypical development. In: Cohen, D., Donellen, A., Paul, R. (Eds.), Handbook of Autism and Pervasive Developmental Disorders. Wiley-Liss, New York, pp. 3–19.

Wing, L., Gould, J., 1979. Severe impairments of social interaction and associated abnormalities in children: Epidemiology and classification. J. Aut. Develop. Disord. 9, 11.

Wolterink, G., Daenen, L.E., Dubbeldam, S., Gerrits, M.A., van Rijn, R., Kruse, C.G., Van Der Heijden, J.A., Van Ree, J.M., 2001. Early amygdala damage in the rat as a model for neurodevelopmental psychopathological disorders. Eur. Neuropsychopharmacol. 11, 51.

Wood, G.K., Quirion, R., Srivastava, L.K., 2003. Early environment contributed to developmental disruption of MPFC after neonatal ventral hippocampal lesions in rats. Synapse 50, 223.

Young, A.W., Hellawell, D.J., Van de Wakl, C., Johnson, M., 1996. Facial expression processing after amygdalectomy. Neuropsychologia 34, 31.

Zald, D.H., 2003. The human amygdala and the emotional evaluation of sensory stimuli. Brain Res. Rev. 41, 88.

Zilbovicius, M., Garreau, B., Samson, Y., Remy, P., Barthelemy, C., Syrota, A., Lelord, G., 2001. Delayed maturation of the frontal cortex in childhood autism. Am. J. Psychitat. 152, 248.