Published in final edited form as:

Genes Brain Behav. 2003 October ; 2(5): 255–267.

Model of autism: increased ratio of excitation/inhibition in key neural systems

J. L. R. Rubenstein[*,†], **M. M. Merzenich**[‡]

[†] Nina Ireland Laboratory of Developmental Neurobiology, Center for Neurobiology and Psychiatry, Department of Psychiatry, San Francisco, CA, USA

[‡] Departments of Physiology and Otolaryngology University of California at San Francisco, San Francisco, CA, USA

Abstract

Autism is a severe neurobehavioral syndrome, arising largely as an inherited disorder, which can arise from several diseases. Despite recent advances in identifying some genes that can cause autism, its underlying neurological mechanisms are uncertain. Autism is best conceptualized by considering the neural systems that may be defective in autistic individuals. Recent advances in understanding neural systems that process sensory information, various types of memories and social and emotional behaviors are reviewed and compared with known abnormalities in autism. Then, specific genetic abnormalities that are linked with autism are examined. Synthesis of this information leads to a model that postulates that some forms of autism are caused by an increased ratio of excitation/ inhibition in sensory, mnemonic, social and emotional systems. The model further postulates that the increased ratio of excitation/inhibition can be caused by combinatorial effects of genetic and environmental variables that impinge upon a given neural system. Furthermore, the model suggests potential therapeutic interventions.

Keywords

Autism; genetics; model; neural excitation; neural inhibition; neural systems

Autism is a severe neurobehavioral syndrome, arising largely as an inherited disorder, and caused by a collection of diseases, which becomes apparent in the first years of life (Rapin & Katzman 1998; Rutter 2000; Tanguay 2000). Its prevalence was once thought to be roughly 2/10 000. There is now evidence that the rate of occurrence is roughly 30/10000, and that its incidence is progressively increasing (Fombonne 2002; Yeargin-Allsopp *et al.* 2003). Autism affects boys about four times more often than girls, a fact that should aid in deciphering its etiologies.

While the autistic phenotype is heterogeneous, abnormalities in language and social skills are at its core (Klin *et al.* 2002; Tager-Flusberg 1993). Autism is often viewed as a type of

[*]Corresponding author: J. L. R. Rubenstein, Nina Ireland Laboratory of Developmental Neurobiology, Center for Neurobiology and Psychiatry, Department of Psychiatry, Box F-0984, 401 Parnassus, University of California at San Francisco,San Francisco, CA 94143-0984, USA. jlrr@itsa.ucsf.edu.

mental retardation, as most autistics have IQs lower than 70. However, autism is distinguished from other mental retardation syndromes by disproportionately severe deficits in language and social skills. Moreover, autistics commonly have severe impairments in expressive language, which bring the validity of conventional mental performance assessment tests into question. Autistic people with conventionally measured IQs >70 are often referred to as having Asperger's syndrome (Gillberg & Billstedt 2000).

Twin studies have shown that autism is a strongly inherited disorder (Folstein & Rosen-Sheidley 2001; Rutter 2000; Veenstra-Vanderweele *et al.* 2003), as monozygotic twins co-inherit this syndrome several times more frequently than do dizygotics. On the other hand, if the reported several-fold increase in the incidence of autism over the past several decades (Yeargin-Allsopp *et al.* 2003) is real, powerful and still undefined environmental factors must be contributing to its origin.

It is likely that much of the heterogeneity of autism's expression relates to the heterogeneity of the genetic factors that underlie it. It is known that mutations in different genes can cause autistic-like syndromes in subsets of children with a variety of genetic diseases including Fragile X syndrome, phenylketonuria, tuberous sclerosis and Retts syndrome (Folstein *et al.* 2001; Veenstra-Vanderweele *et al.* 2002). These diseases are caused by genes that are widely expressed in the nervous system. Therefore, *a priori,* it is unclear how these mutations can ultimately account for the complex combination of relatively specific cognitive and social deficits that characterize autism. Importantly, while some patients with Fragile X or tuberous sclerosis have an array of behavioral abnormalities that relatively closely parallel those of other autistics, many others do not (Bolton *et al.* 2002; Hessl *et al.* 2001; Rogers *et al.* 2001). That fact supports the conclusion that co-inheritance of other, relatively commonly occurring genetic faults, or other variables attributed to environmental factors or to experientially-influenced brain development processes, contribute to the emergence of the syndrome.

Indeed, linkage analyses suggest that there are multiple genetic loci that contribute to causing autism (Risch *et al.* 1999). Furthermore, epigenetic influences, such as environmental toxins, infections or alterations in sensory experience can potentially affect the probability of autistic emergence. Among the environmental effects, there is presently substantial controversy regarding whether an ethylmercury-containing preservative in some vaccinations (thimerosal) contributes to the increasing numbers of people who are diagnosed as autistic (Nelson & Bauman 2003). Non-genetic sources of variance are also implicated in studies of monozygotic twins in which one twin is autistic, while the second twin has a much milder expression of the syndrome (Lainhart & Piven 1995; Le Couteur *et al.* 1996), or is not identified as autistic (Kates *et al.* 1998). Interestingly, the 'less autistic' or non-autistic twin has milder impairments in language abilities and social behaviors, and less marked physical differences in the brain regions that support them. In parallel, the extensive array of additional deficits that mark the autism syndrome do not emerge in these more mildly language- and socially- impaired individuals (Kates *et al.* 1998; Le Couteur *et al.* 1996). Given that autism is characterized by a disproportionate disability of an affected individual's language and social skills, and given that monozygotic twins of autistics that do not develop autism nonetheless suffer milder deficits in these specific faculties, it is likely that neural systems that subserve these behaviors are at the core of the pathophysiology. We

suggest that efforts to understand autism origin should focus on the development of neural circuits and systems that underlie language processing (such as audition, language comprehension, speech production and verbal memory and cognition), along with social and affiliative behaviors. Furthermore, roughly 30% of autistic individuals develop clinically apparent seizures (Gillberg & Billstedt 2000) and 50–70% of autistic children have ongoing 'sharp spike' activity documented in sleeping EEG or magnetoencephalographic recording (Lewine *et al.* 1999; Wheless *et al.* 2002) suggesting that these children have noisy and unstable cortical networks. This suggests that cellular, molecular and local excitatory-inhibitory circuit-plasticity mechanisms, that can cause hyper-excitable cortical and subcortical states, should be an important dimension of autism origins studies. Because these severe, core changes are commonly paralleled in autistics by a complex array of other neurological and behavioral deficits, we propose that special research attention should consider how the many facets of this complex abnormal repertoire of changes could be linked to one another in their emergence.

We hypothesize that at least some forms of autism are caused by a disproportionate high level of excitation (or disproportionately weak inhibition) in neural circuits that mediate language and social behaviors. More excitable (more weakly inhibited) cortex is, by its nature, more poorly functionally differentiated (Merzenich *et al.* 1999; Merzenich 2001); this type of cortex will lead to broad-ranging abnormalities in perception, memory and cognition, and motor control. Moreover, 'noisy' (hyperexcitable, poorly functionally differentiated) cortex is inherently unstable, and susceptible to epilepsy.

As will be discussed below, an imbalance of excitation and inhibition could be due to increased glutamatergic (excitatory) signaling, or to a reduction in inhibition due to a reduction in GABAergic signaling. Hussman (2001) has earlier suggested that suppressed GABAergic inhibition is a common feature of the autistic brain. Such a problem could also be exacerbated by abnormal modulatory control of the learning and memory processes that enable and regulate the normal progressive differentiation and elaboration of information processing in the developing brain, because progressive functional differentiation increases processing reliability and representational salience, and thereby reduces process noise (Merzenich 2001; Merzenich *et al.* 1998a,b, 1999).

As shall be described later, imbalances in excitation vs. inhibition can also be amplified by maturational processes that result in delayed synapse maturation or in abnormal myelination. In the developmental process, synapse maturation and progressive myelination contribute crucially to the generation of more coherent activities in forebrain networks and systems, and thereby, to the progressive strengthening of cortical signaling (or, from the obverse perspective, to the progressive reduction of cortical process 'noise') (Merzenich *et al.* 1998a; Merzenich 2001).

In the following sections, we have attempted to initiate the dissection of mechanisms that may underlie some forms of autism. We begin by considering some aspects of the neural systems that could play central roles in behaviors that are disrupted in autism. Based on the hypothesis that disruption of these neural systems is due to an abnormal balance of the ratio of excitation to inhibition (obversely, to an increase in 'noise' in self-organizing cortical and

subcortical systems), we evaluate potential local circuit and cellular mechanisms that could generate hyperexcitable states, and that could delay or block the normal differentiation of brain processing systems. We then consider some molecular, genetic and local circuit mechanisms that would increase the ratio of excitation to inhibition (noise), paying particular attention to existing candidate genes and molecules. We conclude with a brief outline of theoretical therapeutic treatment strategies that could potentially prophylactically affect the probability that an at-risk infant develop full-blown autism expression, or that could potentially ameliorate the expressions of autism.

Neural systems implicated in autism

Cortical networks

Autism is a disorder in which multiple dimensions of behavior, emotion, language and cognition are disrupted. Among these defects, autistic individuals appear to have a range of perceptual processing abnormalities, expressed especially strikingly by a hypersensitivity to auditory and tactile stimuli (Gomot *et al.* 2002; Kootz *et al.* 1981; Plaisted *et al.* 2003). Developmental studies of perceptual systems in non-human mammals may provide useful insights into mechanisms underlying sensory disturbances in autistic people. In particular, recent investigations of auditory development in rats may shed light onto normal and abnormal developmental progressions in language development, as well as the origins of language deficits in impaired children (Bao *et al.* in press; Chang & Merzenich 2003; Merzenich 2001; Merzenich *et al.* 1998a; Zhang *et al.* 2001).

Rats develop competent hearing at about postnatal day 12, which is when the cochlea first conveys coded auditory inputs to hindbrain auditory nuclei, and through them, to the inferior colliculus, medial geniculate body and auditory cortex. Over three or four subsequent days, the primary auditory cortex develops a coarse, partial, 2-dimensional map of sound frequencies (a ‘tonotopic map’); in the subsequent week, this tonotopic map is almost completed, and neuronal response selectivity within it is substantially further refined (Zhang *et al.* 2001). However, if during this ‘critical period’ the animal is exposed to a limited repertoire of sound frequencies or to specific behaviorally important sounds (e.g., conspecific or other animal vocalizations), the auditory cortex is biased to more powerfully and more selectively ‘represent’ (by its selective, distributed cortical neuronal responses) those specific frequencies or sounds (Zhang *et al.* 2001).

In an important variation of these developmental studies, if an animal is exposed to temporally modulated noise, the tonotopic map degrades, and there is a premature closure of the ‘critical period’ (Zhang *et al.* 2002). This early closure means that the animal advances from an epoch in which the mere exposure to sound results in large-scale plastic cortical change to the post-critical period epoch in which change only arises when the animal is behaving (attending, and rewarded, punished or alerted by inputs or actions inherent in the behavior) (Merzenich 2001).

Exposure of the young rat to continuous, unmodulated noise similarly blocks maturation of the auditory cortex, but in that case, in striking contradistinction to rearing an animal in modulated noise, the critical period window appears to remain open indefinitely (Chang &

Merzenich 2003). In both of these noise-reared rat models, the representation of sound inputs in the cortex remains poorly differentiated because the cortex is undergoing development under very poor signal-to-noise conditions. Given its poor state of differentiation, the cortex in these noise-reared animals is more susceptible to the induction of cortical epilepsy, specifically because this relatively undifferentiated status enables potentially catastrophic positive coupling of cortical neuronal populations across relatively long cortical network distances.

As noted above, in the modulated noise exposure model, the critical period prematurely closes, even while the cortex never functionally matures in the normal way. That is believed to occur because distributed correlated activity known to control the release of brain derived neurotrophic factor (BDNF), which appears to provide the primary signaling for critical period window closure (Maffei 2002), is artificially high at a very young cortical age. The pulsing noise itself hypothetically directly generates that correlated activity because each pulsed noise stimulus simultaneously excites neurons all across the primary auditory cortex (Zhang *et al.* 2001).

When the cortical noise is continuous, the critical period window is indefinitely extended, presumably because neither the noise nor the poorly developing, functionally undifferentiated cortex can generate the schedules of correlated activity necessary for the BDNF up-regulation that is required to end it. As noted earlier, the highly disorganized cortex in this delayed critical period closure model is susceptible to an emergent cortical epilepsy. If epilepsy emerges, it would be expected to again generate an epoch of very heavily correlated cortical activity, which should again result in a spurt of BDNF up-regulation that could abruptly close the critical period.

In both of these hypothetical ‘noisy processing’ developmental scenarios, the auditory/aural speech cortex would mature through the critical period of development and pass into the ‘adult’ epoch of development in a highly undifferentiated and relatively unstable state.

Such experiments indicate that genetic weakness, or environmental or physiological processes that result in or generate relatively high levels of noise (i.e. hyper-excitability) in the neocortex should disrupt the normal formation of cortical ‘maps’, and should predispose the cortex to epilepsy and to other related developmental sequelae that plausibly contribute to brain dysfunction recorded in autism (Merzenich 2001; Merzenich *et al.* 1999). Such studies also indicate that the auditory environment has important impacts on the progression of the functional maturation and specialization of the primary auditory cortex, and implicate a number of specific sensory and other (e.g., toxic chemical) factors that could potentially amplify or otherwise modulate developmental progressions.

Following closure of the critical period, the tonotopic maps and the response specificity of neurons in A1 are not altered by unattended ambient auditory information. Formation of the critical period-shaped auditory processing then serves as a substrate on which higher order processes can generate more complex auditory processing steps. At these later stages in an infant animal or child’s life, plasticity underlying the development of perceptual, cognitive, executive and motoric skills and abilities requires that the individual attend to the auditory

(or other) stimulus. Inthe post-critical period brain, plastic changes are strengthened as a function of attentional intensity, reward, novelty and other factors, with these modulated cortical changes mediated through secondary neurotransmitters delivered from subcortical nuclei, such as acetylcholine, dopamine, norepinephrine or serotonin (Bao *et al.* 2001, in press; Kilgard & Merzenich 1998; Schultz 2002; Weinberger 1998).

Memory systems

While autistic individuals appear to have major defects in processing systems underlying many aspects of perception, cognition, executive functions and motor control, they also have abnormally organized mnemonic abilities. It is thought that there are multiple parallel memory pathways that are responsible for storing distinct types of memories (Davis & Whalen 2001; Packard & Knowlton 2002; Squire & Zola 1996; White & McDonald 2002). These include declarative, procedural, emotional and social memory. Declarative memory is a conscious activity in which explicit information (facts or semantic knowledge) and events (episodic knowledge) are recorded (Squire & Zola 1996). In experimental animals this type of memory is referred to as ‘stimulus-stimulus memory’, as it relates to learning of relationships between multiple stimuli (White & McDonald 2002). Multiple brain regions are involved in this process, but the hippocampal complex appears to be its core in at least the early stages of memory formation and retrieval (Squire & Zola 1996; White & McDonald 2002). At later stages, other brain structures appear to play a role in declarative memory storage (neocortex) and retrieval, scanning and selection (prefrontal cortex and cerebellum).

Procedural memory records implicit information; it is an unconscious activity involving the learning of new (and the control of established) motor and cognitive skills and habits (Squire & Zola 1996). In experimental animals this type of memory is referred to as ‘stimulus-response memory’, because the pairing of a reinforcing stimulus with a response increases the probability that encountering the stimulus in the future will elicit the same response (White & McDonald 2002). Procedural memory involves a number of brain structures. The cortico-basal ganglia-thalamic circuit (Packard & Knowlton 2002; White & McDonald 2002) appears to be at its core. Different parts of the striatum (a basal ganglia component) may participate in different types of memories. Thus, while the dorsal striatum participates in stimulus-response memories, the ventral striatum (including the nucleus accumbens) is implicated in linking motivational states with behavioral action (Packard & Knowlton 2002). The cerebellum is also implicated in regulating cognitive functions similar to those mediated by the basal ganglia (Middleton & Strick 2000).

It has been postulated that distinct aspects of language engage the declarative and procedural memory systems. The declarative system would store vocabulary whereas the procedural system would store grammatical information (Ullman 2001). Autistic individuals may have a relative sparing of declarative memory (Bennetto 1996; VanMeter *et al.* 1997).

A third memory system encodes emotional memories, and uses the amygdala as a central processor (Davis & Whalen 2001; LeDoux 2000; White & McDonald 2002). In a later section, we will discuss how a cellular and molecular mechanism reducing inhibitory tone in the amydgala could potentially intensify context-dependent aversion or fear.

Systems regulating affiliative behaviors

Defects in additional systems are also candidates for causing core autistic symptoms. For example, while poorly understood, there are neuroanatomical pathways that modulate affiliative behaviors in animals. Oxytocin and vasopressin neuropeptides and their receptors are implicated in regulating behaviors like social communication, social bonding and social memory (Kim *et al.* 2002; Young 2001; Winslow & Insel 2002). Oxytocin and vasopressin are expressed in the periventricular and supraoptic hypothalamus; these nuclei have connections with both the posterior pituitary and various brain regions, including the amygdala, nucleus accumbens, septum, thalamus and raphe nuclei (Winslow & Insel 2002; Young 2001). Species-specific differences in the distribution of receptors for these neuropeptides may participate in mediating species-specific differences in behavior (Winslow & Insel 2002).

Neuromodulatory systems

Finally, one should consider the potentially important role of neuromodulatory systems, which regulate the activity of other brain regions, as contributors to autism origin. For instance, the reticular nucleus of the thalamus contains GABAergic neurons that modulate the activity of thalamic output neurons (Jones 2002). The monoamine systems of the raphe nuclei, substantia nigra/ventral tegmental area, locus coeruleus and basal forebrain nuclei widely distribute their axons throughout the brain, and affect neural activity by releasing serotonin, dopamine, norepinephrine and acetylcholine, respectively. Dysregulation of these systems can modify neural activity widely across the forebrain, and thereby affect the progressive refinement and emergent efficiencies of all forebrain-processing systems.

System integration

It is important to note that the functional development of sensory-perceptual, motor control, cognition and mnemonic, affiliative and modulatory control systems are inextricably intertwined. To cite one simple example, the nucleus basalis, which releases aceytcholine as a critical enabler of learning-induced plasticity (Kilgard & Merzenich 1998; Weinberger 1993, 1998), receives trophic factors regulating its functional maturation from the developing cerebral cortex (Lucidi-Phillipi & Gage 1993). Premature or delayed cortical maturation, as occurs in the noise-manipulated auditory cortex discussed earlier, results in the premature or delayed maturation of this very important modulatory control nucleus. By that maturation, the nucleus basalis is converted from a ‘critical period’ functional state, in which it continuously releases acetylcholine enabling cortical plasticity, to a post-critical period (‘adult’) state, in which plasticity-enabling acetylcholine release is limited to epochs in which the animal is in a closely attending behavioral context. Thus, a change in cortical development causes secondary changes in nucleus basalis that further derail cognitive functioning. More generally, delayed or altered development at any system level substantially Impacts developmental progressions at many other levels. The secondary Impacts of such defects may be especially great If they occur In locations that have strong links to other key nuclei or systems (such as the auditory cortex projections to the dorsal amygdala; Davis 1989; LeDoux 1993; LeDoux 2000).

Finally, how should one view the origins of apparently large-scale deficits in procedural and emotional memory, or cognitive and executive control (including 'theory of mind'), affiliative and motor behaviors in autism? From one perspective, a poorly differentiated processing system (e.g., an impaired aural speech representational system) arising from imbalanced excitatory:inhibitory processes (i.e., from 'noisy' self-organizing brain development processes) would affect the salience of representations of speech inputs and language-related processes at every system level (Merzenich 2001; Merzenich & Jenkins 1995; Merzenich *et al.* 1998a, 1999). Because sensory, memory-related and cognitively-related representations of inputs or actions would be degraded at every level in such a brain, the development of normally refined expressive systems and subsequent feedback-guided expression would also be impaired.

Local circuit/cellular mechanisms that could lead to an increase in the excitatory state of the brain

In the cortex, both excitatory and inhibitory neurons receive extensive extrinsic and intrinsic glutamatergic inputs. Pyramidal projection neurons and local-circuit spiny stellate cells in the neocortex have glutamergic (excitatory) connections. In the cerebral cortex, roughly 80% of the neurons are excitatory glutamatergic neurons and 20% are inhibitory GABAergic neurons. It should be noted that during development the GABAergic cortical cells are excitatory (Ben-Ari 2002). In subcortical nuclei, some GABAergic neurons contribute to local circuit properties, whereas the majority have long-range inhibitory projections to other subcortical nuclei or cortical areas. There are multiple types of cortical GABAergic local circuit neurons based on their morphologies, patterns of connectivity, and molecular properties (DeFelipe *et al.* 1990; Lund & Lewis 1993; Somogyi *et al.* 1998). For example, chandelier cells synapse upon the initial segment of pyramidal cell axons, basket cells make synapses upon glutamatergic and GABAergic neuronal somata, and double-bouquet, bitufted, bipolar, neurogliaform and Martinotti cells target their synapses to dendrites spines and shafts.

Basic units of neocortical function are organized in mini-columns (Mountcastle 1997; Silberberg *et al.* 2002), which are vertical columns of functionally-related glutamatergic and GABAergic neurons that together process thalamic inputs. GABAergic local circuit neurons are thought to participate in controlling the functional integrity and segregation in minicolumns by providing lateral inhibition of activity coming from bordering minicolumns (Lund *et al.* 2003; Peters & Sethares 1997). There is substantial evidence that minicolumn dimensions can be altered by cortical plasticity processes (Merzenich & DeCharms 1996; Merzenich & Jenkins 1993; Merzenich *et al.* 1991; Recanzone *et al.* 1992). Minicolumns are smaller, have abnormal structure, and are more numerous in autistics than in normal individuals (Casanova *et al.* 2002). The mechanism(s) underlying this defect is unknown.

The balance of excitation to inhibition in the cortex is controlled by the relative numbers and activities of glutamatergic and GABAergic neurons. Activity levels are regulated in turn by extrinsic excitatory (glutamatergic thalamic afferents), mixed excitatory/inhibitory (serotonin, norepinephrine, dopamine and acetylcholine afferents from the hindbrain,

midbrain and basal forebrain, respectively) and exclusively inhibitory (from the zona incerta) inputs to the cortex. Formally, one should also consider other influences on excitatory or inhibitory processes that could be regulated by glia, the vasculature and the cerebrospinal fluid system.

Processes that increase the numerical or functional balance of excitatory vs. inhibitory cells or effects can lead to a hyper-excitable state; individuals with such imbalances are at risk for epilepsy. For instance, cortical GABAergic neurons in rodents are largely produced in the anlage of the basal ganglia and migrate tangentially to the cortex (Anderson *et al.* 1997; Marin & Rubenstein 2001, 2003). Defects in either the production or migration of cortical GABAergic neurons lead to decreased numbers of cortical GABAergic neurons, that result in a hyper-excitable cortex (Powell *et al.* 2003). Processes that selectively disrupt synaptic maturation of GABAergic neurons would result in a selective enhancement of excitation, and therefore lead to increased 'noise' in the cortex. As noted in the models of developing auditory cortex described earlier, this can have profound effects on circuit/synapse plasticity. In another example, the reduction of inhibition in the mouse cerebral cortex due to a loss-of-function mutation of GAD65, blocks the maturation of binocular vision (Hensch *et al.* 1998). Subsequent pharmacological enhancement of inhibition enables the mutant cortex to develop binocular vision.

Decreased inhibition in the hippocampus and lateral amygdala facilitates long-term potentiation of excitatory synapses (Shumyatsky *et al.* 2002; Steele & Mauk 1999). It has been argued that an increase in long-term potentiation would make circuits less sensitive to modulation by future synaptic activity, and could thereby inhibit learning of new information. A possible example of that phenomenon is illustrated by the effect of reducing GABAergic inhibition in the amygdala. In the lateral amygdala, gastrin-related peptide (GRP) activates GABAergic local circuit neurons, which in turn inhibits the activity of glutamatergic output neurons (Shumyatsky *et al.* 2002). Mice lacking the gastrin-related peptide receptor (GRPR) have decreased inhibitory tone in their lateral amygdala, and exhibit increased long-term potentiation of synapses that activate the excitatory projection neurons (Shumyatsky *et al.* 2002). This neurophysiological effect is linked to increased activity of the neural pathway mediating auditory fear conditioning. These animals show persistent memory of fear-associated auditory sensory stimuli. The phenotype of the GRPR mutant mice may be paradigmatic for how reduction of GABAergic tone in key brain regions could lead to alterations in synaptic plasticity and behavior.

Higher-than-normal noise in cortical processes also frustrates the development of normally differentiated representations, because cortical response selectivity in space and time is a product of balanced inhibitory and excitatory processes. Relatively undifferentiated representations of signal- or fear- associated stimuli in the auditory cortex or amygdala, for example, would result in larger (less selective) and more strongly engaged neural populations. Such over-representation by non-differentiated systems could plausibly account, for example, for the strong aversive reactions to auditory, tactile and visual stimuli that are commonly recorded in autistic individuals.

Molecular/genetic mechanisms that could lead to an increase in excitatory state of the brain

If cortical systems and subcortical nuclei developing under noisy, hyper-excitable conditions underly autism, then one can postulate which types of genes could contribute to that physiological state. Particular attention is paid to genes that map to the sex chromosomes because they plausibly could account for the substantially higher incidence of autism in males.

Neurotransmitter/receptor systems

How could alterations in intrinsic neurotransmitter and neuro-modulatory transmitter systems lead to a hyperexcitable state? What examples of genes in these systems are plausible candidates for contributing to autism?

Glutamate signaling—Glutamate is the most prevalent excitatory neurotransmitter. Mutations (or potentially, environmental factors) that increase glutamate signaling increase excitatory tone. Thus, mutations that increase the activity or number of glutamate receptors, that increase the amount of glutamate in the synapse, or that amplify glutamate-mediated synaptic potentiation can increase the excitatory state of the brain. Recently, several small nucleotide polymorphisms (SmNPs) were identified in the Glutamate Receptor Ionotropic Kainate 2 gene (GRIK2 or GluR6) (chromosome 6q16–21) (Jamain *et al.* 2002). One of these SmNPs was in the intracytoplas-mic C-terminal region of the protein. The effect of this mutation on GRIK2 function is unknown. This polymorphism was present in 8% of autistic subjects and in 4% of the controls, suggesting that this form of GRIK2 may be associated with some forms of autism.

Among environmental factors that could amplify glutamate-based potentiation are chemicals in the PCB family, which have been demonstrated to generate up to five-fold increases in induced LTP amplitudes in cortical slice preparations (Fischer *et al.* 1998).

GABA signaling—GABA is the most prevalent inhibitory neurotransmitter. As such, mutations or environmental factors that decrease GABA signaling would increase the brain's excitatory tone. Decreases in GABA production and signaling are known to contribute to hyper-excitable states (i.e., epilepsy) and cognitive dysfunction (Harkin *et al.* 2002; Hensch *et al.* 1998; Schuler *et al.* 2001). For example, reduction of GAD levels in mice lacking GAD65 is associated with epilepsy and a block in the development of neocortical processing of binocular visual input (Hensch *et al.* 1998). It is intriguing that autistic parietal and cerebellar cortices are reported to have a ~50% reduction in protein levels of the enzymes that synthesize GABA, glutamic acid decarboxylase (GAD) 65 and 67 (Fatemi *et al.* 2002).

GABA receptors are implicated in autism based on human genetic studies. There is a cluster of GABA receptors in the Prader-Willi/Angelman locus on 15q11–13 (Jiang *et al.* 1999). This region is found in a trisomic state in some cases of autism and is now considered a likely susceptibility locus (Shao *et al.* 2003). Furthermore, there is evidence for linkage

dysequilibrium of certain alleles of one of the 15q11–13 GABA receptors (GABRB3) in autistic patients (Buxbaum *et al.* 2002).

Neuropeptides and receptors—While glutamate and GABA are widely distributed throughout the nervous system, specific neuropeptides and their receptors are expressed in subsets of neurons, and appear to participate in neural pathways that mediate specific behaviors. Neuropeptides generally produce slower and longer synaptic responses. Because they tend to be expressed in restricted regions of the brain, they can regulate specific brain systems. For instance, as noted earlier, oxytocin and vasopressin are implicated in regulating affiliative behaviors, in conjunction with their roles as posterior pituitary hormones (Young 2001). Analysis of allelic forms of the argenine vaso-pressin receptor 1A (AVPR1A), which maps to chromosome 12q14–15, provided weak evidence of an association of this gene with autism (Kim *et al.* 2002b).

Gastrin related peptide (GRP) is expressed in restricted regions of the forebrain, many of which are associated with the auditory system (Shumyansky *et al.* 2002). As noted above, within the lateral amygdala, GRP is expressed in glutamatergic projection neurons, whereas its receptor (GRPR) is expressed in GABAergic local circuit neurons. GRPR is implicated in modulating auditory fear conditioning; the function of GRP/GRPR in other aspects of audition has not yet been described. There is a report that GRPR, an X-linked gene which escapes X-inactivation, is associated with autism in a patient with exostoses (Ishikawa-Brush *et al.* 1997). However, further studies have failed to identify additional autistic cases that have GRPR mutations (Heidary *et al.* 1998).

Monoamine neurotransmitters and neuromodulators—Acetylcholine has a major affect on forebrain systems by virtue of its widely ramified projections from basal telencephalic and septal cholinergic neurons, and through the function of striatal cholinergic interneurons. Acetylcholine can be a potent rapid excitatory neurotransmitter if the postsynaptic cell has nicotinic acetylcholine receptors. Acetylcholine can be either an excitatory or inhibitory neuromodulator for neurons with postsynaptic G-protein linked muscarinic acetylcholine receptors. Therefore, *a priori,* it is difficult to predict whether changes in acetylcholine activity will lead to increased or decreased excitation. As noted above, acetylcholine has potent effects on learning and memory through its function in the cerebral cortex (Kilgard & Merzenich 1998; Merzenich 2001; Weinberger 1998) and the striatum (Zhou *et al.* 2002). Because acetycholine modulation is a crucial enabler of plasticity during the critical period and throughout life, it underlies the development of representational differentiation in the developing brain.

There is evidence for alterations in the levels of acetylcholine receptors in the postmortem forebrain and cerebellum of autistic brains (Lee *et al.* 2002; Perry *et al.* 2001). However, it should be noted that nucleus basalis activity may be sharply down-regulated in any brain that is not engaged in a normal, daily learning-and-memory activity schedule.

Dopamine is largely produced in the basal plate of the midbrain and caudal diencephalon, from which widely ramifying axons innervate the telencephalon. The highest levels of both dopamine and acetylcholine innervation are present in the striatum (Zhou *et al.* 2002), but

dopamine neuronal projections are also relatively widely distributed in the frontal and temporal cortex (Lewis *et al.* 2001). Dopamine signaling is through excitatory (D1, D5) or inhibitory (D2, D3, D4) G-protein linked receptors that show regional and cell type-specific expression patterns. There are several hypothetical scenarios by which alterations in dopamine signaling could alter the balance of excitation to inhibition through modifications involving specific dopamine receptors.

As with acetylcholine, dopamine is an important enabler of cortical plasticity (Bao *et al.* 2001, in press). Its impacts are primarily mediated through projections to GABAergic cortical neurons (Gao & Goldman-Rakic 2003). Any defect in its expression or effects would be expected to contribute to increased noise in the cortex, basal ganglia, hippocampus and elsewhere.

Serotonin is produced in the raphe nuclei of the pons and medulla. The pontine raphe nuclei project to the forebrain, where over ten types of excitatory and inhibitory serotonin receptors (5HTR) are expressed in regionally and cell type-specific patterns (Bonasera & Tecott 2000). Serotonin signaling modulates GABAergic inhibition in the prefrontal cortex and temporal cortex (Yan 2002) and is therefore in a position to modulate multiple aspects of language and cognition. Several studies have reported evidence for a link of the serotonin transporter with autism (Cook *et al.* 1997; Kim *et al.* 2002a; Klauck *et al.* 1997; Tordjman *et al.* 2001;Yirmiya *et al.* 2001).

Neural Development

Autism is clearly a disorder of development, as symptoms appear long before the child's brain is mature. As such, one needs to broadly consider the multiple processes and linked developmental progressions that are required to assemble the nervous system (Merzenich 2001; Rubenstein & Puelles in press). Neuropathological analyses of autistic brains (Kemper & Bauman 1998) provide evidence for loss of neurons, particularly in the Purkinje cell layer of the cerebellum. Limbic forebrain regions have a number of defects. Some regions have more tightly packed small neurons (e.g., medial septal nucleus, amygdala, hippocampus, subiculum, entorhinal cortex, mammillary body). The dendritic arbors of neurons in CA1 and CA4 were less complex. In the diagonal band, the neurons were larger than normal in young patients, but were smaller and reduced in number in older patients.

Neuroimaging analyses have revealed that autistic brains in early childhood are larger than normal brains (Aylward *et al.* 2002; Carper *et al.* 2002). Most of this difference appears to be accounted for by greater than normal forebrain myelination (Carper *et al.* 2002). One mechanism that could increase myelination would be higher than normal cortical and subcortical levels of BDNF, as it regulates myelin formation (Huang & Reichardt 2003), among its several roles described earlier. At present, the mechanisms that underlie these abnormalities are unknown, but could arise from many distinct developmental processes, or from abnormal patterns of system activity or usage that derive from them. Below, we briefly review neurodevelopmental steps for which there is some genetic evidence of dysfunction in autism.

Synapse formation/function—Defects in the formation of the correct balance of excitatory and inhibitory synapses in a given local circuit would impact circuit function. Thus, for example, mechanisms that regulate axon pathfinding, dendritic morphogenesis or synaptogenesis need to be considered. Presently, there is some evidence that aspects of synaptic function may be disrupted in autism.

A subset of boys with Fragile X syndrome has autistic features (Rogers *et al.* 2001). This disorder is caused by loss of expression from the FMR1 locus (O'Donnell & Warren 2002). FMR1 encodes a protein that binds subsets of RNA molecules (Darnell *et al.* 2001; O'Donnell & Warren 2002). Mice and humans that lack FMR1 expression have defects in dendritic spines, suggesting that FMR1 is required for morphogenesis of these dendritic specializations that are key postsynaptic sites (Nimchinsky *et al.* 2002).

Recently, mutations in neuroligin3 and neuroligin4 have been identified in some autistic boys (Jamain *et al.* 2003). These X-linked genes encode proteins that are implicated in synaptic development and perhaps function, through their interactions with neurexins.

FMR1, neuroligin3 and neuroligin4 are among several other X-linked genes (OPHN1, PAK3, ARHGEF6, RabGDI1, TM4SF2) that contribute to X-linked mental retardation syndromes (Castellvi-Bel & Mila 2001). While many of the boys with these syndromes are not presently thought to have autism, it is intriguing that FMR1, the neuroligins and OPHN1, PAK3, ARHGEF6, RabGDI1 and TM4SF2 are all implicated in synaptic function. OPHN1, PAK3, ARHGEF6 encode proteins that interact with Rho GTPases; RabGDI1 encodes Rab GTPase; and TM4SF2 encodes a tetraspanin protein that is implicated in the maturation of synapses.

Disruption in synapse formation and/or maintenance could affect neuronal survival. It is conceivable that this mechanism underlies the loss of cerebellar Purkinje cells observed in neuro-pathological analyses (Kemper & Bauman 1998). As such, it raises the possibility that neurotrophic (e.g., BDNF, NT3, NGF) and other molecules that signal across the synapse (e.g., neuregulins) need to be considered. In addition to the role of neuro-trophins in mediating neural survival, they are also key regulators of synaptogenesis and synaptic plasticity (Hanover *et al.* 1999), and as noted earlier, of key aspects of neurodevelopment staging. Among the many functions of neuregulins, they are reported to regulate the expression of cholinergic receptors on GABAergic local circuit neurons, and thus would indirectly regulate the level of their activity (Liu *et al.* 2002).

Tuberous sclerosis is an autosomal dominant syndrome that causes seizures, tumors of the brain, kidney, heart, retina and skin. ~50–60% of patients have mental retardation, and ~40–80% of patients have autistic-like behaviors (Bolton *et al.* 2002). Tuberous sclerosis is caused by mutations in either the hamartin or the tuberin genes. Both genes encode tumor suppressors that interact with each other. These proteins appear to suppress proliferation through positively regulating p27kip1, and may also negatively regulate beta-catenin/Wnt signaling (Mak *et al.* 2003). Hamartin and tuberin regulate Rac and Rho, small GTPases that have central roles in controlling cytoskeletal structure, and thus cell shape, adhesion and migration (Astrinidis *et al.* 2002). Autistic patients with tuberous sclerosis show evidence for

temporal lobe cortical tumors (called tubers) and temporal lobe epilepsy beginning in the first three years of life (Bolton *et al.* 2002). Presently, it is unclear whether autistic symptoms arise solely from the effects of the tubers, or whether the reduction of hamartin and tuberin cause more widely distributed defects.

Regulators of gene expression

Gene regulation is controlled at multiple levels, including chromatin structure, transcriptional control, RNA processing, RNA transport and translation and control of protein activity. To date, mutations have been identified in patients with autism and related disorders in the genes that operate at many of these levels.

Angelman's syndrome causes severe mental retardation, epilepsy and autistic-like behavioral features. It is an imprinting syndrome that is associated with maternal deletions in 15q11–13, and can be caused by maternal loss of function mutations in the ubiquitin-ligase UBE3A gene (Jiang *et al.* 1999). The imprinted paternal gene is methylated, and is not expressed. This enzyme is part of a complex that specifically links ubiquitin to proteins, which targets them for degradation (Jiang *et al.* 1999).

As noted earlier, Fragile X syndrome is caused by mutations of FMR1 that result from a trinucleotide expansion (CGG) in the 5' untranslated region and lead to DNA methylation and lack of transcription. FMR1 encodes an RNA binding protein that is implicated in regulating the expression of subsets of RNAs (O'Donnell & Warren 2002).

Rett syndrome is a neuroregressive disorder in which infant girls first show autistic-like behavioral symptoms between 6 and 18 months of age, then show progressive neurological decline. It is caused by loss of function mutations in the MeCP2 gene, which maps to Xq27.3 (Shahbazian & Zoghbi 2002). Males lacking function of this gene die during gestation; hypomorphic mutations in males have been identified to contribute to about 2% of boys with X-linked mental retardation (Shahbazian & Zoghbi 2002). While hypomorphic mutations have been observed in autistic patients, autism rarely results from MeCP2 mutations (Beyer *et al.* 2002). The MeCP2 protein binds DNA methylated at CpG sites; once bound to DNA it is thought to regulate transcriptional repression mediated by histone deacetylase, cSki, and the nuclear receptor co-repressor (Shahbazian & Zoghbi 2002). Thus, presumably, loss of MeCP2 function leads to inappropriate gene expression programs. It is important to note that Rett's, Fragile X, and Angelman's syndromes all include DNA methylation as an important aspect of their mechanism, which raises the possibility that DNA methylation and imprinting underlie other aspects of gene regulation disorders that cause autism. X chromosome inactivation is another process that involves DNA methylation, and thus X-linked mental retardation/autism syndromes in girls are also impacted by this genetic mechanism.

Arx is an X-linked gene (Xp22.1) that encodes the first transcription factor implicated in causing autism. Boys that inherit a variety of mutations in the Arx homeobox gene have epilepsy and movement disorders. A few also have autism (Turner *et al.* 2002). Apparent loss-of-function mutations of Arx cause lissencephaly and ambiguous genitalia (Kitamura *et al.* 2002). Analysis of the expression and function of Arx in mice has revealed aspects of the

mechanisms underlying these phenotypes. This transcription factor is expressed in several regions and cell types within the forebrain. Arx expression in the diencephalon is required for development of selected thalamic nuclei. Arx expression within progenitor cells in the cerebral cortex appears to positively regulate their proliferation. This may contribute to the lissencephaly in humans. Its expression in late progenitors and postmitotic neurons in the prenatal basal ganglia regulates the development of tangentially-migrating GABAergic neurons that populate the cerebral cortex. Furthermore, Arx is expressed in mature cortical local circuit neurons. Its expression in GABAergic neurons in the basal ganglia and cortex could relate to the epilepsy and movement disorders in humans bearing Arx mutations. How the Arx mutation causes autism in conjunction with mental retardation and movement disorders in some patients is unknown, but may relate to its function in the development of structures that are central memory processing pathways (i.e., neocortex, hippocampus, basal ganglia and thalamus).

The expression of Arx in the basal ganglia is regulated by the Dlx family of homeobox genes (I. Cobos, V. Broccoli and J. L. Rubenstein, unpublished). The six Dlx genes are bigene clusters; of them, Dlx1, 2, 5 and 6 are expressed during development of the majority of forebrain GABAergic neurons, and they regulate several aspects of their phenotypes (Panganiban & Rubenstein 2002). Dlx1/2 and Dlx5/6 clusters map near autism susceptibility loci on chromosomes 2q and 7q, respectively, and therefore, perhaps should be considered candidates for contributing to autism. Like Arx, the Dlx genes are expressed in the basal ganglia, reticular nucleus of the thalamus and cortical local circuit neurons; thus they are in a position to regulate the development and function of forebrain memory and motor systems. Furthermore, they are expressed in the amygdala and hypothalamus, where they could participate in modulating emotional and social behaviors. As they are expressed in GABAergic and not in glutamatergic neurons (Stuhmer *et al.* 2002a,b), Dlx mutations would probably increase the ratio of excitatory/inhibitory tone in forebrain neural systems, and lead to physiological changes as described in the previous sections of this review. On the other hand, to date, there is no evidence for a linkage of Dlx genes and autism (Nabi *et al.* 2003).

Model for a mechanism underlying autism: neural process-specific combinatorial gene dosage model of autism that increases the ratio of excitiation/inhibition in selective brain circuits

The existing evidence discussed above suggests the following characteristics of the genetic contribution to autism:

1. Multiple genes can cause autism alone or in combination with other genes.
2. No one gene is necessarily a major determinant of autism.
3. Genes that cause autism may not do so in all people carrying the same mutation. Differential penetrance may occur if the individual: (i) hasn’t co-inherited other susceptibility genes; (ii) hasn’t been exposed to the same environmental insults; (iii) if there is a stochastic contribution to a relevant developmental process.

These features would be consistent with a model that autism Is caused by co-inheritance of multiple alleles that each contribute to weakening a specific physiological process(es) that is required for the development of language and social skills. A similar genetic model has been suggested by Jones & Szatmari (2002). If autism is caused by an increase in the ratio of excitation/inhibition in one of several key neural systems, then autism could be caused by co-inheritance of alleles that either increase excitation or reduce inhibition in these neural systems. Thus while inheriting one allele which reduces inhibitory signaling (or increases excitatory signaling) in the cortex may not result in a noticeable pathophysiology, coinheritance of two or more such alleles, that further increase the excitation/inhibition ratio, perhaps in conjunction with environmental factors that likewise affect neural signaling, would increase the probability of neural dysfunction.

As described earlier, there are several genes/alleles that are implicated in causing autism. However, we suggest that not all of the genes/alleles have to be present for expression of the autistic phenotype. Indeed, only a subset might be necessary and that subset might differ from patient to patient. For example, there might be 50 alleles that affect the excitation/inhibition ratio; co-inheritance of five alleles might be sufficient to give the autistic phenotype, but it would not necessarily be the same five-allele subset in each patient.

In summary, increasing the ratio of excitation/inhibition in key neural systems, either genetically or epigenetically, is postulated to be the common pathway for causing autism. This hypothesis can be useful for considering the genetic and epigenetic mechanisms that contribute to autism, for generating animal models that may mimic aspects this disorder and for considering potential therapies.

Therapeutic implications of the excitation/inhibition imbalance model of autism origin

While the models postulated in this review are theoretical, it may be worth considering potential therapies for alleviating the effect of an increased ratio of excitation/inhibition, and that potentially reduce cortical ‘noise’. Assuming that a rational therapy based on known molecular defects is not feasible, one could consider treating autistic children with agents that reduce neural excitation. Treatments may only be effective if begun at a young age, before secondary neuropathological effects accumulate. Many pharmacological agents that reduce neural excitation are currently available and include benzodiazapines and anticonvulsants. There are increasing reports that anticonvulsants can be helpful in ameliorating some behaviors associated with autism (Belsito *et al.* 2001; DiMartino & Tuchman 2001; Rugino & Samsock. 2002).

There is much less published about the efficacy of benzodia-zapines in treating autism, although there is concern that they can lead to dyscontrol (Marrosu *et al.* 1987). Benzodiazapines are agonists of GABA A receptors, and have prominent sedating, anxiolytic and addicting properties. Distinct GABA A receptors are implicated in mediating the sedating and anxiolytic effects of GABA and benzodiazapines. Ongoing efforts are aimed at identifying novel benzodiazapines that can selectively activate distinct GABA A receptors, and therefore affect specific symptoms (Mohler *et al.* 2002). Thus, while

medications such as diazepam may not have an optimal side-effect profile for treating children, perhaps newer medications may be worth considering as treatment options.

Intensive perceptual and movement training therapies could also be expected to improve functional signal-to-noise conditions in a 'noisy' forebrain. Therapies designed to differentiate representations of intrasyllabic aspects of speech inputs, for example, have now been successfully applied to more than 350 000 language impaired children (Merzenich *et al.* 1998a,b), including several thousand autistics (Merzenich *et al.* 1999). Recent electrophysiological and imaging studies have directly demonstrated that language-impaired children have more salient representations of speech as a result of such training (Hayes *et al.* 2003; Nagarajan *et al.* 2000 and see Nagarajan *et al.* 1999). They also show that highly abnormal distributed response patterns revealed by fMRI imaging in language and reading behaviors are substantially normalized by such training (Temple *et al.* 2000, 2003).

If such training could be applied in the young, at-risk child, it could have significant prophylactic value for diminishing the probability of autism onset. That would apply if the differentiation of the auditory/aural speech system could be advanced by the exposure to, and the training of the infant to highly emphasized speech inputs. That possibility has been evaluated in the rat model. In this model noise has been used to degrade the auditory cortex, with the rats subsequently successfully trained to re-differentiate it (Bao *et al.* 2003b). While such studies are hopeful, we still do not know how the specific genetic faults might or might not allow or forestall intensive training-based re-normalization. At the same time, it is clear that the more specifically we can define the genetic contributions that result in the complex expression of behavioral abnormalities that we identify as autism, the more sharply we can shape ameliorating or potentially remedial brain plasticity processes by behavior and by pharmacological manipulation in ways that might alter this remarkable pathological course of brain development.

Acknowledgments

This work was supported by the research grants to JLRR from: Nina Ireland, the MIND Foundation and NIMH K02 MH01046-01; to MMM from the MIND and Cure Autism Now foundations. We also thank Susan Yu for her help preparing the manuscript.

References

Anderson SA, Eisenstat DD, Shi L & Rubenstein JL (1997) Interneuron migration from basal forebrain to neocortex: dependence on Dlx genes. Science 278, 474–476. [PubMed: 9334308]

Astrinidis A, Cash TP, Hunter DS, Walker CL, Chernoff J & Henske EP (2002) Tuberin, the tuberous sclerosis complex 2 tumor suppressor gene product, regulates Rho activation, cell adhesion and migration. Oncogene 21, 8470–8476. [PubMed: 12466966]

Aylward EH, Minshew NJ, Field K, Sparks BF & Singh N (2002) Effects of age on brain Volume and head circumference in autism. Neurology 23, 175–183.

Bao S, Chan VT & Merzenich MM (2001) Cortical remodeling induced by dopamine-mediated ventral; tegmental activity. Nature 412, 79–83. [PubMed: 11452310]

Bao S, Chan VT, Zhang LI & Merzenich MM (2003) Suppression of cortical representation through backward conditioning. PNAS 100, 1405–1408. [PubMed: 12538854]

Bao S, Zhang L & Merzenich MM Progressive functional degradation, and subsequent refinement of adult auditory cortex by acoustic stimulation paired with basal forebrain stimulation. J Neurosci in press.

Belsito KM, Law PA, Kirk KS, Landa RJ & Zimmerman AW Lamotrigine therapy for autistic disorder: a randomized, double-blind, placebo-controlled trial. J Autism Dev Disord 31, 175–181. [PubMed: 11450816]

Ben-Ari Y (2002) Excitatory actions of gaba during development: the nature of the nurture. Nat Rev Neurosci 3, 728–739. [PubMed: 12209121]

Bennetto L (1996) Intact and impaired memory functions in autism. Child Dev 67, 1816–1835. [PubMed: 8890510]

Beyer KS, Blasi F, Bacchelli E, Klauck SM, Maestrini E & Poustka A (2002) Mutation analysis of the coding sequence of the MECP2 gene in infantile autism. Hum Genet 111, 305–309. [PubMed: 12384770]

Bolton PF, Park RJ, Higgins JN, Griffiths PD & Pickles A (2002) Neuro-epileptic determinants of autism spectrum dis-orders in tuberous sclerosis complex. Brain 125, 1247–1255. [PubMed: 12023313]

Bonasera SJ &Tecott LH. (2000) Mouse models of serotonin receptor function: toward a genetic dissection of serotonin systems. Pharmacol Ther 88, 133–142. [PubMed: 11150593]

Buxbaum JD, Silverman JM, Smith CJ, Greenberg DA, Kilifarski M, Reichert J, Cook EH Jr,, Fang Y., Song CY. & Vitale R. (2002) Association between a GABRB3 polymorphism and autism. Mol Psychiatry 7, 311–316. [PubMed: 11920158]

Carper RA, Moses P, Tigue ZD & Courchesne E (2002) Cerebral lobes in autism: early hyperplasia and abnormal age effects. Neuroimage 16, 1038–1051. [PubMed: 12202091]

Casanova MF, Buxhoeveden DP, Switala AE & Roy E (2002) Minicolumnar pathology in autism. Neurology 58, 428–432. [PubMed: 11839843]

Castellvi-Bel S & Mila M (2001) Genes responsible for non-specific mental retardation. Mol Genet Metab 72, 104–108. [PubMed: 11161835]

Chang EF & Merzenich MM (2003) Environmental noise retards auditory cortical development. Science 300, 498–502. [PubMed: 12702879]

Cook EH Jr, Courchesne R., Lord C., Cox., Yan S., Lincoln A, Haas R, Courchesne E & Leventhal BL. (1997) Evidence of linkage between the serotonin transporter and autistic disorder. Mol Psychiatry 2, 247–250. [PubMed: 9152989]

Darnell JC, Jensen KB, Jin P, Brown V, Warren ST & Darnell RB (2001) Fragile X mental retardation protein targets G quartet mRNAs important for neuronal function. Cell 16,489–499.

Davis M (1989) Neural systems involved in fear-potentiated startle. Ann N Y Acad Sci 563, 165–183. [PubMed: 2570545]

Davis M & Whalen PJ (2001) The amygdala: vigilance and emotion. Mol Psychiatry 6, 12–34.

DeFelipe J, Hendry SH, Hashikawa T, Molinari M & Jones EG (1990) A microcolumnar structure of monkey cerebral cortex revealed by immunocytochemical studies of double bouquet cell axons. Neuroscience 37, 655–673. [PubMed: 1701039]

Di Martino A &Tuchman RF. (2001) Antiepileptic drugs: affective use in autism spectrum disorders. Pediatr Neurol 25, 199–207. [PubMed: 11587873]

Fatemi S, Halt A, Stary J, Kanodia R, Schulz S & Realmuto G (2002) Glutamic acid decarboxylase 65 and 67 kDa proteins are reduced in autistic parietal and cerebellar cortices. Biol Psychiatry 52, 805. [PubMed: 12372652]

Fischer LJ, Seegal RF, Ganey PE, Pessah IN & Kodavanti PR (1998) Symposium overview: toxicity of non-coplanar PCBs. Toxicol Sci 41, 49–61. [PubMed: 9520341]

Folstein SE & Rosen-Sheidley B (2001) Genetics of autism: complex aetiology for a heterogeneous disorder. Nat Rev Genet 2, 943–955. [PubMed: 11733747]

Fombonne E (2002) Epidemiological trends in rates of autism. Mol Psychiatry 7, S4–S6. [PubMed: 12142931]

Gao WJ & Goldman-Rakic PS (2003) Selective modulation of excitatory and inhibitory microcircuits by dopamine. PNAS 100, 2836–2841. [PubMed: 12591942]

Gillberg C & Billstedt E (2000) Autism and Asperger syndrome: coexistence with other clinical disorders. Acta Psychiatr Scand 102, 321–330. [PubMed: 11098802]

Gomot M, Giard MH, Adrien JL, Barthelemy C & Bruneau N (2002) Hypersensitivity to acoustic change in children with autism: electrophysiological evidence of left frontal cortex dysfunctioning. Psychophysiol 39, 577–584.

Hanover JL, Huang ZJ, Tonegawa S & Stryker MP (1999) Brain-derived neurotrophic factor overexpression induces precocious critical period in mouse visual cortex. J Neurosci 15, RC40.

Harkin LA, Bowser DN, Dibbens LM, Singh R, Phillips F, Wallace RH, Richards MC, Williams DA, Mulley JC, Berkovic SF, Scheffer IE & Petrou S (2002) Truncation of the GABA (A) -receptor gamma2 subunit in a family with generalized epilepsy with febrile seizures plus. Am J Hum Genet 70, 530–536. [PubMed: 11748509]

Hayes EA, Warrier CM, Nicol TG, Zecker SG & Kraus N (2003) Neural plasticity following auditory training in children with learning problems. Clin Neurophysiol 114, 673–684. [PubMed: 12686276]

Heidary G, Hampton L, Schanen N, Rivkin M, Darras B, Battey J & Francke U (1998) Exclusion of the gastrin-releasing peptide receptor (GRPR) locus as a candidate gene for Rett syndrome. Am J Med Genet 78, 173–175. [PubMed: 9674911]

Hensch TK, Fagiolini M, Mataga N, Stryker MP, Baekkeskov S & Kash SF (1998) Local GABA circuit control of experience-dependent plasticity in developing visual cortex. Science 282, 1504–1508. [PubMed: 9822384]

Hessl D, Dyer-Friedman J, Glaser B, Wisbeck J, Barajas RG, Taylor A & Reiss AL (2001) The influence of environmental and genetic factors on behavior problems and autistic symptoms in boys and girls with fragile X syndrome. Pediatrics 108, E88.

Huang EJ & Reichardt LF (2003) TRK Receptors: Roles in Neuronal Signal Transduction. Annu RevBiochem [Epub ahead of print] PMID: 12676795.

Hussman JP (2001) Suppressed GABAergic inhibition as a common factor in suspected etiologies of autism. J Autism Dev Disord 2, 247–248.

Ishikawa-Brush Y, Powell JF, Bolton P, Miller AP, Francis F, Willard HF, Lehrach H & Monaco AP (1997) Autism and multiple exostoses associated with an X; 8 translocation occurring within the GRPR gene and 3' to the SDC2 gene. Hum Mol Genet 6, 1241–1250. [PubMed: 9259269]

Jamain S, Betancur C, Quach H, Philippe A, Fellous M, Giros B, Gillberg C, Leboyer M, Bourgeron T & Paris Autism Research International Sibpair (PARIS) Study (2002) Linkage and association between glutamate receptor 6 and autism. Mol Psychiatry 7, 302–310. [PubMed: 11920157]

Jamain S, Quach H, Betancur C, Rastam M, Colineaux C, Gillberg IC, Soderstrom H, Giros B, Leboyer M, Gillberg C, Bourgeron T & Paris Autism Research International Sibpair Study. (2003) Mutations of the X-linked genes encoding neuro-ligins NLGN3 and NLGN4 are associated with autism. Nat Genet 34, 27–29. [PubMed: 12669065]

Jiang Y, Lev-Lehman E, Bressler J, Tsai TF & Beaudet AL (1999) Genetics of Angelman syndrome.Am J Hum Genet 65,1–6. [PubMed: 10364509]

Jones EG (2002) Thalamic organization and function after Cajal. Prog Brain Res 136, 333–357. [PubMed: 12143393]

Jones MB & Szatmari PA (2002) risk-factor model of epistatic interaction, focusing on autism. Am J Med Genet 114, 558–565. [PubMed: 12116194]

Kates WR, Mostofsky SH, Zimmerman AW, Mazzocco MM, Landa R, Warsofsky IS, Kaufmann WE & Reiss AL (1998) Neuroanatomical and neurocognitive differences in a pair of monozygous twins discordant for strictly defined autism. Ann Neurol 43, 782–791. [PubMed: 9629848]

Kemper TL & Bauman M (1998) Neuropathology of infantile autism. J Neuropathol Exp Neurol 57, 645–652. [PubMed: 9690668]

Kilgard MP & Merzenich MM (1998) Cortical map reorganization enabled by nucleus basalis activity. Science 279, 1714–1718. [PubMed: 9497289]

Kim SJ, Cox N, Courchesne R, Lord C, Corsello C, Akshoomoff N, Guter S, Leventhal BL, Courchesne E & Cook EH Jr (2002a) Transmission disequilibrium mapping at the serotonin transporter gene (SLC6A4) region in autistic disorder. Mol Psychiatry 7, 278–288. [PubMed: 11920155]

Kim SJ, Young LJ, Gonen D, Veenstra-Van der Weele J, Courchesne R, Courchesne E, Lord C, Leventhal BL, Cook EH Jr & Insel TR. (2002b) Transmission disequilibrium testing of arginine vasopressin receptor 1a (AVPR1a) poly-morphisms in autism. Mol Psychiatry 7, 503–507. [PubMed: 12082568]

Kitamura K, Yanazawa M, Sugiyama N, Miura H, Iizuka-Kogo A, Kusaka M, Omichi K, Suzuki R, Kato-Fukui Y, Kamiirisa K, Matsuo M, Kamijo S, Kasahara M, Yoshioka H, Ogata T, Fukuda T, Kondo I, Kato M, Dobyns WB, Yokoyama M & Morohashi K (2002) Mutation of ARX causes abnormal development of forebrain and testes in mice and X-linked lissencephaly with abnormal genitalia in humans. Nat Genet 32, 359–369. [PubMed: 12379852]

Klauck SM, Poustka F, Benner A, Lesch KP & Poustka A (1997) Serotonin transporter (5-HTT) gene variants associated with autism? Hum Mol Genet 6, 2233–2238. [PubMed: 9361027]

Klin A, Jones W, Schultz R, Volkmar F & Cohen D (2002) Defining and quantifying the social phenotype in autism. Am J Psychiatry 159, 895–908. [PubMed: 12042174]

Kootz JP, Marinelli B & Cohen DJ (1981) Sensory receptor sensitivity in autistic children: response times to proximal and distal stimulation. Arch General Psychiatry 38, 271–273.

Lainhart JE & Piven J (1995) Diagnosis, treatment and neurobiology of autism in children. Curr Opin Pediatr 7, 392–400. [PubMed: 7581642]

Le Couteur A, Bailey A, Goode S, Pickles A, Robertson S, Gottesma I & Rutter M (1996) A broader phenotype of autism: The clinical spectrum in twins. J Child Psychol Psychiat 37, 785–801. [PubMed: 8923222]

LeDoux JE (1993) Emotional memory: in search of systems and synapses. Ann N Y Acad Sci 702, 149–157. [PubMed: 8109874]

LeDoux JE (2000) Emotion circuits in the brain. Annu Rev Neurosci 23, 155–184. [PubMed: 10845062]

Lee M, Martin-Ruiz C, Graham A, Court J, Jaros E, Perry R, Iversen P, Bauman M & Perry E (2002) Nicotinic receptor abnormalities in the cerebellar cortex in autism. Brain 125, 1483–1495. [PubMed: 12076999]

Lewine JD, Andrews R, Chez M, Patil AA, Devinsky O, Smith M, Kanner A, Davis JT, Funke M, Jones G, Chong B, Provencal S, Weisend M, Lee RR & Orrison WW Jr (1999) Magnetoencephalographic patterns of epileptiform activity in children with regressive autism spectrum disorders. Pediatrics 104, 405–418. [PubMed: 10469763]

Lewis DA, Melchitzky DS, Sesack SR, Whitehead RE, Auh S & Sampson A (2001) Dopamine transporter immuno-reactivity in monkey cerebral cortex: regional, laminar, and ultra-structural localization. J Comp Neurol 432, 119–136. [PubMed: 11241381]

Liu Y, Ford B, Mann MA & Fischbach GD (2002) Neuregulins increase alpha7 nicotinic acetylcholine receptors and enhance excitatory synaptic transmission in GABAergic interneurons of the hippocampus. J Neurosci 21, 5660–5669.

Lucidi-Phillipi CA & Gage FH (1993) The neurotrophic hypothesis and the cholinergic basal forebrain projection. Prog Brain Res 98, 241–249. [PubMed: 8248513]

Lund JS, Angelucci A & Bressloff PC (2003) Anatomical substrates for functional columns in macaque monkey primary visual cortex. Cereb Cortex 13, 15–24. [PubMed: 12466211]

Lund JS & Lewis DA (1993) Local circuit neurons of developing and mature macaque prefrontal cortex: Golgi and immuno-cytochemical characteristics. J Comp Neurol 328, 282–312. [PubMed: 7678612]

Maffei L (2002) Plasticity in the visual system: role of neuro-trophins and electrical activity. Arch Ital Biol 140, 341–346. [PubMed: 12228987]

Mak BC, Takemaru K, Kenerson HL, Moon RT &Yeung RS. (2003) The tuberin-hamartin complex negatively regulates beta-catenin signaling activity. J Biol Chem 278, 5947–5951. [PubMed: 12511557]

Marin O & Rubenstein JL (2001) A long, remarkable journey: tangential migration in the telencephalon. Nat Rev Neurosci 11 780–790.

Marin O & Rubenstein JL (2003) Cell migration in the forebrain. Annu Rev Neurosci 26, 441–483. [PubMed: 12626695]

Marrosu F, Marrosu G, Rachel MG & Biggio G (1987) Paradoxical reactions elicited by diazepam in children with classic autism. Funct Neurol 2, 355–361. [PubMed: 2826308]

Merzenich MM (2001) Cortical plasticity contributing to child development In McClelland J. & Siegler R. (eds), Mechanisms in Cognitive Development. L. Ehrlbaum Assoc., Mahwah, NJ, pp. 67–96.

Merzenich MM & DeCharms RC (1996) Neural representations, experience and change In Llinas R & Churchland P (eds), The Mind-Brain Continuum. MIT Press, Boston, pp. 61–81.

Merzenich MM, Grajski KA, Jenkins WM, Recanzone GH & Peterson B (1991) Functional cortical plasticity. Cortical network origins of representational changes. Cold Spring Harbor Symp Quant Biol 55, 873–887.

Merzenich MM & Jenkins WM (1993) Cortical representation of learned behaviors In Andersen P et al. (eds), Memory Concepts. Elsevier, Amsterdam, pp. 437–453.

Merzenich MM & Jenkins WM (1995) Cortical plasticity, learning and learning dysfunction In Julesz B. & Kovacs I (eds), Maturational Windows and Adult Cortical Plasticity. Addison-Wesley, New York, pp. 247–272.

Merzenich MM, Miller S, Jenkins W, Saunders G, Protopapas A, Peterson B & Tallal P (1998a) Amelioration of the acoustic reception and speech reception deficits underlying language-based learning impairments In Euler CV (ed), Basic Neural Mechanisms in Cognition and Language. Elsevier, Amsterdam, pp. 143–172.

Merzenich MM, Saunders G & Tallal P (1999) Origins of language impairments for - and impacts of training on - pervasively developmentally disabled children In Broman S & Fletcher J (eds), Role of Neuroplasticity in Rare Developmental Disorders. MIT Press, Cambridge, MA, pp. 365–385.

Merzenich MM, Tallal P, Peterson B, Miller SL & Jenkins WM (1998b) Some neurological principles relevant to the origins of - and the cortical plasticity based remediation of - language learning impairments In Grafman J, Cristen Y. (eds), Neuroplasticity: Building a Bridge from the Laboratory to the Clinic. Springer-Verlag, New York, pp. 169–187.

Middleton FA & Strick PL (2000) Basal ganglia and cerebellar loops: motor and cognitive circuits. Brain Res Brain Res Rev 31, 236–250. [PubMed: 10719151]

Mohler H, Fritschy JM & Rudolph U (2002) A new benzodiazepine pharmacology. J Pharmacol Exp Ther 300, 2–8. [PubMed: 11752090]

Mountcastle VB (1997) The columnar organization of the neocortex. Brain 120, 701–722. [PubMed: 9153131]

Nabi R, Zhong H, Serajee FJ & Huq AH (2003) No association between single nucleotide polymorphisms in DLX6 and Piccolo genes at 7q21-q22 and autism. Am J Med Genet 119B, 98–101. [PubMed: 12707945]

Nagarajan SS, Deutsch G, Hande J & Merzenich M (2000) Plasticity of auditory cortical responses in reading impaired children. Neurosci (Abstract) 26, 9.

Nagarajan S, Mahncke H, Salz T, Tallal P, Roberts T & Merzenich MM (1999) Cortical auditory signal processing in poor readers. PNAS 96, 6483–6488. [PubMed: 10339614]

Nelson KB & Bauman ML (2003) Thimerosal and autism? Pediatrics 111, 674–679. [PubMed: 12612255]

Nimchinsky EA, Sabatini BL & Svoboda K (2002) Structure and function of dendritic spines. Annu Rev Physiol 64, 313–353. [PubMed: 11826272]

O'Donnell WT & Warren ST (2002) A decade of molecular studies of fragile X syndrome. Annu Rev Neurosci 25, 315–338. [PubMed: 12052912]

Packard MG & Knowlton BJ (2002) Learning and memory functions of the Basal Ganglia. Annu Rev Neurosci 25, 563–593. [PubMed: 12052921]

Panganiban G & Rubenstein JLR. (2002) Developmental functions of the Distal-less (Dlx) homeobox genes (Review). Development 129, 4371–4386. [PubMed: 12223397]

Perry EK, Lee ML, Martin-Ruiz CM, Court JA, Volsen SG, Merrit J, Folly E, Iversen PE, Bauman ML, Perry RH & Wenk GL (2001) Cholinergic activity in autism: abnormalities in the cerebral cortex and basal forebrain. Am J Psychiatry 158, 1058–1066. [PubMed: 11431227]

Peters A & Sethares C (1997) The organization of double bouquet cells in monkey striate cortex. J Neurocytol 26, 779–797. [PubMed: 9482155]

Plaisted K, Saksida L, Alcantara J & Weisblatt E (2003) Towards an understanding of the mechanisms of weak central coherence effects: experiments in visual configural learning and auditory perception. Proc Roy Soc 358, 375–386.

Powell EM, Cambell DB, Stanwood GD, Davis C, Noebels JL & Levitt P (2003) Genetic disruption of cortical interneuron development causes region and GABA cell type-specfic deficits, epilepsy, and behavioral disfunctin. J Neurosci 2 622–631.

Rapin I & Katzman R (1998) Neurobiology of autism. Ann Neurol 43, 7–14. [PubMed: 9450763]

Recanzone GH, Merzenich MM & Dinse HR (1992) Expansion of the cortical representation of a specific skin field in primary somatosensory cortex by intracortical microstimulation. Cerebral Cortex 2, 181–196. [PubMed: 1511220]

Risch N, Spiker D, Lotspeich L, Nouri N, Hinds D, Hallmayer J, Kalaydjieva L, McCague P, Dimiceli S, Pitts T, Nguyen L, Yang J, Harper C, Thorpe D, Vermeer S,Young H, Hebert J, Lin A, Ferguson J, Chiotti C, Wiese-Slater S, Rogers T, Salmon B, Nicholas P, Myers RM et al. (1999) A genomic screen of autism: evidence for a multi-locus etiology. Am J Hum Genet 65, 493–507. [PubMed: 10417292]

Rogers SJ, Wehner DE & Hagerman R (2001) The behavioral phenotype in fragile X: symptoms of autism in very young children with fragile X syndrome, idiopathic autism, and other developmental disorders. J Dev Behav Pediatr 22, 409–417. [PubMed: 11773805]

Rubenstein JLR & Puelles L Development of the Nervous System In Epstein CJ, Erikson RP & Wynshaw-Boris A (eds), Molecular Basis of Inborn Errors of Development. Oxford University Press. In press.

Rugino TA & Samsock TC (2002) Levetiracetam in autistic children: an open-label study. J Dev Behav Pediatr 23, 225–230. [PubMed: 12177568]

Rutter M (2000) Genetic studies of autism: from the 1970s into the millennium. J Abnorm Child Psychol 28, 3–14. [PubMed: 10772346]

Schuler V, Luscher C, Blanchet C, Klix N, Sansig G, Klebs K, Schmutz M, Heid J, Gentry C, Urban L, Fox A, Spooren W, Jaton AL, Vigouret J, Pozza M, Kelly PH, Mosbacher J, Froestl W, Kaslin E, Korn R, Bischoff S, Kaupmann K, van der Putten H & Bettler B (2001) Epilepsy, hyperalgesia, impaired memory, and loss of pre- and post- synaptic GABA (B) responses in mice lacking GABA (B (1). Neuron 31, 47–58. [PubMed: 11498050]

Schultz W (2002) Getting formal with dopamine and reward. Neuron 36, 241–263. [PubMed: 12383780]

Shahbazian MD & Zoghbi HY (2002) Rett syndrome and MeCP2: linking epigenetics and neuronal function. Am J Hum Genet 71, 1259–1272. [PubMed: 12442230]

Shao Y, Cuccaro ML, Hauser ER, Raiford KL, Menold MM, Wolpert CM, Ravan SA, Elston L, Decena K, Donnelly SL, Abramson RK, Wright HH, DeLong GR, Gilbert JR & Pericak-Vance MA (2003) Fine mapping of autistic disorder to chromosome 15q11-q13 by use of phenotypic subtypes. Am J Hum Genet 72, 539–548. [PubMed: 12567325]

Shumyatsky GP, Tsvetkov E, Malleret G, Vronskaya S, Hatton M, Hampton L, Battey JF, Dulac C, Kandel ER & Bolshakov VY (2002) Identification of a signaling network in lateral nucleus of amygdala important for inhibiting memory specifically related to learned fear. Cell 111, 905–18. [PubMed: 12526815]

Silberberg G, Gupta A & Markram H (2002) Stereotypy in neocortical microcircuits. Trends Neurosci 25, 227–230. [PubMed: 11972952]

Somogyi P, Tamas G, Lujan R & Buhl EH (1998) Salient features of synaptic organisation in the cerebral cortex. Brain Res Brain Res Rev 26, 113–135. [PubMed: 9651498]

Squire LR & Zola SM (1996) Structure and function of declarative and nondeclarative memory systems. Proc Natl Acad Sci USA 93, 13515–13522. [PubMed: 8942965]

Steele PM &Mauk MD. (1999) Inhibitory control of LTP and LTD: stability of synapse strength. J Neurophyslol 81, 1559–1566.

Stuhmer T, Puelles L, Ekker M & Rubenstein JLR (2002a). Expression From A Dlx Gene Enhancer Marks Adult Mouse Cortical GABAergic Neurons. Cerebral Cortex 12, 75–85. [PubMed: 11734534]

Stuhmer T, Anderson SA, Ekker M & Rubenstein JLR (2002b) Ectopic Expression of the Dlx genes induces Glutamic Acid Decarboxylase and Dlx expression. Development 129, 245–252. [PubMed: 11782417]

Tager-Flusberg H (1993) What language reveals about the understanding of other minds in children with autism In Baron-Cohen S, Tager-Flusberg H & Cohen DJ (eds), Understanding Other Minds. Oxford University Press, New York, pp. 138–157.

Tanguay PE (2000) Pervasive developmental disorders: a 10-year review. J Am Acad Child Adolesc Psychiatry 39, 1079–1095. [PubMed: 10986804]

Temple E, Deutsch GK, Poldrack RA, Miller SL, Tallal P, Merzenich MM & Gabrieli JD (2003) Neural deficits in children with dyslexia ameliorated by behavioral remediation: evidence from functional MRI. PNAS 100, 2860–2865. [PubMed: 12604786]

Temple E, Poldrack RA, Protopapas A, Nagarajan S, Salz T, Tallal P, Merzenich MM & Gabrieli JD (2000) Disruption of the neural response to rapid acoustic stimuli in dyslexia: evidence from functional MRI. PNAS 97, 13907–13912. [PubMed: 11095716]

Tordjman S, Gutknecht L, Carlier M, Spitz E, Antoine C, Slama F, Carsalade V, Cohen DJ, Ferrari P, Roubertoux PL & Anderson GM (2001) Role of the serotonin transporter gene in the behavioral expression of autism. Mol Psychiatry 6, 434–439. [PubMed: 11443529]

Turner G, Partington M, Kerr B, Mangelsdorf M & Gecz J (2002) Variable expression of mental retardation, autism, seizures, and dystonic hand movements in two families with an identical ARXgene mutation. Am J Med Genet 112, 405–411. [PubMed: 12376946]

Ullman MT (2001) A neurocognitive perspective on language: The declarative/procedural model. Nature Rev Neuroscience 2, 717–726. [PubMed: 11584309]

VanMeter L, Fein D, Morris R, Waterhouse L & Allen D (1997) Delay versus deviance in autistic social behavior. J Autism Dev Disord 27, 557–569. [PubMed: 9403372]

Veenstra-Vanderweele J, Cook E Jr & Lombroso PJ. (2003) Genetics of childhood disorders: XLVI. Autism, part 5: genetics of autism. J Am Acad Child Adolesc Psychiatry 42, 116–118. [PubMed: 12500084]

Weinberger NM (1993) Learning-induced changes of auditory receptive fields. Curr Opin Neurobiol 3, 570–577. [PubMed: 8219724]

Weinberger NM (1998) Physiological memory in primary auditory cortex: characteristics and mechanisms. Neurobiol Learn Mem 70, 226–251. [PubMed: 9753599]

Wheless JW, Simos PG & Butler IJ (2002) Language dysfunction in epileptic conditions. Semin Pediatr Neurol 9, 218–228. [PubMed: 12350043]

White NM & McDonald RJ (2002) Multiple parallel memory systems in the brain of the rat. Neurobiol Learning Memory 77, 125–184.

Winslow JT & Insel TR (2002) The social deficits of the oxytocin knockout mouse. Neuropeptides 36, 221–229. [PubMed: 12359512]

Yan Z (2002) Regulation of GABAergic inhibition by serotonin signaling in prefrontal cortex: molecular mechanisms and functional implications. Mol Neurobiol 26, 203–216. [PubMed: 12428756]

Yeargin-Allsopp M, Rice C, Karapurkar T, Doernberg N, Boyle C & Murphy C (2003) Prevalence of autism in a US metropolitan area. JAMA 289, 49–55. [PubMed: 12503976]

Yirmiya N, Pilowsky T, Nemanov L, Arbelle S, Feinsilver T, Fried I & Ebstein RP (2001) Evidence for an association with the serotonin transporter promoter region polymorphism and autism. Am J Med Genet 105, 381–386. [PubMed: 11378854]

Young LJ (2001) Oxytocin and vasopressin as candidate genes for psychiatric disorders: Lessons from animal models. Am J Med Genet 105, 53–54. [PubMed: 11424998]

Zhang LI, Bao S & Merzenich MM (2001) Persistent and specific influences of early acoustic environments on primary auditory cortex. Nat Neurosci 4, 1123–1130. [PubMed: 11687817]

Zhang LI, Bao S & Merzenich MM (2002) Disruption of primary auditory cortex by synchronous auditory inputs during a critical period. PNAS 99, 2309–2314. [PubMed: 11842227]

Zhou FM, Wilson CJ & Dani JA (2002) Cholinergic interneuron characteristics and nicotinic properties in the striatum. J Neurobiol 53, 590–605. [PubMed: 12436423]