Neural Dynamics of Autistic Behaviors: Cognitive, Emotional, and Timing Substrates

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Cognitive, Emotional, and Timing Substrates

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Abstract

What brain mechanisms underlie autism and how do they give rise to autistic behavioral symptoms? This article describes a neural model, called the iSTART model, which proposes how cognitive, emotional, timing, and motor processes may interact together to create and perpetuate autistic symptoms. These model processes were originally developed to explain data concerning how the brain controls normal behaviors. The iSTART model shows how autistic behavioral symptoms may arise from prescribed breakdowns in these brain processes.
Introduction

Autism is a complex developmental disorder of pervasively distorted development. Social and communication abilities are especially affected. No single scientific perspective has provided a solid understanding of autism. Molecular genetics, neurochemistry, neuropathology, embryology, neurophysiology, and various different schools of psychological analysis have all contributed significantly to understanding of this disorder, but the most progress has occurred integrating across multidisciplinary contexts.

This article describes a neural network model, called the Imbalanced START (iSTART) model, whose properties clarify possible brain mechanisms of autism and how they give rise to autistic behavioral symptoms. The model includes interactions between cognitive, emotional, timing, and motor mechanisms, and is consistent with convergent data from a variety of disciplines that implicates early onset dysfunction of the cerebellar and limbic systems in autism as an initiator of brain dysfunction. The START (Spectrally Timed Adaptive Resonance Theory) model of normal cognitive-emotional behavior was derived over a period of years to explain many data about the brain mechanisms that control normal cognitive, emotional, timing, and motor behaviors (Grossberg, 1972a, 1972b, 1980, 1982a, 1982b, 1984a, 1984b, 1987, 2000b; Grossberg and Levine, 1987; Grossberg and Merrill, 1992, 1996; Grossberg and Schmajuk, 1987, 1989). The iSTART model clarifies how autism may arise from prescribed breakdowns in these mechanisms. The model hereby provides a unifying interdisciplinary perspective that links normal to autistic behaviors, and embodies a number of predictions about autistic mechanisms which may help to integrate research from diverse fields. The article first reviews data about autism before describing how the model attempts to explain them.

Key Features of Autism

Autism manifests during the first three years of life. The core features of autism (American Psychiatric Association, 1994) are qualitatively impaired socialization, impaired verbal and nonverbal communication, and restricted and repetitive patterns of behavior. Autistic children are impaired in at least one or more of: social interaction; language as used in social communication; and symbolic or imaginative play. Some autistics are mentally retarded, but it would be more precise to describe the disorder as being characterized as deviances of development to a greater extent than of delays.

The first manifestation of autism is often a failure to develop basic imitation skills. Normal children usually show basic imitative behaviors by the end of the first year, and are imitating actions like wiping a table by fifteen months. Not so most autistics. The normal ability to adaptively mirror the actions of others is significantly impaired.

The communication deficits of autism often have onset before spoken language typically begins. Preverbal communication by way of gestures, sounds, and expressions are deficient. An autistic baby is, for example, unlikely to reach his arms in the air to express a desire to be picked up, and is unlikely to point to objects that he wants. Other communication deficits follow and are not mere delays of the normal pattern of development, but are instead wide-ranging and complex disorders (Filipek et al., 2000). Some autistics remain mute; others have agrammatism.
Autistics have deficits in understanding communication within social situations and language pragmatics is often disturbed. Then usual turn-taking of conversational language is disturbed. Inappropriate and idiosyncratic word usages, such as inappropriate generalizations of meaning and odd analogies, are common. A complete phrase from a videotape may always be quoted verbatim instead of a simple “no.” Often, individual words may be used with hyperspecificity and without ever being able to apply the word to a more general concept. Prosody (tone of voice) is commonly “off”, sometimes flat, sometimes sing-song. Echolalia is not uncommon and consists of echoing back what they have heard, sometimes immediately, and sometimes after significant delays. Hyperlexia, often included as an autistic spectrum disorder, is a disorder in which reading skills are extremely precocious but with little comprehension and otherwise with severely deficient verbal language and social skills (Kupperman, Bligh, and Barowski).

Extreme unevenness in cognitive skills is typical among autistics. In general, the cognitive pattern in autistics is notable for having significantly higher performance IQ than verbal IQ. Many autistics have “islands” of normal or superior ability and a few autistics have narrow skill sets that are so vastly superior to normal populations that they are referred to as “savants”. These areas of higher ability often include mathematical and musical skills.

The autistic cognitive style is also notable for its extreme concreteness and hypervigilance. This can present by eighteen months as a lack of imaginary play. A typical toddler will pretend to talk on a toy phone, creating a fantasy of talking to Grandma, or Mommy at work, for example. The autistic toddler will instead attend to specific features of the toy, such as the dial, or the cord. Rather than engaging in imaginary play, he is more likely to either drop the toy quickly or to tenaciously perseverate on one of these specific features. He is unlikely to play the “what if” game: what if this was a real phone; what if my toy bear was real; what if I was Daddy? He is more likely to repetitively spin the wheels of a toy truck than to pretend to build a road. Moreover, a favorite object must be exactly right (i.e., how it was when he first noticed it) and is often played with according to a very specific and exact routine. They learn in a hyperspecific manner, without the typical formation of more abstract categories and the flexible thought that abstraction allows. If an autistic child learns that a particular object in his environment is a “red chair”, he is likely to apply those words to that object only as “redchair”. He is unlikely to appropriately generalize either “red” or “chair” to other objects. At a broader behavioral level there is a “need for sameness” in many situations and behavioral decompensation often occurs in response to even minor variations in routines. It is as if each situation is learned as a complete specific whole and any variation from that standard invalidates any understanding that they have of the situation and what to expect.

Attentional differences are often felt to be a key feature of autism. An early identifiable manifestation of autism is often deficient “shared” or “joint” attention (Filipek et al., 2000). Shared attention, which usually emerges during a normal child’s first year of life, and refers to the ability to follow a significant other’s gaze and thus to share attention in external objects with others, is characteristically deficient among autistics. Autistics also commonly experience difficulties with disengaging or shifting attention and difficulties with splitting attention between different objects.

Autistic individuals are relatively less subject to visual perceptual illusions (Happe, 1996).
Visual illusions depend upon integration of perceptual features for their effect. In one study, standard visual illusions, such as Titchner circles, Muller-Lyer figures, the Kanisza triangle, and the Hering illusion, and control figures, were presented to a group of autistic children, children matched by verbal mental age, and children with moderate nonspecific learning difficulties. Autistics were less likely to make the typical errors of either control group when presented with visual illusions.

Autistics also have a facilitated skill at detecting hidden, embedded figures (Jolliffe and Baron-Cohen, 1997). In this task, a subject is asked to find a shape embedded within a drawing of an object such as a bicycle. Normal controls are impaired by the presence of the perceived object to a greater degree than are autistics. A related finding is found when autistics and normal controls matched for motor ability and training are both asked to copy figures, both “possible” and geometrically “impossible.” There was no significant difference in the speed or accuracy between groups in the copying of “possible” objects, but normal controls took significantly longer to copy “impossible” figures, and there was less of this “impossibility effect” in the autistic group.

Other sensory abnormalities common among autistics include hypersensitivity to, and/or preoccupation with, smells, touch, and noise (Filipek et al., 2000; O'Neill and Jones, 1997). In distinct contrast to the autistic lack of responsiveness to social stimuli, such as facial reactions and praise, strong apparent emotional outbursts often occur in response to such basic sensory stimuli, such as clothing tags, background noise, and odors. An autistic child may respond poorly to many stimuli that other children commonly react to, such as his name being called, but respond excessively to the noise of a vacuum cleaner or traffic sounds. This excessive response can take the form perseverative interest in these aspects of an object (e.g., closely smelling all objects, including people) or reacting with tantrums to low levels of stimulation, such as to background noise.

Autistics are prone to have repetitive stereotypic movements, such as rocking, hand flapping, and head banging. They have poor motor planning and high functioning autistics tend to have macrographia even when controlled for educational level.

Finally, it must be noted that the phrase “autism” is no longer used only for those individuals who fit Kanner’s original description. It currently includes a spectrum of disorders, which differ mainly according to the specific type of social impairment and associated comorbidities (Bonde, 2000; Wing, 1997). Children with Pervasive Developmental Delay (PDD) do not meet all of the criteria for autistic disorder but are considered part of the autistic spectrum of disorders (Filipek et al., 2000).

What Brain Abnormalities Cause Autism?

Autism has been studied in a variety of ways, and convergent lines of analysis have implicated cerebellar and/or limbic system disturbances of likely early prenatal onset. Neocortical abnormalities have been identified as well, but are less consistent findings. These convergent lines of evidence include: cytoarchitectural abnormalities of early embryologic onset found in the
cerebellum and limbic areas; MRI studies documenting gross anatomic differences in the cerebellum of autistics and some inconsistent findings in limbic areas; distortions of function in these areas as evidenced by studies showing disturbed patterns of metabolic activity; the finding in genome screens that many candidate genes for autism having significant expression in cerebellar structures and the awareness that many syndromes that commonly express an autistic phenotype share a pattern of cerebellar developmental distortions; studies which document that teratogens effecting cerebellar development commonly result in an autistic phenotype; and lesion studies of the cerebellum and of the limbic system that reproduce various aspects of autistic behavior.

Cytoarchitectural abnormalities
Cytoarchitectural abnormalities of cerebellar and some limbic structures have been among the most consistent pathologic findings in autism, and have been reviewed elsewhere (Fatemi et al., 2002; Rapin and Katzman, 1998; Trottier, Srivastava, and Walker, 1999). Postmortem studies show cerebellar Purkinje neuron loss in autistic cases. Neuronal size and branching pattern seem to be effected. The loss of cerebellar neurons was not associated with gliosis, supporting the contention that it is the result of an early embryonic insult. Increased neuron packing density has been noted in the amygdala, hippocampus, septal nuclei and mammillary body; the onset of these lesions is unclear. Diminished dendritic branching has been noted in the hippocampus.

MRI studies
Cerebellar and limbic structures are not only affected at a microscopic level. Multiple MRI studies have documented hypoplasia of the cerebellar vermis in many autistics and hyperplasia in a few (Saitoh and Courchesne, 1998). One study contained a fairly ideal control (Kates et al., 1998). Seven year old monozygotic twin boys, one of whom met the strict definition of autism, and the other of whom was diagnosed as having a less florid autistic spectrum disorder, had brain MRIs compared to each other and age-matched controls. The effected twin had smaller cerebellar vermis lobules VI and VII and decreased caudate, amygdaloidal, and hippocampal volumes. An MRI study of the basal ganglia in thirty-five high functioning autistics documented caudate enlargement (proportional to increased total brain volume).

Other brain regions have had some, albeit less consistent, MRI findings. The parietal cortex has volume loss in some autistics (Courchesne, Press and Yeung-Courchesne, 1994) and, interestingly, frontal lobe volume increase has been noted to vary inversely with cerebellar vermal deficits (Carper and Courchesne, 2000). Studies of the amygdala and hippocampus have been inconsistent, but one study of ten high functioning autistic individuals documented increased amygdala volume. The same study noted smaller hippocampal volumes among autistics (Aylward et al., 1999; Howard et al., 2000).

Metabolic studies
The cytoarchitectural and MRI studies document consistent physical differences in the cerebellum and in some limbic structures in autistics of embryologic onset, but do not document that these structures function differently in that population. One way of gauging the physiologic

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function of these areas is by imaging of metabolic activity. These studies document decreased and distorted metabolic activity of the cerebellum and limbic system in autistics.

Magnetic resonance spectroscopy documented decreased cerebellar N-acetyl-aspartate (NAA) in the cerebellums of nine autistic children compared to five sibling controls in one study (Chugani et al., 1999). Twenty-seven autistics compared to ten normal controls, with a similar protocol, were found to have decreased NAA in both the cerebellum and the hippocampal-amygdala region (Otsuka et al., 1999). NAA is an indicator of neuronal function and maturity.

Asymmetric alterations of serotonin synthesis along the dentothalamocortical pathway were found in autistic boys with positron emission tomography (Chugani et al., 1997): autistic boys were found to have unilaterally elevated serotonin synthesis in the cerebellar dentate nucleus with contralateral increase of serotonin synthesis in the contralateral thalamus and frontal cortex. This finding was the right cerebellar increase/left thalamus and frontal cortex decrease in five of seven cases, and reversed in the remaining two.

Cerebellar dentate neurons receive input from Purkinje cells and are the main efferent from the cerebellum to the contralateral thalamus, which in turn projects to frontal cortical targets, including prefrontal cortex, Broca’s area, and the motor cortex. In fetal development, serotonin contributes to neuronal development, possibly effecting synaptogenesis and neuronal differentiation; later it is a critical transmitter in the function of these circuit (Kwong et al., 2000).

Genetic studies

Genetic factors clearly play a significant but complex role in autism. Multiple gene loci have been associated with autism and more are likely to discovered as newer genomic techniques are applied (Hoh and Ott, 2000; Lamb et al., 2000; Veenstra-Vanderweele, 2003).

At this point many genes have been associated with a greater vulnerability to autism, but no single gene seems to be causative. The nature of gene-gene and gene-environment interactions is an area of active research.

It is of note, however, that several genetic syndromes associated autism have either demonstrated cerebellar anomalies, or known expression of their gene products in the cerebellum in early development, and that genes associated with autism have products expressed in the cerebellum. While cerebellar expression of these autism-associated genes is a common thread, in no case is the cerebellum the only location in which they are expressed.

Fragile X syndrome is frequently associated with autism (7%) and very commonly with language dysfunction. Cerebellar Purkinje cells show a high expression of fragile X mental retardation protein (FMRP) (Oostra, 1996). Most other forms of mental retardation are associated with fewer cortical neurons but Fragile X, like autism, often has a greater number. MRI studies of Fragile X brains document cerebellar vermal hypoplasia. A small post-mortem study documented focal cerebellar Purkinje cell loss (Sabaratnam, 2000).
Tuberous Sclerosis Complex (TSC) is also associated with autism. Autism and PDD are common in TSC: 25% and 40 – 45% respectively (Smalley, 1998). Two genetic loci are responsible for TSC: TSC1 (hamartin) and TSC2 (tuberin); of these TSC2 has been found to predominately localize to the cerebellum and spinal cord and particularly to the perinuclear region of the Purkinje cell (Geist et al., 1996).

HOXA1 is another gene locus associated with autism. HOXA1 knockout mice have strikingly similar deficits to brainstem anomalies seen in some autistics and variant HOXA1 alleles in have been found in some human autistics (Rodier, 2000).

Genome screens of autistic populations have identified associated cytogenetic abnormalities in several locations. The genomic approach presumes that genes in these regions are candidates for a genetic susceptibility to autism. Duplications of material from 15q region from the maternal chromosome, and submicroscopic genomic deletions in the same area, are among the most common of the chromosomal anomalies identified with autism so far. Not all studies have documented anomalies in this area, however. Among the candidate genes in this area are the genes which code for GABA-A receptor subunits. Cerebellar Purkinje cells are GABAnergic (Trottier et al., 1999).

Abnormal expression of mRNA for glutamate receptor AMPA 1, excitatory amino acid transporter 1, and of other members of the glutamate family of genes were identified on a postmortem cerebellar study (Purcell et al., 2001). The same study found decreased density of AMPA-type glutamate receptor density.

Teratogens

Genes are not alone in affecting the embryologic development of brain structures. Environmental factors also alter the course of development. Teratogens that influence the early embryologic development of hindbrain structures also provide evidence for the significance of an early disruption in normal cerebellar development. Teratogens known to affect the early embryologic development of structures derived from the basal plate of the rhombencephalon, such as the early-forming cranial motor nuclei and the cerebellum, are associated with autistic spectrum disorders.

Children exposed prenatally to thalidomide, at and only at 20 to 24 days after conception (when rhombencephalon basal plate derivatives including cranial motor nuclei V, XII, V, and III develop and immediately preceding the period of greatest production of cerebellar Purkinje cells), experienced a high incidence of autism (4 – 5%) and have documented brain stem anomalies (Rodier et al., 1996).

Valproate embryopathy also has a common association with autism and an animal model for this damage has been developed. Rats exposed to valproate on embryonic day 12.5 had brain stem anomalies similar to those found in human thalidomide cases and had significantly fewer cerebellar vermal Purkinje cells. Behavioral studies were not done (Ingram et al., 2000; Rodier et al., 1996).
Lesion Studies

The teratogen data is, in a sense, a means of demonstrating that lesions of pertinent structures result in autistic behaviors. It is, however, limited in that the lesions that result from teratogens are not clearly isolated from any other damage. This issue is addressed by studies of isolated damage in both human and animal models. Features of autism result from isolated lesions to a variety of cerebellar and limbic structures during development.

Amygdala lesions result in deficits of the identification of the facial expression of fear, of perception of eye gaze direction, and of facial recognition, similar to those measured in high functioning autistics (Howard et al., 2000).

Isolated bilateral hippocampal sclerosis of early childhood onset results in behaviors and development very similar to autism, (DeLong and Heinz, 1997) with failure of language learning and learning of complex social and adaptive skills in general.

Children who had surgical resection of posterior fossa tumors were documented to have impairments in executive function, including planning and sequencing, and in visual-spatial function, expressive language, verbal memory and modulation of affect (Levisohn et al., 2000). Vermal lesions were most associated with affective dysregulation, including blunted affect, and disinhibited and inappropriate behaviors. Another group studied were further stratified by lesion location. These children manifested linguistic deficits, visuospatial deficits, or autistic-like behaviors contingent upon the lesion location. Children who had removal of right cerebellar tumors manifested difficulties with auditory sequential memory and language processing. Those who had resections of left cerebellar tumors presented with difficulties on spatial and visual sequential memory. Children who had vermal tumors removed had either: an immediate mutism evolving into language disorders; or behavior disorders “reminiscent of autism” (Riva and Giorgi, 2000).

Animal studies also confirm autistic-like behaviors after early cerebellar vermal lesions (Bobee, 2000). Rats who were subjected to midline lesions of the cerebellum on day ten were studied as adults. They showed perseverative behaviors and were less affected by environmental distractors.

Behavioral Studies

Abnormalities of autistic performance occur during classical conditioning of the eye-blink response (Sears et al., 1994). The classically conditioned eye-blink response is one of the best studied example of associative learning in vertebrates and multiple studies have established that cerebellar and limbic areas are critical for this sort of learning in both animals and humans. The hippocampus also plays an important role in this response. Compared to controls, autistic subjects learned the task more quickly, but performed short-latency, high-amplitude responses. These findings are consistent with aberrant cerebellar modulation of the timing and amplitude of the expression of learned motor representations to sensory inputs in autism.

Not all eye movement data are consistent with cerebellar dysfunction, however (Minshew et al.,
Some data from a study of autistic reflexive and volitional saccades are more consistent with prefrontal effects. No difference was found between the autistic and the control group on measures of saccade metrics, while there was an increase in response suppression errors on both antisaccade and oculomotor delayed-response tasks.

Other studies document motor planning deficiencies in autistics, which may be consistent with cerebellar dysfunction. High functioning autistics have macrographia in a study that compared them to controls matched by age and IQ, and when covaried with educational level (Beversdorf et al., 2001). Another study (Rinehart et al., 2001) used a simple motor reprogramming task to reveal atypical movement preparation characterized by "a lack of anticipation" in autistics.

One study showed that visual attention deficits, including slowed covert orienting of attention, are similar in both adult autistics and other models of cerebellar damage (Townsend et al., 1999). Functional MRI studies show cerebellar activation in tasks of visual selective attention and attention shifting devoid of motor components. Patients with cerebellar damage from strokes or from tumor are slow to orient attention in space, and approach normal performance only after a 800-1200 msec delay. This slowed orientation of attention is independent of gaze shifting effects. Autistic performance was comparable to patients with cerebellar damage from stroke or tumor. Similar slowed orienting of visual attention has been documented in children with autism (Harris et al., 1999) and is correlated with the degree of cerebellar hypoplasia.

Work in motor learning paradigms has shown how the cerebellum helps coordinate the timing and amplitude of neuronal population responses. Cerebellar-mediated adaptive timing fine-tunes the timing and amplitude of neuron population responses in such a way as to allow motor responses to become paired with sensory representations across various time spans according to their motivational importance. The classically conditioned eye-blink response serves as a model. A sensory stimulus, such as a light or tone, is previously paired with puff of air after some interval. This stimulus results in a neuronal population response, which is a cortical sensory representation. The exact timing and amplitude of a different neuronal population response, the motor representation, which results in the eyeblink response, is modulated by cerebellar mechanisms.

Most often the classically conditioned response models the learning of associations between activities of neuronal populations in the sensory cortex and the motor cortex. The timing functions of the cerebellum appear may also be involved in processing representations in other brain locations as well. These representations may be part of "where" stream processing but may not be involved, directly, in voluntary motor functions. One documented example of a cerebellar mediation of a response other than within a motor cortex neuronal population is rabbit conditioned bradycardia (Ghelarducci and Sebastini, 1999). In this model vermal cerebellar lesions resulted in an increase in the amplitude of the conditioned bradycardic response when compared to controls.

Testing the hypothesis of cerebellar adaptive timing of nonmotoric coordinates requires observing and measuring some surrogate for sensory and higher-order representations. The best current measure of these activities may be event related potentials (ERPs) and magnetoencephalograms (MEGs). ERPs measure the timing of the electrical activity in multiple
populations of neurons in response to various stimuli by means of scalp recorded EEGs. MEGs are the magnetic equivalent to an ERP and measure the magnetic field induced by the electrical response. ERP and MEG to date are supportive of such an adaptive timing hypothesis. Two sets of ERP data investigate effects on the ERP P300, which is well studied and correlates with stimulus probability and task relevance.

Patients with idiopathic late-onset cerebellar degeneration show timing abnormalities of P300 and have demonstrated impairments in a variety of nonmotoric functions. In the study (Tachibana et al., 1999), 15 patients were compared to 10 age matched controls. General cognitive function was normal in both groups. There was no difference between the latency timing for the N100 (early sensory processing) but there was a significant latency delay of P300 compared to age-matched controls. This timing difference of a sensory processing ERP was not correlated with motor disability, which suggested an independent effect. The generators of P300 are believed to include multiple cortical sites including the frontal lobe, the temporoparietal junction, and the medial temporal lobe, and a variety of subcortical areas. Patients in this study were felt to have isolated cerebellar degeneration and the P300 effects were felt to be secondary to disruption of cerebellar effects.

ERP work in autistics also documents timing and amplitude anomalies of ERPs. In autistics, N100 does not have the normal increase with stimulus intensity (Brunceau et al., 1999). N100 amplitude increases bilaterally with increasing stimulus intensity in controls. Autistics fail to demonstrate this intensity effect on the left side while preserving it on the right. Also, P300 amplitude is smaller in autistics than in controls; specifically P300 is smaller for phonetic stimuli at left hemisphere recording sites and not at right hemisphere sites, while no differences were found for musical chord stimuli at any site (Dawson et al., 1988). This result is consistent with the concept that adaptive timing for non-language auditory input (musical chord stimuli) is intact, whereas the topography of a language-related auditory stimuli (phonetic stimuli) is impaired.

Finally, a case report of MEG data in an autistic man further documents timing and amplitude differences (Hurley et al., 2000). This case report looked at the MEG at 100 ms latency in an autistic 33-year-old male. The stimuli were tones presented at various interstimulus intervals (ISIs). The right hemisphere demonstrated the normal progressive decrease in the response as ISI decreased. The left hemisphere response demonstrated abnormality of its amplitude response with the shortest ISI triggering the largest response and abnormal waveform morphology at longer ISIs.

iSTART: A Neural Model of How Autistic Symptoms Can Arise

The data above summarize the case for characterizing autism as resulting from early onset dysfunction in parts of the limbic and/or cerebellar systems. The remainder of this article reviews models of how the brain gives rise to normal behaviors, and shows how these models can generate formal symptoms that resemble autistic behaviors when their mechanisms are imbalanced and/or lesioned in prescribed ways. This approach suggests how autism may arise from mechanisms for the control of normal behaviors, and makes predictions about how malfunctions of these mechanisms can give rise to autistic behaviors.
Figure 1. (a) The simplest CogEM model: Three types of interacting representations (sensory, drive, and motor) that control three types of learning (conditioned reinforcer, incentive motivational, and motor) may be used to explain many learning data. Sensory representations temporarily store internal representations of sensory events. Drive representations are sites where reinforcing and homeostatic, or drive, cues converge to activate emotional responses. Motor representations control the read-out of actions. Conditioned reinforcer learning (CRL) enables sensory events to activate emotional reactions at drive representations. Incentive motivational learning (IML) enables emotions to generate a motivational set that biases the system to process information consistent with that emotion. Motor learning allows sensory and cognitive representations to generate actions. In order to work well, a sensory representation must have (at least) two successive stages, so that sensory events cannot release actions that are motivationally inappropriate. These stages are interpreted as sensory cortex and prefrontal cortex representations of the sensory event, respectively. The prefrontal stage requires motivational support from a drive representation to be fully effective. The amygdala is interpreted as one important part of a drive representation. Amygdala inputs to prefrontal cortex cause feedback to sensory cortex that selectively amplifies and focuses attention upon motivationally relevant sensory events. (b) When a drive representation like the amygdala gets depressed (gray box), diminished activation of its outputs in response to sensory events depresses motivational inputs to the prefrontal cortex in response to emotionally important events, and hereby attenuates motivationally-appropriate signals to and from the prefrontal cortex (dashed lines). As a result, motivationally irrelevant events are not attentionally suppressed, and prefrontally-mediated plans and actions are insufficiently activated.
Cognitive-Emotional Learning and Affective Depression

The models in question explain aspects of cognitive information processing and cognitive-emotional interactions, and how they control adaptively timed motor responses. A key theme in these models is that constraints on brain development and learning may greatly constrain the kinds of information processing that govern both normal and abnormal behaviors. One of these models is called a CogEM model, because it joins together Cognitive, Emotional, and Motor processes (Grossberg, 1982, 1984b, 2000b); see Figure 1a. The CogEM model tries to explain how emotional centers of the brain, such as the amygdala, interact with sensory and prefrontal cortices—notably ventral, or orbital, prefrontal cortex—to generate affective states, attend to motivationally salient sensory events, and elicit motivated behaviors. Activating the feedback loop between cognitive and emotional centers is predicted to generate a cognitive-emotional resonance that can support conscious awareness.

When such emotional centers become depressed in a particular way, formal analogs of schizophrenic negative symptoms emerge in the model (Grossberg, 1984a, 2000b); see Figure 1b. One component of our explanation of autism includes the possibility of emotional depression, albeit a type of depression that may not occur in many schizophrenics.

![Gated dipole opponent processes exhibit an Inverted-U behavioral response as a function of arousal level, with underaroused and overaroused depressive syndromes occurring at the two ends of the Inverted-U. See text for details. [Reprinted with permission from Grossberg (2000).]](image)
Emotional depression arises in the model from the fact that its emotional centers are organized into opponent affective processes, such as fear and relief. The response amplitude and sensitivity to external and internal inputs of these opponent-processing emotional circuits, which are called *gated dipoles* for reasons described below, are calibrated by an arousal level and chemical transmitters that slowly inactivate, or habituate, in an activity-dependent way. These opponent processes exhibit an Inverted-U whereby behavior becomes depressed if the arousal level is chosen too large or too small (Figure 2). Underaroused and overaroused depression can be distinguished clinically by their parametric properties, as briefly noted in Figure 2. Some symptoms of autism are proposed to be due to underaroused depression and the way in which this property interacts with other circuits, notably cognitive and motor circuits, throughout the brain. In particular, if the amygdala experienced underaroused depression, then this deficiency could ramify throughout the brain, as schematically shown in Figure 1b.

**Perceptual and Cognitive Learning, Expectation, Attention, and Fantasy**

A related model suggests how brain mechanisms of perceptual and cognitive learning, attention, and volition work. This Adaptive Resonance theory, or ART, model (Grossberg, 1980, 1999b) proposes an answer to the “stability-plasticity dilemma;” namely, how the brain can learn quickly throughout life without being forced to forget previously learned memories just as quickly. ART proposes how normal learning and memory may be stabilized through the use of learned top-down expectations (Figure 3a). In other words, we are “intentional” beings so that we can learn quickly without suffering catastrophic forgetting. These expectations learn prototypes that are capable of focusing attention upon the combinations of features that comprise conscious perceptual experiences (Figure 3b). When top-down expectations are active in a priming situation in the absence of bottom-up information, they can modulate or sensitize their target cells to respond more effectively to future bottom-up information that matches the prototype. Such expectations cannot, however, fully activate these target cells under most circumstances. When bottom-up inputs do occur, an active top-down expectation selects the cells whose input features are consistent with the active prototype, and suppresses those that are not, thereby generating an attentional focus on the combinations of features that may be expected in that situation. This matching and attentional process can synchronize and amplify the activities of selected cells, leading to a context-sensitive state of “resonance.” Such a matching process has been mathematically proved to be necessary to stabilize the memory of learned representations in response to a complex input environment (e.g., Carpenter and Grossberg, 1991). In order to realize these matching properties, top-down expectations and attention were predicted to be controlled by top-down on-center off-surround networks (Figure 3c). A balance between top-down excitation and inhibition in the on-center of this network leads to a modulatory effect of top-down attention in the on-center on its target cells, even while cells that are in the off-surround may be strongly inhibited. Recent psychophysical and neurophysiological data have supported many of these ART predictions; see Raizada and Grossberg (2003) for a review.
Figure 3. (a) Patterns of activation, or short-term memory (STM), across feature-selective cells at a lower processing level send signals via bottom-up pathways to a higher processing level. Cells at the higher level respond selectively to prescribed combinations of features at the lower level. For example, such cells may represent recognition categories, as in inferotemporal cortex. The selective activation of category cells is achieved by multiplying the bottom-up signals with adaptive weights, or learned long-term memory (LTM) traces at the ends of the bottom-up pathways, before these learning-gated signals activate target category cells. The active category cells, in turn, activate top-down pathways that read-out learned expectations via their own LTM traces. These top-down expectations are matched against the STM pattern that is active at the lower featural level. (b) This matching process confirms, synchronizes, and amplifies STM activities of features that are supported by large LTM traces in an active top-down expectation, and suppresses STM activities of features that do not get top-down support. The size of the hemidisks at the end of the top-down pathways represents the strength of the learned LTM trace that is stored in that pathway. (c) The ART Matching Rule may be realized by a modulatory top-down on-center off-surround network. In particular, bottom-up inputs, such as in pathways 1 and 2, can activate their feature-selective cells when no top-down expectation is active. When a top-down expectation is active whose prototype (the learned on-center with positive pathways) does not include the feature activated by pathway 1, then the top-down off-surround cancels the bottom-up input, thereby suppressing activation of that feature. Since the feature that is activated by pathway 2 is included in the top-down prototype, the top-down excitation and inhibition approximately cancel (typically, with a small positive priming bias), so that activation of the corresponding feature-selective cell is preserved, synchronized, and even amplified. [Reprinted with permission from Grossberg (1999).]
The ART model proposes how the brain has exploited the modulatory property of expectations and attention to enable fantasy, imagery, and planning activities to occur. In particular, phasic volitional signals can shift the balance between excitation and inhibition to favor net excitatory activation when a top-down expectation is active. Such a volitionally-mediated shift enables top-down expectations, in the absence of supportive bottom-up inputs, to cause conscious experiences of imagery and inner speech, and thereby to enable fantasy and planning activities to occur. If, however, these volitional signals become tonically hyperactive during a mental disorder, the top-down expectations can give rise to conscious experiences in the absence of bottom-up inputs and volition. Data about schizophrenic hallucinations have been rationalized by these model properties (Grossberg, 2000a). Related work has predicted the detailed laminar circuits within the visual cortex wherein these top-down expectations and volitional signals may act, and by extension in other sensory and cognitive neocortical areas (Grossberg, 1999a, Grossberg and Raizada, 2000; Raizada and Grossberg, 2003). The ability of top-down expectations to activate internal representations that support imagery, fantasy, and planning activities raises the question of how these expectations are themselves controlled? Below it is suggested how interactions between cognitive-emotional mechanisms from CogEM and of cognitive and perceptual mechanisms of ART help to clarify this issue.

Before turning to these interactions, it is worthwhile to mention another property of ART which seems to be relevant to autism. This property concerns the manner in which the brain controls the contents, particularly the level of abstractness, of learned prototypes. It proposes an answer to the basic question: How is the generality of knowledge controlled? This issue is of particular importance in the light of the concreteness, hypervigilance, and hyperspecificity of autistic behavioral symptoms.

**How is the generality of knowledge controlled? Exemplars, prototypes, and vigilance**

What information is bound together into object or event representations? Some evidence suggests that exemplars, or individual experiences, can be learned and remembered, like those of familiar faces (Medin, Altom, and Murphy, 1984; Medin and Shaffer, 1978; Medin and Smith, 1981). However, this cannot be the final answer to this question, since storing every exemplar, or at least every memory as an exemplar, can lead to a combinatorial explosion of memory storage, to unwieldy memory retrieval, and to an inability to learn general or abstract properties of the world. Others believe that we learn prototypes (Posner and Keele, 1970; Smith and Minda, 1998, 2000; Smith, Murray, and Minda, 1997) that represent more general properties of the world, such as that everyone has a face. But then how do we learn specific episodic memories, and how is the appropriate level of generalization and abstraction determined?

ART provides an answer to this question that overcomes these problems and clarifies how the inferotemporal cortex, interacting with prefrontal cortex and the hippocampal system, learns to recognize and classify objects and events. In particular, one class of thirty human cognitive experiments (the so-called 4/5 category structure) has been used to test conflicting views in the prototype-exemplar debate, but cognitive models have not described how categories are learned (Medin, Altom, and Murphy, 1984; Nosofsky, Kruschke, and McKinley, 1992; Smith and Minda, 2000). Neurophysiology labs have also collected data about monkey cell responses from inferotemporal cortex during recognition tasks (Desimone, 1991; Desimone and Ungerleider, 1996).
1989; Gochin, Miller, Gross, and Gerstein, 1991; Harries and Perrett, 1991; Mishkin, 1978, 1982; Mishkin and Appenzeller, 1987; Perrett, Mistlin, and Chitty, 1987; Schwartz, Desimone, Albright, and Gross, 1983). An ART model has been developed that quantitatively simulates the human data from the 4/5 category structure experiments and clarifies neurophysiological data about how monkeys learn to categorize both prototypes and exemplars (Carpenter and Grossberg, 1991; Ersoy, Carpenter, and Grossberg, 2002; Grossberg, 1980, 1999b).

In this proposal, ART learns prototypes that consist of the critical feature patterns to which an individual attends. The generality of these prototypes is determined by the network's vigilance, which is controlled by environmental feedback or internal volition. Low vigilance permits learning of general categories with abstract prototypes. High vigilance forces memory search to occur when even small mismatches exist between an exemplar and the category that it activates. Given high enough vigilance, a category prototype may encode an individual exemplar. Normal behavior enables vigilance to track the demands of a particular environment, creating specific or general categories as needed to solve environmental problems. In a network whose vigilance is fixed through time at an abnormally high level, the system would be literally "hypervigilant," with the consequence that environmental events would be classified with extreme concreteness and hyperspecificity, because all categories would code highly specific, exemplar-like information.

Given that vigilance control can enable a learning individual to learn either abstract and general, or concrete and specific, information as a particular learning environment demands, it is important to understand how vigilance control is realized under normal circumstances. Vigilance control is part of the process whereby top-down expectations attempt to match incoming bottom-up information, and determines whether a match is deemed good enough to trigger new learning.

**How are learning, attention, memory search, hypervigilance, and hyperspecificity related?**

In particular, a sufficiently bad mismatch between an active top-down expectation and a bottom-up input, say because the input represents an unfamiliar type of experience, can drive a memory search, or hypothesis testing in the following way: A mismatch within the attentional system, where bottom-up and top-down information are matched, is proposed to activate a complementary orienting system, which is thus activated by unexpected and unfamiliar events (Figure 4). ART suggests that this orienting system includes the hippocampal system, which has long been known to be involved in mismatch processing, including the processing of novel events (e.g., Otto and Eichenbaum, 1992; Vinogradova, 2001). Output signals from the orienting system rapidly reset the recognition category that has been reading out the poorly matching top-down expectation (Figure 4b and 4c). The cause of the mismatch is hereby removed, thereby freeing the system to activate a different recognition category (Figure 4d). The reset event hereby triggers a memory search, which automatically leads to the selection of a recognition category that can better match the input. If no such recognition category exists, say because the bottom-up input represents a truly novel experience, then the search process automatically activates an as yet uncommitted population of cells, with which to learn a new recognition category to represent the novel information.
Figure 4. Search for a recognition code within Adaptive Resonance Theory: (a) The input pattern $I$ is instated across the feature detectors at level $F_1$ as a short term memory (STM) activity pattern $X$. Input $I$ also nonspecifically activates the orienting subsystem $A$. STM pattern $X$ is represented by the gray pattern across $F_1$. Pattern $X$ both inhibits $A$ and generates the output pattern $S$. Pattern $S$ is multiplied by long term memory (LTM) traces, or learned adaptive weights. These LTM-gated signals are added at $F_2$ nodes to form the input pattern $T$, which activates the contrast-enhanced STM pattern $Y$ across the recognition categories coded at level $F_2$. (b) Pattern $Y$ generates the top-down output pattern $U$ which is multiplied by top-down LTM traces and added at $F_1$ nodes to form the prototype pattern $V$ that encodes the learned expectation of the active $F_2$ nodes. If $V$ mismatches $I$ at $F_1$, then a new STM activity pattern $X^*$ is generated at $F_1$. $X^*$ is represented by the gray pattern. It includes the features of $I$ that are confirmed by the top-down expectation $V$. Mismatched features are inhibited. The inactivated nodes corresponding to unconfirmed features of $X$ are unhatched. The reduction in total STM activity which occurs when $X$ is transformed into $X^*$ causes a decrease in the total inhibition from $F_1$ to $A$. (c) If inhibition decreases sufficiently, $A$ releases a nonspecific arousal wave to $F_2$, which resets the categorical STM pattern $Y$ at $F_2$. (d) After $Y$ is inhibited, its top-down prototype signal is eliminated, and activity pattern $X$ can be reinstated at $F_1$. Enduring traces of the prior reset lead $X$ to activate a different STM pattern $Y^*$ at $F_2$. If the top-down prototype due to $Y^*$ also mismatches $I$ at $F_1$, then the search for an $F_2$ code continues until a more appropriate $F_2$ representation is selected. Then an attentive resonance develops and learning of the attended data is initiated. [Adapted with permission from Grossberg and Merrill (1996).]

Vigilance is computed within the ART orienting system ($\rho$ in Figure 4). Here, bottom-up excitation from each of the feature-activating pathways in an input pattern $I$ is balanced against inhibition from each of the activated feature-selective cells (Figure 4a). These feature-selective cells reside at the processing level labelled $F_1$ in Figure 4. If a top-down expectation also acts on $F_1$, then only the “matched features” are active there, due to the ART Matching Rule (Figure 4b). That is, the activity pattern $X$ caused solely by the bottom-up inputs $I$ across the feature-selective cells (Figure 4a) is transformed into the pattern $X^*$ across the matched features (Figure 4b), thereby reducing the total inhibition to the orienting system. As a result of this reduction in inhibition, if the mismatch between the bottom-up input pattern and the prototype of the top-down expectation is too great to satisfy the vigilance criterion, then a reset or “novelty” wave is activated (Figure 4c). Such a novelty wave takes the form of a burst of nonspecific activation.
that inhibits the active recognition category at level $F_2$ in Figure 4c, and thereby triggers a search for another, better-matching, recognition category, as in Figure 4d. More specifically, vigilance $\rho$ weighs how similar an input exemplar $I$ must be to a top-down prototype $V$ in order for resonance to occur. Resonance occurs if $\rho$ times the total bottom-up input $I$ to the orienting system is less than the total inhibition from $X^*$ to the orienting system. Then the orienting system is inhibited, and resonance between levels $F_1$ and $F_2$ can develop. If, however, this inequality is reversed, then the orienting system can be activated, leading to a nonspecific novelty wave that can reset the presently active category and initiate search for a better-matching one. Vigilance $\rho$ is thus the relative gain of excitation to inhibition to the orienting system.

ART suggests how this vigilance gain criterion can be adjusted up and down within the orienting system to learn more specific or general information, respectively, in response to predictive failures within each environment. For example, if a predictive failure causes vigilance to increase, then it becomes easier to reset the category which caused the failure and to search for a better representation of the world. ART hereby clarifies how the brain can try to learn an efficient representation of the type of information that is useful in any given situation, which will typically include combinations of both specific and general categories; that is, of both exemplars and more general prototypes. If, however, the vigilance gain criterion gets “stuck” at a high level, then concreteness, hyperspecificity, and hypervigilance will ensue.

Given that persistently high vigilance can cause the learning of concrete and hyperspecific category prototypes, both in the bottom-up filtering and top-down expectation pathways, it follows from the influence of these top-down expectations on attentional focusing that attentional deficits may also be expected in a hypervigilant individual.

Gated Dipole Opponent Processing: Inverted-U, Antagonistic Rebound, and Perseveration

Given this background, let us now consider in somewhat greater detail how opponent emotions, like fear and relief, or hunger and frustration, may be organized in the brain, and how they may become depressed. More generally, it has been proposed that opponent emotions are a special case of a more general brain design for opponent processing, including opponent perceptual features, like red and green colors, or downward and upward motions, or horizontal and vertical orientations. All of these different examples have the property of generating antagonistic rebounds whereby, say, offset of a sustained fearful cue can elicit relief, or removal of a desired food can elicit frustration, or offset of a sustained red image can yield a green aftereffect, or offset of a sustained downward motion of water can yield an upward motion aftereffect, or offset of a sustained image with radial spokes of a wheel can yield an aftereffect of concentric circles, and so on. In all of these cases, there are ON and OFF channels that can experience an antagonist rebound. ART predicts that all of these examples are special cases of a general opponent processing design, and proposes how opponent processing rebounds may play a key role in controlling reset and search, as discussed above, as well as in rebalancing sensory, cognitive, emotional, and motoric representations in response to rapidly changing environmental inputs.
Figure 5. A gated dipole opponent process can generate habituative ON responses and transient OFF rebounds in response to the phasic onset and offset, respectively, of the input \( J \) to its ON channel. Term \( I \) delivers the nonspecific arousal that energizes antagonistic rebounds when the phasic input \( J \) shuts off. Terms \( y_1 \) and \( y_2 \) are the habituative transmitter gates in the ON and OFF channels. They convert the step-on-baseline activity pattern \( x_1 \) into the overshoot-habituation-undershoot-habituation pattern at activity \( x_5 \). Next, the opponent interaction works; namely, the baseline activity \( x_4 \) in the OFF channel due to the arousal \( I \) is subtracted from the habituative ON activity \( x_3 \) to yield \( x_5 \). When activity \( x_5 \) is thresholded to generate an ON output signal, it has an initial overshoot of activation, followed by habituation. When the signs are reversed in the OFF channel, the antagonistic rebound is generated as the mirror-image of the undershoot-habituation part of the ON channel activity at \( x_6 \), when it is thresholded to generate the transient OFF output signal. [Reprinted with permission from Grossberg (2000).]

Such opponent processing circuits exhibit a Golden Mean of optimal behavior at an intermediate arousal level (Grossberg, 1972b, 1980, 1984a, 1984b, 2000b), as noted in Figure 2. For larger or smaller levels of arousal, behavior deteriorates in different ways, thereby giving rise to an Inverted-U in network performance as a function of its arousal level. Both the Inverted-U and the antagonistic rebound are the result of habituative transmitters that exist in the opponent channels, where they multiply, or gate, the signals on their way to the opponent, or competitive, processing stage (Figure 5). Due to the factors that are summarized in Figure 5, when arousal is too small, such an opponent process experiences an elevated response threshold in response to an ON channel input, since there is not enough arousal to support a more normal response threshold. Paradoxically, it also gives rise to hyperexcitable, or larger than normal, responses to increments in the ON input that exceed this elevated threshold. When arousal is too large, the opponent process experiences a low behavioral threshold. Paradoxically, it also gives rise to hypoexcitable, or smaller than normal, responses, in response to increments in the ON input that exceed this reduced threshold. Due to these properties, an increase in arousal can decrease the sensitivity of an underaroused opponent process of this kind, and can bring it into the normal behavioral range.
This opponent processing model is called a “gated dipole” because habituative transmitters “gate,” or multiply, signal processing in each of the channels of the opponent “dipole.” Due to the particular Inverted-U property of a gated dipole, a pharmacological “up” like amphetamine can reduce the supra-threshold hypersensitivity of patients with underaroused circuits, such as certain attention deficit disorder patients.

Another paradoxical property of an underaroused dipole is that an unexpected event, that triggers a nonspecific arousal burst, can cause a paradoxical amplification of activity in the ON channel of the dipole, instead of the more normal antagonistic rebound of activity in the OFF channel. Thus, instead of resetting the dipole in response to the unexpected event, an unexpected event can instead cause the dipole to maintain, even enhance, the activity in its currently active channels. Such an enhancement can result in perseveration, rather than flexible disengagement and shifting of attention. Split attention, shifting attention, and joint attention, which requires a flexible shift of the balance of split attention from an object of social value, such as a mother’s gaze to another object, and back again, may thus all impaired in such an underaroused model and is observed among autistics. If, however, an arousal burst is sufficiently strong, then an unusually intense antagonistic rebound can be caused.

These perseverative and rebound properties emerge through interactions across an entire gated dipole circuit. They cannot be understood just by looking at the pharmacology or neurophysiology of individual cells within the circuit. When their effects ramify throughout the sensory and prefrontal cortices with which they interact, as in Figures 1 and 4, they can lead to a number of clinical symptoms.

When Hypervigilant and Hyperspecific Learning Modulates Underaroused Opponent Circuits

Let us suppose that certain autistics are underaroused, and consider what can happen when this property is combined with their hyperspecific and hypervigilant learning. That is, consider how an underaroused CogEm model interacts with a hypervigilant ART model. In this combined system, various formal symptoms emerge that may be interestingly compared with the behavior of autistic patients. For example, suppose that positive affect or approach motivates an action. Underaroused emotional and sensory dipoles can exhibit a paradoxical enhancement of their ON channel activities in response to a nonspecific arousal burst that is caused by an unexpected event. Such an enhancement could be caused by an arousal burst in response to the high probability that sensory events will mismatch the hyperspecific top-down expectations of an autistic individual. A persistent perseverative behavior can result, which might manifest itself in persistently inspecting the same sensory cue. Suppose, however, that the arousal burst is larger, say due to a larger mismatch of the world with the presently active hyperspecific category. Then an unusually intense, and negative, antagonistic rebound can be caused. Thus, novel experiences can be highly aversive when hyperspecific categories mismatch them and suddenly generate a burst of arousal to the system’s underaroused dipoles. These negative rebounds may be one reason why autistics are prone to tantrums.

When one considers the plight of any individual who combines these two mechanisms, it
becomes clear that one coping strategy is to avoid the type of novelty that will cause unbearable negative rebounds. The other side of the coin is perseveration on small details of the environment. Such a combination of properties may help to understand the autistic "need for sameness" in many situations, and the fact that behavioral decompensation often occurs in response to what a normal person would view as relatively minor variations in routines.

**Resonant Interactions between Sensory Cortices, Amygdala, and Prefrontal Cortex**

The most immediate effect of a depressed response in the outputs of emotion-representing areas is flat affect, although how this is understood must be carefully evaluated, as indicated in the preceding discussion, as to whether a stimulus exceeds the elevated threshold for responsiveness. This defect, in turn, may cause an inability to represent others' beliefs and intentions, in the sense that all mental states that depend upon interpreting one's own emotional state, or the emotional states of others, can be diminished. Such a deficiency can cause major difficulties in social communication. It happens in the CogEM model of Figure 1 because emotionally charged sensory inputs, such as the expressions on other people's faces or their tone of voice, will activate the appropriate part of temporal cortex but may not elicit an appropriate emotional response from the amygdala and related emotion-representing circuits.

A problem with impoverishment of will, as well as with the setting of goals and intentions, can then indirectly arise. This happens in the model because the depressed response of the emotional representations depresses the incentive motivational signals that would normally activate the prefrontal cortex in response to motivationally salient events (Figure 1). As a result, the prefrontal cortex will not be adequately activated, and a hypofrontal condition can emerge. Due to this hypofrontality, the working memory representations and plans that are ordinarily formed within the prefrontal cortex will be degraded, so social goals and plans will not form in a normal fashion.

Given such a hypofrontal response, top-down signals from the prefrontal cortex to the sensory cortices will also be reduced or eliminated (Figure 1). As a result, the sensory representations will not be able to use these top-down signals to organize information processing according to its emotional meaning or motivational goals. Said in another way, motivationally irrelevant information will not be blocked from attention, so it will be able to continually intrude, leading to abnormal distractability.

**Adaptively Timed Learning, Motivation, Attention, and Action**

The above discussion illustrates one aspect of a major conceptual dichotomy that is often used in research about normal and amnesic learning and memory. This dichotomy concerns the distinction between processes that are variously called declarative memory and procedural memory, knowing that and knowing how, memory and habit, or memory with record and memory without record (Bruner, 1969; Mishkin, 1982, 1993; Ryle, 1949; Squire and Cohen, 1984). The amnesic patient HM exemplified this distinction by learning and remembering motor skills like assembly of the Tower of Hanoi without being able to recall having done so (Bruner, 1969; Cohen and Squire, 1980; Mishkin, 1982; Ryle, 1949; Scoville and Milner, 1957; Squire and Cohen, 1984). HM's surgical lesion included extensive parts of the hippocampal formation.
and amygdala. Subsequent animal studies have shown that damage to the hippocampal formation (Ammon's horn, dentate gyrus, subiculum, fornix) and the parahippocampal region (entorhinal, perirhinal, and parahippocampal cortices) can reproduce analogous amnesic symptoms (Mishkin, 1978; Squire and Zola-Morgan, 1991). These results implicate this aggregate hippocampal system in the processes that regulate declarative memory, or "knowing that". Such processes support a competence for learning recognition categories and being able to flexibly access them in a task-specific way (Eichenbaum, Otto, and Cohen, 1994). The discussion of ART above is about declarative memory, particularly about the learning of recognition categories, and involves predicted interactions between cortical and hippocampal representations. Indeed, ART has been used to propose an explanation of various data about medial temporal amnesia (Carpenter and Grossberg, 1993).

A parallel line of research has implicated the cerebellum in the processing of procedural memory, or "knowing how". The cerebellum is an essential circuit for conditioning discrete adaptive responses during eye movements, arm movements, nictitating membrane movements, and jaw movements (Ebner and Bloedel, 1981; Gilbert and Thach, 1977; Ito, 1984; Lisberger, 1988; Optican and Robinson, 1980; Thompson, 1988; Thompson et al., 1984, 1987). Models of cerebellar learning have been developed over the years to help explain these motor conditioning data (Albus, 1971; Fiala, Grossberg, and Bullock, 1996; Fujita, 1982a, 1982b; Grossberg, 1969, 1972b; Grossberg and Kuperstein, 1986; Ito, 1984; Lisberger, 1988; Marr, 1969).

A key property of cerebellar learning is that it is adaptively timed, so that learned responses are emitted at times that are appropriate within the constraints of the learning paradigm. Cognitive-emotional learning is also adaptively timed, so that motivated attention can be maintained on salient goal objects for the necessary amount of time to carry out goal-directed actions. Unless motivated attention and action are both adaptively timed, an animal or human could be condemned to either emit premature goal-oriented responses, or to generate maladaptive orienting and exploratory movements in any situation wherein a goal object does not immediately appear. These two types of adaptively timed learning cooperate in normal learning subjects so that both attention and action can be timed to generate adaptive behavior in each environment.

In particular, during classical conditioning, a conditioned stimulus (CS) such as a tone or light, when paired with an unconditioned stimulus (US) such as a shock, can learn to generate conditioned responses (CR), such as fear or limb withdrawal, that were originally elicited only by the US. Such learning is optimal at a range of positive interstimulus intervals (ISI) between the CS and US that are characteristic of the animal and the task, and is greatly attenuated at zero ISI and long ISIs. Within this range, learned responses are timed to match the statistics of the learning environment (Smith, 1968). Although the amygdala has been identified as a primary site in the expression of emotion and stimulus-reward association (Aggleton, 1993), as summarized in Figure 1, the hippocampal formation has been implicated in the adaptively timed processing of cognitive-emotional interactions. For example, Thompson et al. (1987) distinguished two types of learning that go on during conditioning of the rabbit Nictitating Membrane Response: adaptively timed "conditioned fear" learning linked to the hippocampus and adaptively timed "learning of the discrete adaptive response" within the cerebellum.
Figure 6. The simplest version of the START model. Processing stages $S^{(1)}$ and $S^{(2)}$ play the role of sensory cortex and prefrontal cortex, respectively, in the CogEM model circuit of Figure 1. Stage $D$ is an emotional center, or drive representation, like the amygdala in Figure 1. Stage $M$ schematizes motor output pathways. The feedback pathways $D \rightarrow S^{(2)} \rightarrow S^{(1)}$ from a particular drive representation to sensory representations are capable of focusing attention on motivationally consistent events in the world. The excitatory pathways from $S^{(1)} \rightarrow D$ learn the conditioned reinforcer properties of a sensory cue, such as a CS, whereas the pathways $D \rightarrow S^{(2)}$ learn the incentive motivational properties of cues. Representations in $S^{(2)}$ can fire vigorously only if they receive convergent signals from $S^{(1)}$ and $D$, corresponding to the sensitivity of orbitofrontal cortex to both sensory and reinforcing properties of cues. Then they deliver positive feedback to $S^{(1)}$ and bias the competition among sensory representations to focus attention on their respective features and to attentionally block inhibited features. Prior to conditioning, a CS can be stored at $S^{(1)}$ and can prime $D$ and $S^{(2)}$ without supraliminally firing these representations. After conditioning, the CS can trigger strong conditioned $S^{(1)} \rightarrow D \rightarrow S^{(2)} \rightarrow S^{(1)}$ feedback and rapidly draw attention to itself as it activates the emotional representations and motivational pathways controlled by $D$. Representation $D$ can also inhibit the orienting system $A$ as it focuses attention upon motivationally valued sensory events. Here is one way in which the CogEm and ART models interact: Emotionally salient goal objects can inhibit the orienting system and thus prevent irrelevant distractors from attracting attention when there is an ART mismatch. This inhibition of the orienting system becomes adaptively timed as follows: The sensory representations $S^{(1)}$ send pathways to a spectral timing circuit $T$, assumed to be in the dentate-CA3 region of the hippocampus (see the text), whose adaptive weights $z$ are trained by a Now Print, or teaching signal, $N$. The teaching signal $N$ is transiently activated by changes in the activity of the drive representation $D$ that occur when a reinforcing event activates $D$. After conditioning of $T$ takes place, adaptively timed readout from $T$ can maintain attention on task-relevant cues by amplifying their cortical representations $S^{(2)}$, while inhibiting the orienting system $A$ for an adaptively timed duration. In the figure, the simplest such inhibitory path is depicted, directly from $T$ to $D$ and thereupon to $S^{(1)}$ and $A$. In vivo, a more complex set of pathways exists. [Reprinted with permission from Grossberg and Merrill (1992).]
An extension of the ART model, called the START model (Fiala, Grossberg, and Bullock, 1996; Grossberg and Merrill, 1992, 1996; Grossberg and Schmajuk, 1987), for Spectrally Timed ART model, proposes a unified explanation of why both the hippocampal system and the cerebellum may need adaptive timing circuits for their normal functioning (Figures 6 and 7). The START model proposes that the motivational mechanisms within the amygdala, and related emotion-representing brain areas, by rapidly drawing motivated attention to salient cues, could prematurely release motor commands, via the circuits in Figure 1a, were these commands not adaptively timed by the cerebellum. Figure 7 summarizes a model of how the cerebellum adaptively times its motor commands by using a “spectrum” of learning sites that are each sensitive to a different range of delays between CS and US. A process of “spectrally timed learning” selects that subset of sites whose reaction rates match the ISIs between the CS and the US. Such learning enables the cerebellar output to be released at around the time when the US is expected.

Figure 7. A model of adaptively timed cerebellar learning: A conditioned stimulus (CS), say via the motor output pathway M in Figure 6, activates pathways to both a subcortical cerebellar nucleus and to cerebellar cortex parallel fibers that synapse on Purkinje cells. US-activated climbing fibers provide a teaching signal that also converges upon the parallel fiber/Purkinje cell synapses. This teaching signal causes synapses to become weaker (Long Term Depression) if they are activated by the CS when the US teaching signal becomes active. Synapses whose activity does not overlap the climbing fiber signals become stronger (Long Term Potentiation). Because the Purkinje cells tonically inhibit their subcortical target cells, their adaptively timed inhibition by the CS disinhibits the effect of tonic Purkinje cell outputs on cerebellar nuclear cells. In other words, a timed gate opens and allows the subcortical cells to fire. The climbing fibers also control learning of adaptive gains along subcortical pathways through the nuclear cells. Thus, when the adaptively timed Purkinje cell gate opens, the learned gains can be expressed at the correct time and with the correct amplitude to cause a correctly calibrated motor response. [Reprinted with permission from Grossberg and Merrill (1996).]

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In addition to adaptive timing within the cerebellum, there is a need for adaptively timed, motivated attention to prevent irrelevant novel events from prematurely resetting the thalamocortical representations that actively read out adaptively timed responses. For example, suppose that an animal inspects a food box right after a signal occurs that has regularly predicted food delivery in six seconds. Why is not the mismatch between the learned expectation of food and the percept of no-food treated like a predictive failure? Why, as often occurs when a previously rewarded cue is no longer rewarded, does not such an expected non-occurrence of food trigger reset of attention, frustration, forgetting, and exploratory behavior? Were this to happen, humans and animals would restlessly explore their environments without being able to wait for delayed rewards.

The ART model clarified how attentional and orienting systems interact to categorize information and to develop resonant states if the top-down prototype and the bottom-up input form a sufficiently good match. If the mismatch is too big for resonance to occur, then other things being equal, the orienting subsystem can trigger a search for a better category with which to categorize the information. The hippocampus is proposed to be part of the orienting system that is activated by these mismatches and relays them as novelty-sensitive reset bursts to the thalamocortical system. Such an ART-mediated activation of the orienting system is not, however, sensitive to whether the novel event that caused the mismatch is relevant to the task. The START model clarifies how mismatches may be modulated by task-relevance in an adaptively timed way. In particular, Figure 7 suggests how adaptively timed learning within the dentate-CA3 circuits of the hippocampus (Berger, Berry, and Thompson, 1986) is proposed to inhibit the activation of the orienting system during an interval wherein a valued and predictable goal is being achieved. Indeed, hippocampal dentate-CA3 cell firing commonly reflects the learned delays observed during the rabbit nictitating membrane response. A model simulation of this sort of adaptive timing is summarized in Figure 8. The START model proposes how adaptively timed inhibition of the hippocampal orienting system and adaptively timed disinhibition of cerebellar nuclear cells are coordinated to enable motivated attention to be maintained on a goal while adaptively timed responses are released to obtain the goal.
Figure 8. A computer simulation of spectral timing in the dentate-CA3 circuit. The functions $g_{ij}$ represent differently timed activations in response to a CS input. The CS input turns on at the time marked by the leftmost vertical dashed line. The US turns on at the time marked by the rightmost vertical dashed line. Functions $h_{ij}$ are the functions $g_{ij}$ multiplied by the corresponding adaptive weights that gate, or multiply, each of them. When these adaptively weighted signals are added up, they form a total output signal $R$ that is adaptively timed to peak at around the ISI where the US turns on. Thus, spectral timing is a property of an entire population of adaptively gated pathways. (Reprinted with permission from Grossberg and Merrill (1992).

A great deal of data has been rationalized using these circuits, including data about how lesions of the hippocampal system may lead to symptoms of medial temporal amnesia, and about data from delayed non-match to sample (DNMS) experiments wherein both temporal delays and novelty-sensitive recognition processes are involved (Gaffan, 1974; Mishkin and Delacour, 1975). In summary, as shown in Figures 6 and 7, the START model enables three key properties to simultaneously obtain:

1. **Fast Motivated Attention.** Rapid focusing of attention on motivationally salient cues occurs from regions like the amygdala to prefrontal cortex (the $D \to s^{(2)}$ pathway in Figure 6). Without further processing, fast activation of the CS-activated $s^{(2)}$ sensory representations could prematurely release motor behaviors.

2. **Adaptively Timed Responding.** Adaptively timed read-out of responses via cerebellar circuits, as in Figure 7, enables learned responses to be released at task-appropriate times, despite the fact
that CS cortical representations can be quickly activated by fast motivated attention.

3. **Adaptively Timed Duration of Motivated Attention and Inhibition of Orienting Responses.**

Adaptively timed inhibition of mismatch-sensitive cells in the orienting system of the hippocampus (pathway $T\rightarrow D\rightarrow A$ in Figure 6) prevents the premature reset of active CS representations by potentially distracting irrelevant cues during variable task-specific delays. This inhibition is part of the competition that exists between consummatory and orienting behaviors (Staddon, 1983). This mechanism helps the CS representations to remain active, as does the adaptively timed incentive motivation that enhances their activation in short-term memory. As a result, the CS representations can continue to read-out the sensory signals that will elicit adaptively timed responding.

Our main proposal in the present article is that when various START-like mechanisms become imbalanced in the brain—notably, underaroused depression in the drive representations of regions like the amygdala, hypervigilant learning in the recognition learning circuits of sensory and prefrontal cortices, and a failure of adaptive timing in the hippocampal and cerebellar circuits—then many formal analogs of autistic behavioral symptoms emerge. That is why we call the model the Imbalanced START, or iSTART, model. For example, flexible shifts of attention can be impaired because, if the timing circuit $T$ is damaged, attention may more easily be distracted from goal objects during task-related delays. On the other hand, if the orienting system is also damaged, then flexible reset of attention in response to novel events is impaired, thereby eliminating a key mechanism whereby a distracting event could undermine performance. If the attentional system remains intact, then direct activations of individual recognition codes in response to a familiar event is still possible, and the matching process can partially update short-term memory. However, the network can no longer flexibly search for the proper configuration of targets to attend, especially in the presence of complex spatial layouts that include distracting cues. The lack of timed control over variable delays can thus harm behavior more when it is necessary to shift attention among different sets of cues. Gaffan (1992) has described analogous data from hippocampectomized monkeys.

Adaptive timing, reward, motivational, and cognitive circuits all interact in the iSTART model via feedback. For example, rewards and punishments can feed into the cerebellar-mediated adaptive timing circuits in the hippocampus, and assure that properly timed responses are reinforced. The adaptive timing circuits, in turn, help to assure that responses are released at the proper times to be rewarded during subsequent experiences.

**A Link Between Hypervigilance and Adaptive Timing**

The above discussion considered how various model properties similar to autistic symptoms could arise if cognitive learning was hypervigilant and cognitive-emotional interactions were modulated by underaroused depression of motivational centers. Let us now consider how adding adaptive timing to the discussion can further clarify how autistic symptoms may arise. In particular, early in development, emotional needs may begin to be met by responding with simple motor patterns in response to basic sensory stimuli. Successful development requires the ability to learn to adaptively time new actions to receive the potentially rewarding consequences of these actions. If new adaptively timed movements cannot be learned, then the rewards that
would normally be contingent upon them may not be forthcoming. If behaviors are not adaptively timed, then spurious resets of attention may more readily occur, as noted in item (3) above. Social skills and language development, in particular, are learned through adaptively timed releases of behavior in a process of shared attention and imitation. Under these circumstances, a wide variety of social behaviors do not get a chance to be learned, and attention is instead maintained on lower-order sensory representations and tasks. The above considerations suggest that part of the reason that representations of typical social significance may fail to develop is that they may not get a chance to be strongly reinforced. One can also speculate that the breakdown of the normal cycle of behavior and reward, with a dramatic reduction in behaviorally appropriate rewards, can in itself contribute to a reduction in the arousal of emotional centers, thereby leading to the types of symptoms, reviewed above, that occur when drive representations are underaroused.

The frequent spurious orienting resets that can occur due to dysfunctional adaptive timing may also contribute to hyperspecific learning. If sensory inputs are prematurely reset, then this can interfere with the normal cycle of adaptively timed shifting of attention to the expected consequences of motor actions. Such a learner could not easily test whether variations on a sensory event predict similar consequences, so abstract prototype formation may not have a chance to occur. If drive satisfaction requires behaviors contingent upon having developed a more generalized, abstract prototype, then drives may consequently become depressed.

A depressed drive representation, in itself, can make it more difficult to generate the drive-mediated learning signals that are needed to trigger adaptively timed hippocampal and cerebellar learning, as shown in Figure 6 (see the Now Print signal N). A vicious feedback circuit can result in which depressed drives fail to trigger the learning of adaptively timed behaviors, whose absence enables the orienting system to be spuriously reset during times when attention should be given to a particular task, which then leads to hyperspecific learning, which then makes it easier to generate mismatch events, which then prevents the normal frequency of behaviorally-appropriate rewards from being received, which then contributes to the maintenance of depressed drives.

In addition, as noted above, depressed drive representations may cause a hypofrontal syndrome; see Figure 1. As a result, the normal motivationally-selective top-down attentional priming signals to sensory cortices do not occur, attentional blocking fails, and motivationally irrelevant information can flood the sensory system, thereby making it even harder to process motivationally-relevant sensory cues, so that drives continue to be unmet, rewards unreceived, and the cycle perpetuates itself through this route as well.

Among the motivationally irrelevant information flooding the system are a variety of lower-order sensory representations, which, having built-in pathways to emotional centers, can overcome their elevated threshold due to underarousal with resultant maladaptive excessive responses. This property is consistent with the hypersensitivity of autistics to a variety of lower order stimuli, such as noise and touch.

Deficient development of language would be predicted within this model. Language development requires several factors. It requires shared attention with a caretaker and splitting
attention between the objects of that shared attention, analysis of the sounds being produced, of
the sounds just heard, and of the motor actions required to make those sounds. Language
development requires the formation and application of high-level top-down representations of
linguistic structure and word meaning. Indeed, ART dynamics have been used to explain a
variety of data about speech perception and word recognition, including the need to use top­
down expectations and attention to dynamically group an evolving sequences of incoming
sounds (e.g., Grossberg, Boardman, and Cohen, 1997; Grossberg and Myers, 2000). Language
development also requires adaptive timing to produce complex sequential motor patterns in
imitation of sequential sensory inputs, and cerebellar adaptive timing mechanisms have been
implicated in the ability to learn complex sequential behaviors through imitation (Grossberg and
Paine, 2000). Conversation requires sustaining attention and the ability to flexibly disengage it. It
requires delaying a motor response appropriately so that reciprocal communication may occur. It
requires recognition of representations of social value. All of these steps are impaired within the
iSTART model herein described.

In comparison, other processing streams may be relatively less affected by dysfunctional
adaptive timing, and they may develop with normal or even enhanced levels of function, due to
a lack of competition during developmental critical and sensitive periods, or even by benefiting
from hypervigilant processing. Thus autistic development is distorted rather than delayed.

Multiple lesions within the cognitive-emotional-timing circuit that is summarized above may
combine to result in symptoms of autism. The model suggests how several different
combinations of deficits can all contribute to a full set of symptoms. Given the combination of
cytocerbral, embryologic, and genetic data that was summarized above, it seems reasonable
to hypothesize that multiple “hits” may occur in different portions of the brain for autism to fully
manifest itself.

The model raises several questions that do not seem to be clarified by available experimental
evidence. In particular, can underaroused emotional depression and hypervigilant cognitive
learning both be directly caused by a similar underlying defect? This is a reasonable question to
ask, because both underaroused depression and hypervigilant learning are problems due to
incorrectly calibrated gains: in the former case, the gain of the excitatory signals that arouse the
drive representation; in the latter case, the gain of the excitatory signals that try to activate the
orienting system. Or can one defect cause the other, as in the case where underaroused
depression can weaken adaptive timing, which can lead to spurious “hypervigilant” resets of
attention and learning even if the vigilance parameter is chosen in the normal range? Or are they
both indirect consequences of a failure within the hippocampal and/or cerebellar adaptive timing
circuits themselves? Whichever routes may be there at the outset, the above discussion clarifies
how they may perpetuate themselves via a system-wide vicious cycle.

Comparison with Other Theories of Autism

The iSTART model provides a more precise analysis of how breakdowns of brain mechanisms
can lead to autistic symptoms than other proposed models of autism. It is, in fact, compatible
with many of them, but differs from them in that it explains how each of their hypotheses may be
manifestations of a dysfunctional network, rather than prime causes.
One alternative model (Howard et al., 2000) supposes autism to be secondary to an amygdala deficit. This hypothesis is based on studies showing that the amygdala of autistics fails to activate in normal ways to a variety of social stimuli such as faces, and some similarities in the neuropsychological profiles of high functioning autistics and patients with amygdala damage. The iSTART model is compatible with the amygdala hypothesis because it considers a depressed, notably underaroused depressed, drive representation within a region like the amygdala to be a critical network feature. The iSTART model also notes, however, that autistic symptoms may arise even if the prime lesion is not in the amygdala, since amygdala depression can also result from imbalances elsewhere in the brain.

A similar comment can be made about the executive dysfunction hypothesis (Hughes et al., 1996). Here again, the iSTART model includes executive dysfunction as a result of underaroused depression. While hypofrontality could also cause depression in drive circuits, due to their reciprocal connections, there does not seem to be experimental evidence for the prime lesion of autism as occurring in the frontal lobes. Executive dysfunction is also not the earliest manifestation of the condition. A study of preschoolers with autism found no group differences between autistics and normal controls on eight executive function tasks, but did find that autistic children initiated fewer joint attention and social interaction behaviors (Griffen et al., 1999). This result has been confirmed in a larger study, comparing children with autistic spectrum disorder, children with developmental delay, and normal children, matched for mental age, on both dorsolateral and ventromedial prefrontal tasks (Dawson et al., 2002). Children with autistic spectrum disorders performed comparably to both comparison groups on all executive function tasks.

Another group of related hypotheses are the “weak central coherence” model (Happe, 1996), and the “deficient hierarchization” model (Mottron et al., 1999). While differing in subtle ways, both of these hypotheses focus on deficiencies in binding perceptual inputs into higher-order representations. Neither of these models explain all key autistic features, or attempt to fit with known neuropathologic data. The iSTART model proposes an ART-based learning mechanism whereby this processing deficiency can occur and places it in context wherein many data about normal learning and binding can be explained.

Gustafsson has described autism as deficient self-organization of feature maps (Gustafsson, 1997). This characteristic is created within the model presented in this paper by the state of hypervigilant ART-based learning. Indeed, ART models contain feature maps as part of their dynamics, notably the bottom-up flow of information in Figure 6. Gustafsson speculated that excessive lateral inhibition, as a primary deficit, may prevent adequate feature maps from forming. This concept is not incompatible with the model presented. On the other hand, it is not needed to explain the data if the other mechanisms discussed herein are at work.

Courchesne and Allen have proposed that the parietal lobe and the cerebellum are both involved in the pathophysiology of autism with cerebellar modulation of the use of attentional resources (Allen and Courchesne, 2001). The iSTART model is compatible with this proposal, but also points to a series of interacting mechanisms that give rise to autistic symptoms that go beyond the Courchesne proposal.
Andreason and coworkers (Andreason et al., 1999) have not put forth a model for autism, but their model of schizophrenia has some overlap with the systems presented here. They proposed dysfunction in a corticocerebellumocortical loop in their attempt to explain certain findings in schizophrenia, which they characterize as a “cognitive dysmetria”. In addition to lesion studies and functional imaging studies, they support the contention of a significant role for the cerebellum in cognition on several additional grounds: the volume of the cerebellum and the prefrontal cortex both are one third greater in humans than in non-human primates; the cerebellum also has extensive and reciprocal interconnections with a variety of neocortical regions, including the prefrontal cortex and limbic circuits. They define “cognitive dysmetria” as “a disruption of the interaction between cortical (especially frontal) functions such as initiation of memory retrieval or working memory and cerebellar functions such as timing and sequencing, leading to ‘cognitive misconnections’ and a disruption of the fluid coordination of mental activity.” As in the iSTART model, the focus is not on any one anatomic locus of origin, but on the dysfunction of the circuit as a whole. As noted above, some of the mechanisms described here have also been used to analyse negative symptoms of schizophrenia (Grossberg, 1984, 2000b), with an emphasis on the possibility that some schizophrenics are overaroused, rather than underaroused, depressives. However, the particular role of adaptive timing by cerebellum and hippocampus was not needed to qualitatively explain various schizophrenic negative symptoms.

Conclusion

The Imbalanced START model proposes how particular types of imbalanced mechanisms in different parts of the brain can generate autistic symptoms through brain-wide interactions. Although the model hereby provides a crucial linking hypothesis between brain mechanisms and behavioral symptoms, it is not without its limitations. In its present form, the model can show how various combinations of imbalanced interactions between cognitive, emotional, and timing systems can lead to autistic symptoms, but it cannot explain their underlying genetic or biochemical causes. However, by clarifying links between underlying brain mechanisms and behavioral outcomes, the iSTART model may help future research to focus more directly on characterizing the types of mechanisms that can lead to these behavioral outcomes.

As various authors have proposed (Deuel, 2002), it may be most accurate to think of autism, not as a single disease, but as a common phenotype, characterized and explainable by an early-onset dysfunction of a circuit that involves cerebellar adaptive timing, the limbic system, and neocortical systems. Understanding the means by which genotypes produce these phenotypic products will be complex, if only because the genes that are known to be associated with autism do not express exclusively in any isolated part of the brain, nor in just the brain alone. For example, many genes that operate in hindbrain development also control gut development (Allman, 2000). Autistics may consequently have abnormal absorption of various substances which may affect brain function. The possibility exists that multiple environmental or infectious triggers might influence the timing and/or severity of autistic symptoms. Despite these limitations, the iSTART model proposes a new framework whereby research at multiple levels may be integrated without losing sight of how all of these levels contribute to the behavioral symptoms that characterize the lives of autistics.

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REFERENCES


