The Role of Cerebellum in Autistic Spectrum Disorder: Toward a Comprehensive Model

Angela Chapman
Department of Cognitive and Neural Systems
Boston University
677 Beacon Street
Boston, MA 02215
achapman@bu.edu

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Abstract

Converging anatomical and behavioral evidence from lesion, imaging, and postmortem studies demonstrates a significant, but poorly understood, involvement of the cerebellum in autistic spectrum disorders. Well-documented physiological abnormalities in the cerebellum appear to play a role not only in motor and conditioning deficits, but in cognitive and affective symptoms as well. Although autism research is an active field, very few computational models for autism have been advanced, and none offer simulations which address specific data on the cerebellum. This paper offers a comprehensive review of experimental evidence in this area, and provides both specific and general constraints for future modeling work in this area. As an example, a specific model of the cerebellum, the spectral timing model of Bullock, Fiala and Grossberg (1994), is considered in relation to how it might be modified to produce experimentally-observed autistic symptoms.
Introduction

Autistic spectrum disorder is a multi-symptom syndrome defined by a triad of socialization deficits, impaired verbal and nonverbal communication, and restricted, repetitious patterns of behavior (American Psychiatric Association, 1994). A number of subdivisions exist within the autistic spectrum: autism proper exhibits all three symptoms, and may be divided into 'low-functioning' autistic individuals, who are mentally retarded, and 'high-functioning' autistic individuals, who exhibit high levels of intelligence (Bishop, 1989). The spectrum is further subdivided into syndromes which each exhibit some, but not all, of the same symptoms: Asperger's syndrome, semantic-pragmatic disorder, and pervasive developmental disorder not otherwise specified (PDD-NOS). Autism was first described by Leo Kanner (1943) in a series of child case reports. In addition to the three formal symptoms that define autism, there are other behavioral traits common to many autistic children; these include repetitious play, 'parallel' play, greater interest in objects than people, increased sensitivity to touch and loud noises, perseveration, echolalia, pronoun reversal, repetitive behaviors such as rocking or hand flapping, avoidance of eye contact, and motor difficulties, among others (Belmonte, 2004).

Although a great deal of work has been devoted to autism research over the past fifty years, the syndrome is still a riddle to brain researchers. Behavioral, psychophysical, and lesion studies have pinpointed several intriguing qualitative symptoms of autism, while postmortem, genetic, imaging, and cell physiology studies have implicated various brain areas, genes, and cell types in the syndrome. As a result, several different, widely-spread brain regions, including the limbic system, the association cortical areas, and the cerebellum, are known to play a role in the syndrome.

This paper will focus on one specific area: the cerebellum. The cerebellum is physiologically abnormal areas in almost all autistic subjects, and there is a wide body of evidence relating cerebellar dysfunction to specific motor, conditioning, cognitive and affective aspects of autism. Here, I will review the literature implicating cerebellar dysfunction in autism and discuss how such evidence might be applied to computational models in order to help elucidate the causes of the syndrome.
Evidence for Cerebellar Dysfunction in Autism

Cerebellar Physiology and Cell Structure

Numerous imaging and autopsy studies over the past two decades have concentrated on the search for consistent physiological abnormalities in autistic subjects. A wide variety of non-cerebellar physiological and cellular differences from the norm have been demonstrated, including superior olive agenesis, decreased size or near-absence of facial motor nuclei, decreased arborization in the hippocampus, and abnormal structure in cerebral minicolumns, among others (Courchesne 1997; Akshoomoff et al. 2004). The most consistent observation, however, has been cerebellar abnormality. Hypoplasia of the cerebellar posterior vermis and hemispheres is one common observation, along with reduced area and volume of cerebellar cortex (Courchesne 1997; Allen & Courchesne, 2003). Every postmortem autistic study to date has shown a reduced number of Purkinje cells in the cerebellum; cell loss typically ranges between 35 and 50%, although it ranges up to 95% in a few cases (Courchesne 1997). Furthermore, cellular studies have shown that the remaining Purkinje cells are significantly reduced in volume, by an average of about 35% when compared to normal populations (Fatemi et al., 2002). Deep cerebellar nuclear cells (DCN) in the autistic cerebellum are abnormally large in children, and decrease in number as the child ages (Bauman, 1991). Receptor abnormalities are being documented as well; one recent study showed decreased numbers of AMPA glutamate receptors in the cerebellar cortex, while another demonstrated abnormalities in nicotinic receptor composition (Purcell et al. 2001; Allen & Courchesne 2003).

Developmental or genetic reasons for this kind of cell loss and biochemical abnormality are still being investigated. Significant associations have been found between a diagnosis of autism and a gene called Engrailed 2, which is strongly involved in the development of cerebellar cortex (Allen et al. 2004). Some researchers suggest that the etiology of autism can be traced back to problems in cell migration as early as the fifth week of embryonic gestation (Courchesne 1997). Others have suggested that Purkinje loss in particular may be related to a failure of early synapse formation, since cells which do not form synapses are known to die off soon after birth (Rubenstein and Merzenich, 2003). Regardless of the causes, though, this distinct set of physiological differences provides specific clues and constraints for models of autism. Loss of Purkinje cells, reduced Purkinje cell volume, hypoplasia of the vermis, and abnormal size and development of DCN cells may all be related to specific motor deficits, conditioning problems, and cognitive-affective issues observed in autistic populations.
**Motor Coordination and Balance**

It is well-established that the cerebellum is involved in motor coordination and balance (Ito, 1984). Thus, if the cerebellum is implicated in autistic syndromes, there should be observable motor deficits which correlate with physiological deficits. This is in fact the case. Behavioral and imaging studies have revealed motor deficits in autism which imply both generalized cerebellar dysfunction and specific vermal dysfunction.

General cerebellar dysfunction is indicated in autism by a suggestive dichotomy between clumsy gross motor control and good fine motor control (Ghaziuddin & Butler, 1998; Kanner, 1943). This could occur if the cerebellum was dysfunctional with primary motor cortex (M1) essentially intact, since M1 is primarily responsible for digit control (Schaal, 2003). Autistic children also exhibit impaired volitional eye saccades and lack the ability to perform smooth pursuit eye movements, which are under partial cerebellar control (Minshew, Luna & Sweeney, 1999). Furthermore, functional imaging studies reveal abnormal profiles of cerebellar activation during simple motor tasks. Allen and Courchesne (2003) used functional magnetic resonance imaging (fMRI) to compare cerebellar activation of normal and autistic children during a simple button-press task. Although there was no significant difference between the accuracy and speed of the two groups, the autistic group showed significantly higher and more diffuse cerebellar activation during the task than the control group. The authors hypothesized that this excessive activation results from neocerebellar areas attempting to compensate for Purkinje cell loss in the paleocerebellum.

The vermis of the cerebellum is specifically involved in posture, locomotion, gaze, and balance, and contains a fragmented somatosensory map of the head, neck and trunk (Ghez & Thach, 2001). It is the only cerebellar area to receive direct spinal inputs, and it sends output to the vestibular nuclei, M1 (via thalamus), and reticular formation (among other targets) via the cerebellar fastigial nucleus (Ito, 1984). Vermal deficiencies, then, correlate specifically to difficulties with gait, posture, balance and facial control. In fact, Teitelbaum et al. (1998) report that abnormalities in “mouth shape, lying, righting, sitting, and crawling” are the first diagnosable symptoms of autism to appear in early infancy. Kanner (1943) noted that a distinct characteristic of autistic infants was an inability to adjust their posture to being held. While normal infants assume an anticipatory posture before being picked up and adjust their bodies to the posture of the person holding them, autistic infants fail to adjust. Difficulties with posture and balance persist throughout childhood (Molloy et al. 2003), although the severity of postural problems is correlated to the severity of autistic disorder. The
problems are largely resolved by adulthood, but autistic adults still exhibit subtle locomotion abnormalities: Gait velocity and step length is normal, but they show a decreased range of ankle motion (Hallett et al. 1993). All of these symptoms point toward underlying vermal dysfunction.

**Classical Conditioning**

In addition to being involved with motor coordination, the cerebellum has been strongly implicated in classical conditioning and adaptive timing of the conditioned response (Fiala et al., 1996). One particularly well-studied classical conditioning paradigm is eye-blink conditioning, in which a puff of air to the retina is used as the conditioned stimulus (CS) and a tone or other sensory cue as the unconditioned stimulus (US). The interpostitus nucleus (IP) of the cerebellum has been shown to be vital for the control of the eyeblink, and lesions of the IP, or cortex projecting to IP, can completely disrupt acquisition and expression of the conditioned response. In addition, a lesion of the cerebellar vermis as small as 2 square millimeters can disrupt acquisition of the response (Kandel et al., 2001). This paradigm can prove useful for studying autistic responses, since it is independent of IQ (Sears et al., 1994) and has been well-studied in normal populations.

Sears et al. (1994) used trace conditioning with an air puff CS and tone US to study timing of conditioned responses in high-functioning autistic children and adolescents. They found that, compared to age- and gender-matched controls, autistic subjects both acquired the response faster and exhibited more rapid extinction of the response. Speed of conditioned response (CR) acquisition and extinction decreased with age; older autistic subjects showed no significant differences from their counterpart control subjects. The eye-blink responses of the autistic subjects were similar in duration to those of the control group; however, the autistic CRs occurred too early, and had a larger magnitude.

This result implies some dysfunction in the cerebellar cortex projecting to IP, possibly due to Purkinje cell loss as discussed above. Animal studies have shown that lesions in IP or in cerebellar cortex projecting to IP also lead to a maladaptively timed and poorly-scaled response (Perrett et al., 1993). However, there is an important difference: while cortical or deep nuclear lesions led to a small-magnitude CR, autistic subjects exhibited a larger-than-normal CR. Sears et al. (1994) suggest that this is due to the abnormally large DCN cells which have been observed in autistic children; since DCN cells decrease in number as autistic subjects age (Bauman 1991), this would also
explain the age-related effects of response acquisition. This topic will be revisited in a modeling context, below.

_Cognition and Affect_

More controversial than the cerebellum's involvement in motor control and conditioning is its involvement in cognitive and affective functions. Although it is now widely accepted that the cerebellum has some cognitive and affective roles, and that the cerebellar hemispheres are at least indirectly connected to associational areas of frontal and parietal cortex, its specific functions are still being debated (Riva & Giorgi, 2000). Evidence from several lesion and imaging studies suggests that the cerebellum is involved in cognitive and affective characteristics of autism including attention, abnormal affect regulation, and even language and mnemonic difficulties.

Since the cerebellum projects to the superior colliculus, it makes sense that it has recently been shown to be involved in attention. Attentional deficits are among the most commonly observed cognitive symptoms in autism (Allen & Courchesne, 2003). An fMRI study by Allen & Courchesne (2003) demonstrated that high-functioning autistic subjects showed significantly less cerebellar activation during an attentional task than did IQ-matched normal controls; the autistic subjects were also less accurate on the task. This suggests that the cerebellum's limited cortical resources are being redirected to more 'primitive' motor – as opposed to attentional - functions in autistic populations. Further evidence emerges from lesion studies in which children or adults have had a tumor removed from the cerebellum. Riva and Giorgi (2000) observed a large slowing of attentional switching in children with lesions of either cerebellar hemisphere. Levisohn et al. (2000) observed visual attention deficits in children with cerebellar hemisphere lesions. In adults, cerebellar lesions were followed by exhibitions of perseveration, inattention, and distractibility (Schmahmann & Sherman, 1998).

Evidence is accumulating for an affective role of the cerebellum as well, particularly the vermis. I speculate that a vermal role in affect could be linked to the fastigial nucleus's projections to the reticular formation and the rostral forebrain, including the septum, amygdala and hippocampus (Ito, 1984). Like the attentional evidence, evidence for a vermal role in affect is largely qualitative, but highly suggestive. Over the past two decades, vermis alterations in psychiatric and schizophrenic patients, who exhibit affective symptoms, have been well-documented (Riva & Giorgi, 2000). In autistic children, impairment of exploratory behavior has been significantly correlated with the area of the vermis (Allen et al., 2004).
Lesion studies offer some interesting observations regarding vermal role in affect as well. Riva and Giorgi (2000) noted that children with vermal lesions showed marked affective and personality changes in the first few months after surgery, whereas children with cerebellar hemisphere lesions did not. These affective changes were reminiscent of autistic behaviors and included gaze aversion, avoidance of physical contact, and an intolerance for the presence of other people, including family members. General irritability, mood swings, and disinhibited social behaviors were also observed. In one case, a young girl's behavior was modified enough after surgery that she actually tested positive for the DSM IV autism criteria; her behavior prior to the vermal lesions had been normal (Riva & Giorgi, 2000). Levisohn et al. (2000) reported similar results for another set of children with cerebellar vermis lesions. Schmahmann & Sherman (1998) observed the same in adults, who showed flattened affect, disinhibition, or even emergent obsessive-compulsive behaviors after vermis lesions. The effect was so dramatic that Schmahmann (1998) actually postulates a 'cerebellar cognitive affective syndrome,' and suggests that the vermis is the “limbic system of the cerebellum”.

Additional deficits in linguistic and mnemonic functions have been observed following cerebellar lesions. Riva and Giorgi (2000) observed dramatic linguistic impairments in children with vermal lesions, including postsurgical mutism with an inability to voluntarily move the mouth and tongue. After speech was recovered, in many cases they observed grammatical disturbances reminiscent of a language disorder. Similarly, in adults, complete agrammatism appears after vermal lesions (Schmahmann & Sherman, 1998). It should be noted that this is not a motor deficit, but a deficit in the cognitive structure of the patients’ language. Mnemonic deficits, particularly in sequential memory, appear after lesions of the cerebellar hemispheres in children (Riva & Giorgi, 2000; Levisohn et al. 2000).

It should be noted that, in all the lesion studies, severe cognitive and affective symptoms only appeared for a limited amount of time (typically two months to a year) after surgery before attenuating. The one exception to this rule was a man with adult cortical atrophy of the cerebellum; in his case, the attentional, mnemonic, affective, and verbal symptoms actually worsened with time (Schmahmann & Sherman, 1998). This is of particular interest since cortical atrophy is more analogous to the cellular condition of autistic cerebella than are cortical lesions.

In sum, the autistic cerebellum has a number of documented physiological and cellular deficits. Although the picture is still murky, imaging, behavioral and lesion studies have established links between the cerebellum and motor coordination,
conditioning and cognitive-affective issues in autistic spectrum disorders. Keeping this information in mind, the next section will discuss how some of these data can be immediately applied to modeling work of autism and the autistic cerebellum in particular.

Modeling the Autistic Cerebellum

Previous Work and General Constraints

Despite the number of studies linking autism to cerebellar dysfunction, few models have been offered to account for these effects. A large number of non-computational theories regarding autism have been forwarded. Some are highly qualitative, such as “Extreme Male Brain Theory”, which posits that autism is the result of an over-expression of male brain traits, and “Mindblindness” theory, which suggests that autism consists in a deficient theory of mind (Baron-Cohen, 2002). Other, more biochemical or genetic, theories have been advanced, such as that of Belmonte et al. (2004), who suggest that autism is a disorder of brain connectivity, with overconnection in local circuits and underconnection in long-range circuits. Along similar lines, Rubenstein and Merzenich (2003) suggest a model of autism as an increased ratio of excitation to inhibition in certain neural systems. Still others have suggested that autism is due to amygdala or executive dysfunction (Grossberg & Seidman, in press).

Few neural simulations of autism have been offered, and they have thus far been restricted to 'neocortical', cognitive and attentional effects such as hyperspecificity and 'weak central coherence' (e.g., O'Laughlin and Thagard, 2000). The iSTART (imbalanced Spectral Timing Adaptive Resonance Theory) model of Grossberg and Seidmann (in press) seems to be the most comprehensive effort thus far to computationally link autistic symptoms to dysfunction in specific limbic, cerebellar, and cortical neural circuits. Furthermore, the iSTART model is based on previously existing models of the normally functioning brain, which is a more balanced approach than starting from the autistic brain. Unfortunately, their paper is a preliminary, qualitative discussion of the circuit's (possible) dynamics rather than an actual, refined simulation.

From the preceding discussion, it is becoming clear what a model of cerebellar dysfunction in autism might entail. First, a model of autism should first be based on a model of a healthy, functioning brain circuit. Specific imbalances should then be introduced which correspond to the known physiological deficits; at the very least, a model of the autistic cerebellum should mimic the decreased number and size of Purkinje cells, the abnormal size and number of DCN cells, the decreased area and volume of the vermis, and the decreased number of nicotinic and GABA receptors. The computational
implications of other physiological data, such as increased white matter volume, might be more difficult to determine.

In order to model the impact of abnormal cerebellar physiology on behavioral function, the cerebellum model will in most cases need to be embedded within a preexisting circuit. This should not be difficult to do for motor and conditioning effects, since there are many existing models of motor coordination and classical conditioning which use the cerebellum. In the case of cognition and affect, however, such modeling work will be remarkably more difficult due to the complexity of these effects and the lack of agreement as to precise cerebellar involvement in this circuit. However, as the cerebellum's role in cognition and affect becomes clearer within the normal population, it will become easier to investigate the cognitive and affective effects of the autistic cerebellum as well.

**The Specific Case of Timed Response Learning**

As a specific example of how such constraints might be applied to a preexisting model, we will return to the Grossberg and Seidman (in press) iSTART model. In this paper, Grossberg and Seidman refer to previously-published work on adaptive timing in the hippocampus and cerebellum (Bullock, Fiala, and Grossberg, 1994; Fiala, Grossberg, and Bullock, 1996) to suggest how adaptive timing deficits might come about in autism.

Figure 1a shows the basic cerebellar circuit used by Bullock et al. in the 1994 model. Note that the model also contained a deep nuclear inhibitory interneuron (not shown in the figure), which receives projections from Purkinje cells and mossy fibers, and acts to regulate the activity of the deep nuclear cell. The model includes several equations which interact in a complex manner, but the three most relevant equations for this discussion are:

\[
\frac{dr}{dt} = -\alpha r - \gamma p + \beta (1-r)(s+q) \quad (1)
\]

\[
f(r) = \frac{(r-\mu)^2}{\sigma^2 + (r-\mu)^2} \quad (2)
\]

\[
\frac{dq}{dt} = \gamma (-q + sw - pf(r)) \quad (3)
\]

Here, \( r \) is the activation of the nuclear inhibitory neuron, \( p \) is the Purkinje cell activation, and \( q \) is the DCN output, which corresponds to the CR. The other variables are as follows: \( \alpha, \gamma, \beta, \mu, \) and \( \sigma \) are dimensionless parameters, \( s \) is the mossy fiber signal, and \( w \) is the modifiable weight between the mossy fiber and the excitatory DCN cell. \( F(r) \) is a
sigmoidal signal function modulating the effect of the inhibitory DCN neuron \( r \) on the excitatory DCN output neuron \( q \).

The top half of Figure 1b shows both the normal functioning of the Bullock et al. (1994) model after conditioning, while the bottom half of the figure shows the model's response when the circuit is “lesioned” by setting \( p = 0 \) in equations (1) and (3). The result is an early, small-magnitude CR; it is early because the Purkinje cell controls adaptive timing in the model, and it is small-magnitude because the DCN output \( q \) is quickly quenched by the inhibitory interneuron \( r \) before the CR has time to grow to full magnitude.

This model result corresponds nicely to the lesion studies of Perrett et al. (1993). However, it does not correspond to the results of eyeblink conditioning in autism subjects in Sears et al (1994), as discussed above. Recall that autistic subjects show earlier responses than normal subjects, but that their responses are high-magnitude rather than low-magnitude.

It is easy to see how this result might be obtained from the Bullock et al. (1994) model, with some slight modifications. The activation of the Purkinje cell should be set to some small, but nonzero value; given the model dynamics, this would cause the response to be timed too early. This would also mimic the decreased number and volume of Purkinje cells observed in autistic subjects, as discussed above. Second, the output activation \( q \) should be made larger to mimic the oversized DCN cells observed in autistic children. This could be effectively accomplished in several ways: first, the weights \( w \) should grow faster than they do in the present model; second, the parameter \( \gamma \) should be made larger in order to increase the DCN output cell's responsivity, and third, the parameter \( \sigma \) should be made larger in order to quench some of the inhibitory cell's effect on \( q \). Finally, it would probably be worthwhile to explicitly add the effect of the inferior olive on the DCN output activation.

Although it is difficult to say with certainty what the precise result of these modifications would be without performing the actual simulation, it seems intuitive that they should produce an early, high-magnitude response reminiscent of that seen in autistic children. If so, this would satisfy several of the modeling constraints discussed in the previous section: it would be based on a model of the normally-functioning brain, it would be based on the physiology of autism, and it would produce a measurable 'behavioral' result which corresponds to the effects observed in autistic subjects. It is models such as this that are needed in order to deepen our understanding of the neural underpinnings of autism.
Discussion and Future Directions

This paper has reviewed a wide body of evidence linking cerebellar dysfunction to a variety of motor coordination, classical conditioning, cognitive, and affective effects seen in autism, and it has shown how the physiological data might be applied to existing models of cerebellar function in order to extract effects similar to those seen in the autism literature. Despite its narrow focus, this paper does not intend to suggest that cerebellar dysfunction is the sole locus or cause of autism. Autism is a widely-distributed syndrome which involves many different brain system abnormalities; hence the difficulty that researchers have had in unraveling its etiology. This paper simply intends to elucidate how the cerebellum might be involved in certain autistic symptoms, and how models of autism might seek to incorporate such data. It is hoped that, through the reciprocal use of computational models, behavioral studies, and physiological studies, the field will be able to advance much closer toward an explanation of the riddle that is autism.
References


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Figure Captions

Figure 1


(b) Above: Bullock et al. (1994) model response after conditioning. Note that the peak DCN activation, corresponding to the CR, is correctly timed, at the moment of the CS. Below: Bullock et al. (1994) model response when the circuit is “lesioned” by setting the Purkinje activation to zero. Note that the CR now occurs too early, and is of small magnitude. Taken from Grossberg & Seidman (in press).
Figure 1

a)

b)