Autism - Open Access
ISSN: 2165-7890

Heck and Howell, Autism 2013, S4
DOI: 10.4172/2165-7890.S4-001

Review Article Open Access

# Prefrontal Cortical-Cerebellar Interaction Deficits in Autism Spectrum Disorders

**Detlef H Heck[1]* and James W Howell[2,3]**

[1]Department of Anatomy and Neurobiology, University of Tennessee Health Science Center, Memphis, TN, USA
[2]Department of Psychiatry, University of Tennessee Health Science Center, Memphis, TN, USA
[3]The Urban Child Institute, Memphis, TN, USA

## Abstract

This review reveals possible explanations for the link between cerebellar neuropathology and cognitive disorders, with an emphasis on autism and schizophrenia. There is a growing body of evidence showing these two conditions to be related. The loss of Purkinje cells, the principal neurons of the cerebellar cortex, is one of the most consistent neuropathologies found in autistic brains. Cerebellar neurophathologies are a common finding in schizophrenia, as well. The cerebellum has long been considered a pure motor structure, and it's involvement in cognitive disorders remained obscure. The cognitive deficits typically associated with autism and schizophrenia strongly implicate prefrontal cerebral cortical pathology. We review recent findings, which provide new insights into suggest possible neuronal mechanisms through which the cerebellum might interact with the prefrontal cortex during cognitive tasks. In addition to exploring the link between autism and schizophrenia, we point out several opportunities for further study, including the selective pruning of nerve cells and collaterals during development, communication systems between the prefrontal cortex and the cerebellum, exploration of the genome, effects of autism and schizophrenia on intelligence, and a focus on the epidemiology of autism.

**Keywords:** Autism spectrum disorders; Schizophrenia; Dopamine

## Review of Literature

Autism in the human presents both a positive and a negative opportunity for understanding the disorder. Invasive experiments are limited to animal models, but behavioral and clinical observations and direct questioning are useful.

Many primary questions about autism are still much argued in the literature. A good example of this is a study described by Dawson et al. [1], concerning the level of autistic intelligence compared to that of non-autistic control subjects. Their conclusion was that the intelligence of autistic people has been too often underestimated, but the true value of the paper was their careful and systematic development and presentation of their methodology. This was a refreshing educated insight into the nature of autism.

Of course, we know that genetic mutations have been linked to autism. It is thought these could number in the hundreds [2]. Epigenetics also plays a role [3], just as it does in normal brain development.

Courchesne et al. [4] have taken good advantage of the limited amount of brain tissue available from autistic people who died. From these studies, he found a 67% increase in the number of brain cells of the prefrontal cortex, when compared to corresponding tissue from people of the same age who were not autistic. Brain weight and size were also greater. This was consistent with earlier reports of autism being related to overgrowth of the head and brain in the frontal region. In fact, Stanfield et al. [5] pointed out that in autistic subjects they studied with Magnetic Resonance Imaging (MRI), although the corpus callosum was reduced, the total brain, the caudate nucleus, and the cerebral hemispheres, exhibited an increased volume.

Several investigators over the years have discussed the overgrowth of nerve cells in the prefrontal cortex as characteristic of autism, and Courchesne et al. [4] continuation of this study has quantified some specific processes leading to this condition. The lack of selective pruning of collaterals during development in this region of the brain seems to be a primary factor. We know that pruning of nerve cells is a major component of brain development in the early years of life. This has been studied in several specific areas of brain development. One of the most striking investigations of this was of the role of nerve cell pruning in the development of stereo vision [6,7]. Improper pruning would lead to impaired vision, or even blindness. In the case presented by Courchesne et al. [4], the massive prenatal build up of nerve cells resulting from lack of pruning in the prefrontal cortex leaves the individual with "noise" in this portion of the cognitive system.

Evidence suggests that the cerebral-cerebellar connection is greatly impaired in autism [8], and this portion of the problem is a central factor of the pathology of autism. That cerebral-cerebellar function of fine-tuning movement and muscle action is impaired, is easily seen in many people with autism because of their lack of smooth movement and various other motor deficits [9]. On a simplistic level, this is understandable, considering that it is generally accepted that the prefrontal cortex normally takes longer to mature than the cerebellum, and in autism, the cerebellum is left with the almost impossible task of communicating with a prefrontal cortex overpopulated with nerve cells (many of which are malformed and not functioning properly, since the pruning process had not culled the misfit neurons and synaptic connections), and the resultant "noise" [4].

Crespi [10,11] hypothesized that Autism Spectrum Disorder (ASD) and psychotic-affective spectrum disorders (schizophrenia,) both involve problems with social interaction. He characterized ASD

***Corresponding author:** Detlef H Heck, Department of Anatomy and Neurobiology, University of Tennessee Health Science Center, Memphis, TN, USA, Tel: +1-901-448-1678; Fax: +1-901-448-7193; E-mail: dheck@uthsc.edu

**Received** February 16, 2013; **Accepted** March 22, 2013; **Published** March 27, 2013

**Citation:** Heck DH, Howell JW (2013) Prefrontal Cortical-Cerebellar Interaction Deficits in Autism Spectrum Disorders. Autism S4: 001. doi:10.4172/2165-7890.S4-001

as exhibiting an over-development and schizophrenia, revealing an under-development of what he called the "human-specific social brain phenotypes." He and his colleagues supported their view with studies of how autism risk alleles affect manifestations of the disorder, and through analysis of the literature. Developmental neurogenesis work, physiological and genetic studies of synaptic function in the mouse, support Crespi's hypothesis [12-14].

Another comparison between autism and schizophrenia can be made relative to the awareness of self or self-consciousness. Schizophrenia has been called a disorder of self, which can take various forms and to varying degrees, but there is a general distortion of consciousness and lack of self presence [15]. Autism can also be characterized by a lack of self-consciousness, but high-functioning autism or people with Asperger syndrome may have or acquire self-consciousness through learning [16]. Memory tests by Toichi et al. [17] also revealed deficits in the consciousness of self by people with autism. So far it seems that many of the genes implicated in autism and schizophrenia are active only during specific stages of the developing brain [14], suggesting the existence of critical periods for the normal development of consciousness of self.

Experiments in animals, in particular in genetic mouse models of ASD, provide important clues, as to possible neuronal pathways and mechanisms of interaction between the cerebellum and the cerebral prefrontal cortex, and their involvement in autism. Tracing studies in primates have shown that the cerebellum projects (*via* the thalamus) to the prefrontal cortex [18]. In turn, the prefrontal cortex projects back to the cerebellar areas from where prefrontal cortical projections originated, forming what might amount to parallel loops of cerebral-cerebellar connections [19]. While these anatomical connections clearly suggest targeted neuronal interactions between the two structures, how cerebellar activity modulates prefrontal cortical activity and vice versa, and how their interaction is related to behavior is poorly understood.

Recent experiments in mice have revealed a surprising new aspect of prefrontal cortical interaction with the cerebellum. When stimulating the cerebellar dentate nucleus in healthy mice, Mittleman et al. [20] discovered an increase in dopamine release in the medial prefrontal cortex. Dopamine is a neuromodulatory transmitter generated by cells in the substantia nigra and Ventral Tegmental Area (VTA), and is most widely known for its importance in the failure and disinhibition of movement initiation in Parkinson's and Huntington's disease, respectively [21]. But, dopamine is also strongly implicated in reward and pleasure seeking behavior, drug addiction and cognitive functions [22]. Abnormal function of the dopaminergic system has been implicated in a variety of cognitive disorders, including autism spectrum disorders and schizophrenia [23,24]. Cerebellar controlled dopamine release in the mouse medial prefrontal cortex was mediated by two independent and equally contributing pathways, one involving the Ventral Tegmental Area (VTA), which contains dopaminergic cells projecting to the prefrontal cortex, the other involving the thalamus [25]. Increased dopamine release *via* cerebellar activated thalamic projections involved stimulation of mesocortical dopaminergic terminals *via* appositional excitatory glutamatergic synapses [26,27]. A recent study in a mouse model of fragile X syndrome, an autism spectrum disorder, showed a reorganization of the pathways involved in cerebellar modulation of mPFC dopamine release, resulting in a weakening of the VTA, and a strengthening of the thalamic pathway *via* the ventro-lateral nucleus [28]. Together with the known cerebellar deficits associated with autism [8,29-31], these findings suggest that a dysfunction of cerebellar dependent reward circuits may play a role in at least some forms of autism. Consistent with this hypothesis are recent findings by Dichter et al. [32], who used functional Magnetic Resonance Imaging (fMRI), to compare reward circuit responses in autistic and control subjects, and reported hypo-activation of reward circuit activity in autistic individuals [32]. While more studies are needed to determine how strongly the cerebellum is involved in reward seeking tasks, like those chosen by Dichter et al. [32], a role of the cerebellum in human cocaine-related behavior has already been demonstrated. Together these studies suggest that the cerebellum modulates prefrontal cortical activity *via* dopamine, thus contributing to a broad spectrum of sensorimotor and cognitive functions, especially behaviors involving reward seeking and positive reinforcement [22].

These dopamine mediated modulatory actions are unlikely to take place at the millisecond temporal resolution, often associated with cerebellar coordination of movements [33-38]. The time course of dopamine release in response to cerebellar stimulation, the experiments by Mittleman et al. [20] could span tens of seconds. This suggest that the cerebellum can operate at much slower time scales, modulating PFC activity during slow complex processes, such as the analysis and interpretation of facial expressions, social contexts, and theory of mind. Whether cerebellar modulation of PFC dopamine release does indeed serve any of these functions remains to be shown. But, with the close association of cerebellar and PFC abnormalities with autism [39,40], it is at least an intriguing hypothesis yet to be tested.

While we have focused on the interaction between the cerebellum and the prefrontal cortex, which is an association cortical area not involved in motor control. However, motor deficits are common in ASD patients [9,41], and at least some of those seem to be caused by cerebellar neuropathology [31,42]. Several studies in mouse models of single gene autism spectrum disorders, such as Angelman, fragile X syndrome and Smith-Magenis syndrome, have documented motor deficits in the mutant mice (e.g. [43-46]). It is, thus, likely that cerebellar deficits associated with ASD contribute to both, motor and cognitive deficits. Further complicating the issue from a translational perspective is the recent discovery suggesting that prefrontal cerebellar interactions in rodents are involved in motor learning [47]. Whether the same holds true for humans remains to be determined.

## Conclusion and Future Directions

The study of brain connectivity and cerebro-cerebellar interactions will provide important clues about the neuronal mechanisms, underlying some forms of autism and autism spectrum disorders. However, based on our review of the literature, there are several other opportunities in the study of autism and autism spectrum disorders that cry out for attention:

1) Much can be learned about schizophrenia and autism from constant comparisons in the studies of the two conditions. Following Bernard Crespi's lead, studies of everything from genomics to perception in people who have one of these conditions will enhance our understanding of both.

2) We know that much of the proper development of the brain depends on the mechanisms involved in selective pruning of nerve cells and collaterals. We need to know more about neurological pruning overall and specifically about its role in cognitive brain function.

3) The communications systems between the prefrontal cortex and the cerebellum have been studied to some extent, but we still far from understanding how these systems operate in the normal brain, which is likely a prerequisite to understanding its dysfunction in autism.

4) As we continue to explore the human genome, our appreciation of its complexity grows, and this will provide new avenues to try to understand autism. For example, we know that the retrogene GLUD2 is derived from glutamate dehydrogenase. This agent is responsible for clearing the by-products of neuron activity from the system [48]. The possible excessive buildup of by-products from the overpopulation of nerve cells of the prefrontal cortex of autism patients may be one of many factors contributing to the ill effects of autism. Or does some other gene compensate?

5) There is a special opportunity in the study of autism to learn much more about the basic nature of human intelligence.

6) There is a wealth of epidemiological evidence that the environment might affect the prevalence of ASD in certain geographical areas [49]. We have not addressed this here. However, the importance of the environment on the occurrence of autism is quite apparent from an extensive recent study by Suren et al. [50], of over 85,000 children. Those children whose mothers took folic acid around the time of conception had a distinctly lower risk of autistic disorder than those whose mothers did not. This and similar studies strongly suggest that more effort should be directed towards the study of environmental factors in ASD.

### Acknowledgements

DHH is supported by grants from the National Institute of Health (NIH, NS060887, NS067201 and R01NS063009). The content of this publication is solely the responsibility of the authors, and does not necessarily represent the official views of the NIH.

### References

1. Dawson M, Soulières I, Gernsbacher MA, Mottron L (2007) The level and nature of autistic intelligence. Psychol Sci 18: 657-662.
2. Buxbaum JD, Daly MJ, Devlin B, Lehner T, Roeder K, et al. (2012) The autism sequencing consortium: large-scale, high-throughput sequencing in autism spectrum disorders. Neuron 76: 1052-1056.
3. Shulha HP, Cheung I, Whittle C, Wang J, Virgil D, et al. (2012) Epigenetic signatures of autism: trimethylated H3K4 landscapes in prefrontal neurons. Arch Gen Psychiatry 69: 314-324.
4. Courchesne E, Mouton PR, Calhoun ME, Semendeferi K, Ahrens-Barbeau C, et al. (2011) Neuron number and size in prefrontal cortex of children with autism. JAMA 306: 2001-2010.
5. Stanfield AC, McIntosh AM, Spencer MD, Philip R, Gaur S, et al. (2008) Towards a neuroanatomy of autism: a systematic review and meta-analysis of structural magnetic resonance imaging studies. Eur Psychiatry 23: 289-299.
6. Ding SL, Elberger AJ (2001) Postnatal development of biotinylated dextran amine-labeled corpus callosum axons projecting from the visual and auditory cortices to the visual cortex of the rat. Exp Brain Res 136: 179-193.
7. Ding SL, Elberger AJ (2000) Neuropeptide Y- and somatostatin-immunoreactive axons in the corpus callosum during postnatal development of the rat. Brain Res Dev Brain Res 124: 59-65.
8. Skoyles JR (2002) Is autism due to cerebral-cerebellum disconnection? Med Hypotheses 58: 332-336.
9. Donnellan AM, Hill DA, Leary MR (2012) Rethinking autism: implications of sensory and movement differences for understanding and support. Front Integr Neurosci 6: 124.
10. Crespi BJ (2010) Revisiting Bleuler: relationship between autism and schizophrenia. Br J Psychiatry 196: 495.
11. Crespi B, Stead P, Elliot M (2010) Evolution in health and medicine Sackler colloquium: Comparative genomics of autism and schizophrenia. Proc Natl Acad Sci U S A 107 Suppl 1: 1736-1741.
12. Kaphzan H, Hernandez P, Jung JI, Cowansage KK, Deinhardt K, et al. (2012) Reversal of impaired hippocampal long-term potentiation and contextual fear memory deficits in Angelman syndrome model mice by ErbB inhibitors. Biol Psychiatry 72: 182-190.
13. Heck DH, Lu L (2012) The social life of neurons: synaptic communication deficits as a common denominator of autism, schizophrenia, and other cognitive disorders. Biol Psychiatry 72: 173-174.
14. Hoerder-Suabedissen A, Oeschger FM, Krishnan ML, Belgard TG, Wang WZ, et al. (2013) Expression profiling of mouse subplate reveals a dynamic gene network and disease association with autism and schizophrenia. Proc Natl Acad Sci U S A 110: 3555-3560.
15. Sass LA, Parnas J (2003) Schizophrenia, consciousness, and the self. Schizophr Bull 29: 427-444.
16. Frith U, Happe F (1999) Theory of mind and self-consciousness: What is it like to be autistic? Mind Lang 14: 1-22.
17. Toichi M, Kamio Y, Okada T, Sakihama M, Youngstrom EA, et al. (2002) A lack of self-consciousness in autism. Am J Psychiatry 159: 1422-1424.
18. Middleton FA, Strick PL (2001) Cerebellar projections to the prefrontal cortex of the primate. J Neurosci 21: 700-712.
19. Kelly RM, Strick PL (2003) Cerebellar loops with motor cortex and prefrontal cortex of a nonhuman primate. J Neurosci 23: 8432-8444.
20. Mittleman G, Goldowitz D, Heck DH, Blaha CD (2008) Cerebellar modulation of frontal cortex dopamine efflux in mice: relevance to autism and schizophrenia. Synapse 62: 544-550.
21. Graybiel AM, Aosaki T, Flaherty AW, Kimura M (1994) The basal ganglia and adaptive motor control. Science 265: 1826-1831.
22. Iversen L, Iversen S, Dunnett S (2010) Dopamine Handbook. Oxford University Press, Oxford, UK.
23. Dichter GS, Damiano CA, Allen JA (2012) Reward circuitry dysfunction in psychiatric and neurodevelopmental disorders and genetic syndromes: animal models and clinical findings. J Neurodev Disord 4: 19.
24. Sesack SR, Carr DB (2002) Selective prefrontal cortex inputs to dopamine cells: implications for schizophrenia. Physiol Behav 77: 513-517.
25. Rogers TD, Dickson PE, Heck DH, Goldowitz D, Mittleman G, et al. (2011) Connecting the dots of the cerebro-cerebellar role in cognitive function: neuronal pathways for cerebellar modulation of dopamine release in the prefrontal cortex. Synapse 65: 1204-1212.
26. Del Arco A, Mora F (2005) Glutamate-dopamine in vivo interaction in the prefrontal cortex modulates the release of dopamine and acetylcholine in the nucleus accumbens of the awake rat. J Neural Transm 112: 97-109.
27. Pinto A, Jankowski M, Sesack SR (2003) Projections from the paraventricular nucleus of the thalamus to the rat prefrontal cortex and nucleus accumbens shell: ultrastructural characteristics and spatial relationships with dopamine afferents. J Comp Neurol 459: 142-155.
28. Rogers TD, Dickson PE, McKimm E, Heck DH, Goldowitz D, et al. (2013) Reorganization of circuits underlying cerebellar modulation of prefrontal cortical dopamine in mouse models of autism spectrum disorder. Cerebellum.
29. Courchesne E (1997) Brainstem, cerebellar and limbic neuroanatomical abnormalities in autism. Curr Opin Neurobiol 7: 269-278.
30. Webb SJ, Sparks BF, Friedman SD, Shaw DW, Giedd J, et al. (2009) Cerebellar vermal volumes and behavioral correlates in children with autism spectrum disorder. Psychiatry Res 172: 61-67.
31. Fatemi SH, Aldinger KA, Ashwood P, Bauman ML, Blaha CD, et al. (2012) Consensus paper: pathological role of the cerebellum in autism. Cerebellum 11: 777-807.
32. Dichter GS, Felder JN, Green SR, Rittenberg AM, Sasson NJ, et al. (2012) Reward circuitry function in autism spectrum disorders. Soc Cogn Affect Neurosci 7: 160-172.
33. Anderson CM, Maas LC, Frederick Bd, Bendor JT, Spencer TJ, et al. (2006) Cerebellar vermis involvement in cocaine-related behaviors. Neuropsychopharmacology 31: 1318-1326.
34. Fox CA, Snider RS (1967) The Cerebellum, Volume 25 (Progress in Brain Research). (1st Edn), Elsevier, Amsterdam, the Netherlands.
35. Welsh JP, Lang EJ, Suglhara I, Llinas R (1995) Dynamic organization of motor control within the olivocerebellar system. Nature 374: 453-457.

36. Heck DH, Thach WT, Keating JG (2007) On-beam synchrony in the cerebellum as the mechanism for the timing and coordination of movement. Proc Natl Acad Sci U S A 104: 7658-7663.

37. Jacobson GA, Rokni D, Yarom Y (2008) A model of the olivo-cerebellar system as a temporal pattern generator. Trends Neurosci 31: 617-625.

38. Yarom Y, Cohen D (2002) The olivocerebellar system as a generator of temporal patterns. Ann N Y Acad Sci 978: 122-134.

39. Townsend J, Westerfield M, Leaver E, Makeig S, Jung T, et al. (2001) Event-related brain response abnormalities in autism: evidence for impaired cerebello-frontal spatial attention networks. Brain Res Cogn Brain Res 11: 127-145.

40. Carper RA, Courchesne E (2000) Inverse correlation between frontal lobe and cerebellum sizes in children with autism. Brain 123: 836-844.

41. Leary MR, Hill DA (1996) Moving on: autism and movement disturbance. Ment Retard 34: 39-53.

42. Takarae Y, Minshew NJ, Luna B, Sweeney JA (2004) Oculomotor abnormalities parallel cerebellar histopathology in autism. J Neurol Neurosurg Psychiatry 75: 1359-1361.

43. Roy S, Watkins N, Heck DH (2012) Comprehensive analysis of ultrasonic vocalizations in a mouse model of Fragile X syndrome reveals limited, call type specific deficits. PloS One 7: e44816.

44. Heck DH, Gu W, Cao Y, Qi S, Lacaria M, et al. (2012) Opposing phenotypes in mice with Smith-Magenis deletion and Potocki-Lupski duplication syndromes suggest gene dosage effects on fluid consumption behavior. Am J Med Genet A 158A: 2807-2814.

45. Roy S, Zhao Y, Allensworth M, Farook MF, Reiter LT, et al. (2011) Comprehensive motor testing in Fmr1-KO mice exposes temporal defects in oromotor coordination. Behav Neurosci 125: 962-969.

46. Heck DH, Zhau Y, Roy S, LeDoux MS, Reiter LT (2008) Analysis of cerebellar function in Ube3a-deficient mice reveals novel genotype-specific behaviors. Hum Mol Genet 17: 2181-2189.

47. Kalmbach BE, Ohyama T, Kreider JC, Riusech F, Mauk MD (2009) Interactions between prefrontal cortex and cerebellum revealed by trace eyelid conditioning. Learn Mem 16: 86-95.

48. Burki F, Kaessmann H (2004) Birth and adaptive evolution of a hominoid gene that supports high neurotransmitter flux. Nat Genet 36: 1061-1063.

49. Moldin SO, Rubenstein JL (2006) Understanding autism: From basic neuroscience to treatment.CRC Press, Boca Raton, USA.

50. Suren P, Roth C, Bresnahan M, Haugen M, Hornig M, et al. (2013) Association between maternal use of folic acid supplements and risk of autism spectrum disorders in children. JAMA 309: 570-577.

This article was originally published in a special issue, **Neurobiology of Autism** handled by Editor. Dr. Afaf El-Ansary, King Saud University, Saudi
Arabia