Autism Spectrum Disorders and Ataxia

96

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Contents

Abstract

Autism is a neurodevelopmental disorder characterized by pervasive deficits in language, behavior, and cognition. Pathology exists throughout the brains of subjects with autism including the cerebellum. These abnormalities include changes in cerebellar and vermal volume, changes in pyramidal cell density, and changes in gray and white matter. Additionally, a number of brain markers associated with GABAergic function, brain development, inflammation, oxidative stress, immune system function, and apoptosis have shown altered expression in the cerebellum of subjects with autism. Initially, it was thought that cerebellar pathology contributed mainly to impaired motor function in autism. Over the past 20 years, however, there has been an increased

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understanding that the cerebellum is involved in emotional processing, cognition, and other higher brain functions, many of which are impaired in autism. Ataxia, or abnormal gait, is often accompanied by degeneration of the cerebellum. Moreover, similar to autism, ataxia is often associated with deficits in executive function, emotional processing, and cognition. The purpose of this chapter is to summarize findings of cerebellar pathology in autism and how cerebellar pathology may contribute to the behavioral and cognitive aspects of autism and ataxia.

Keywords

Autism · Cerebellar pathology · Cognition · Fragile X mental retardation protein · Spinocerebellar ataxia

Introduction

Autism is a neurodevelopmental disorder that is characterized by deficits in communication, behavior, and cognition (APA 2013). There are both genetic (reviewed by Abrahams and Geschwind 2010; El-Fishawy and State 2010) and environmental (reviewed by Kinney et al. 2008; Herbert 2010) contributions to autism. Autism has a rising incidence of 15.8 per 1,000 (1 in 54) in the United States (CDC 2020). Autism is a heterogeneous disorder and is often comorbid with a number of other disorders including fragile X syndrome (FXS) (Hagerman et al. 2005), seizure disorder (Tuchman and Rapin 2002), tuberous sclerosis (Witnitzer 2004), and Down syndrome (Starr et al. 2005). Extensive brain pathology has been documented in subjects with autism (Bauman and Kemper 1985, 2003, 2005). While much research has focused on the prefrontal cortex, amygdala, and hippocampus, the cerebellum has emerged as a site of study in recent years (Fatemi et al. 2012; Hampson and Blatt 2015). The purpose of this chapter is to describe the role of the cerebellum in functions that are impaired in autism, the pathology of the cerebellum in subjects with autism, and finally, a discussion of multiple markers that are altered in the cerebella of subjects with autism.

The Cerebellum Has a Role in Multiple Domains Impaired in Autism

While traditionally, the cerebellum was believed to be primarily associated with motor control, recent evidence indicates roles in language, cognition (including visual, spatial, executive, and working memory), and behavior (Salman and Tsai 2016; Stoodley 2012). Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies have shown activation of the cerebellum for a number of tasks largely thought to be controlled by prefrontal cortex and the limbic system. A meta-analysis of fMRI and PET studies has found activation of distinct

areas of the cerebellum in response to a variety of tasks (Stoodley and Schmahmann 2009). The study found that motor and sensorimotor tasks were localized primarily to the anterior lobe, while higher function tasks including working memory, executive function, and language were localized to the posterior lobe of the cerebellum (Stoodley and Schmahmann 2009). Emotional processing was localized to vermal lobule VII and lateral posterior hemisphere (Stoodley and Schmahmann 2009). The involvement of the cerebellum with these processes is due to functional connections between the cerebellum and frontal cortices via the cerebello-thalamo-cortical and cortico-ponto-cerebellar loops that have been identified in anatomical studies (Kelly and Strick 2003; Middleton and Strick 1994; Schmahmann and Pandya 1989). Middleton and Strick (1994) provided anatomical evidence for connections between the cerebellum and frontal and parietal association areas. Connections between the posterior parietal cortex and the cerebellum have been identified (Schmahmann and Pandya 1989). Moreover, connections between dorsolateral prefrontal cortex and cerebellum have been characterized more recently (Kelly and Strick 2003).

Additional evidence for the cerebellum playing a role in multiple domains aside from motor function come from studies of behavioral deficits in individuals where abnormalities or lesions of the cerebellum exist. Cerebellar cognitive affective syndrome (CCAS) describes impaired executive function, verbal fluency, abstract reasoning, and emotional processing in subjects with cerebellar lesions (Schmahmann and Sherman 1998; Schmahmann et al. 2007; Schmahmann 2010). Lesions in the right cerebellar hemisphere have been associated with impaired language, while lesions in the left cerebellar hemisphere have been associated with visual-spatial deficits (Scott et al. 2001; Gottwald et al. 2004). More recently, Stoodley et al. (2016) found that patients with lesions of the posterior cerebellum displayed lower scores on language (right crus I and II, extending through IX), spatial function (bilateral crus I and II, right lobule VIII), and executive function (lobules VII and VIII). Schmahmann et al. (2007) identified deficits that are similar to those observed in subjects with autism spectrum disorders, obsessive-compulsive disorder, attention-deficit hyperactivity disorder, and bipolar disorder, among others.

Structural Pathology of the Cerebellum in Autism

Multiple structural pathologies of the cerebellum in autism have been identified (Fatemi et al. 2012; Hampson and Blatt 2015). Changes in overall cerebellar and vermal volume, in gray and white matter, as well as in density of Purkinje cells and altered connectivity to the frontal cortex have all been characterized. Studies of cerebellar size comparing subjects with autism and matched controls have shown inconsistent results. Larger volumes of cerebellum and cerebellar hemispheres have been found in subjects with autism (Hardan et al. 2001). Children with autism have shown increased cerebellar volume (Sparks et al. 2002; Herbert et al. 2003; Palmen et al. 2005), while another study found no effect in children (Hazlett et al. 2005). In contrast, a study of adults with autism spectrum disorders (ASD) found significantly reduced cerebellar volumes (Hallahan et al. 2009). No differences in cerebellar

volume between ASD groups (autism, Asperger's syndrome, pervasive developmental disorder – not otherwise specified) have been found (Hallahan et al. 2009). Other groups have found no difference between subjects with autism and matched controls (Piven et al. 1997; Manes et al. 1999; Scott et al. 2009).

A number of investigators have examined potential changes in volume of the cerebellar vermis. Hypoplasia of vermal lobules VI–VII in subjects with autism was identified by Courchesne et al. (1988, 1994, 2001). Other studies have shown no difference in the size of the vermis or vermal lobules in subjects with autism when compared with controls (Holttum et al. 1992; Kleiman et al. 1992; Hardan et al. 2001; Scott et al. 2009). However, Scott et al. (2009) found that when ASD subjects were broken down to low-functioning autism, high-functioning autism, and Asperger's syndrome groups, there was a significant reduction in volume of the vermis in the high-functioning autism group. A meta-analysis of vermal hypoplasia in subjects with autism found significantly reduced volumes for vermal lobules I–V and V–VII (Stanfield et al. 2008). Additionally, a study of children with autism found reduced total vermal area as well as areas for vermal lobules I–V and VI–VII when controlled for cerebral or cerebellar volume (Webb et al. 2009).

Multiple studies have demonstrated significant reductions in gray matter in the cerebella of subjects with autism (D'Mello et al. 2015; McAlonan et al. 2005; Rojas et al. 2006; Stoodley 2014; Toal et al. 2009). Rojas et al. (2006) found reduced gray matter in multiple regions of the cerebellum (left cerebellar crus I, left cerebellar lobule VIII, left cerebellar lobule IX, right cerebellar crus I). Moreover, these reductions correlated with scores assessing repetitive and stereotyped behavior, and social behavior and communication (Rojas et al. 2006). McAlonan et al. (2005) found reduced gray matter in children with autism. Toal et al. (2009) found reduced gray matter in autistic subjects with or without psychosis. Moreover, autistic subjects with psychosis also displayed reduced white matter in the cerebellum. A more recent study examining regional gray matter changes in the cerebella of children with autism identified reduced gray matter in cerebellar lobule VII (crus I/II) (D'Mello et al. 2015). A meta-analysis similarly identified reduced gray matter in vermal lobule IX, left lobule VIIB, and right crus I of subjects with autism (Stoodley 2014).

Purkinje cell (PC) loss has been a fairly constant finding in the cerebella of subjects with autism (Williams et al. 1980; Bauman and Kemper 1985, 2003, 2005; Ritvo et al. 1986; Bailey et al. 1998; Palmen et al. 2004; Skefos et al. 2014; Vargas et al. 2005; Wegiel et al. 2014a). PC loss has been associated with presence of seizures (Crooks et al. 2000) which is relevant to autism as estimates of comorbid seizure disorder in autism range from 4% to 44% (Tuchman and Rapin 2002). Wegiel et al. (2014b) also observed a reduction in overall PC number and density in both children and adults with autism.

Animal models of autism have demonstrated the importance of PC number and density and function on symptoms of autism. In a mouse model of PC loss, Martin et al. (2010) found that reduced PC number correlated with greater activity and repetitive behavior, suggesting a role for the cerebellum in these symptoms of autism. A number of proteins including autism susceptibility candidate 2 (Auts2), phosphatase and tensin homolog (Pten), Reelin, SH3 and multiple ankyrin repeat

domains 2 (Shank2), and tuberous sclerosis 1 (Tsc1) have been associated with altered PC density, function, and autistic-like behavior in mouse models of autism (Bedogni et al. 2010; Cupolillo et al. 2016; Magliaro et al. 2016; Peter et al. 2016; Tsai et al. 2012). In a mouse model where PTEN inactivation was induced in PCs, mice displayed impaired sociability, presence of repetitive behaviors, and deficits in motor learning (Cupolillo et al. 2016). Heterozygous reeler mice (HRM) display approximately half the amount of Reelin as wild-type mice (for a discussion of Reelin and autism, please see section "Deficits in Specific Proteins in Autistic Cerebellum"). Magliaro et al. (2016) found reduced PC density in the cerebellar vermis of male and female HRM mice and that these cells displayed a disorganized arrangement. PCs in Shank2 knockout mice display impaired plasticity and long-term potentiation with inhibitory input to these cells being elevated (Peter et al. 2016). The selective inactivation of Tsc1 in PC cells in the developing cerebellum of mice resulted in impaired social interaction and repetitive behavior and vocalizations (Tsai et al. 2012). Finally, a developmental study identified that Auts2 in the cerebellum was initially localized to multiple cell types including PCs and granule neurons but by adulthood was exclusively localized to PCs (Bedogni et al. 2010). Taken together these findings point to the importance of PCs to symptoms of autism and that dysfunction of specific autism candidate genes may contribute to these observed deficits.

Other groups, however, have failed to find a difference in PC density in subjects with autism (Fatemi et al. 2002a; Whitney et al. 2008a). Fatemi et al. (2002a) found no difference in PC density between subjects with autism and matched controls (Fatemi et al. 2002a). However, there was a reduction in the cross-sectional area of PCs in subjects with autism, suggesting atrophy of these cells in subjects with autism (Fatemi et al. 2002a). Similarly, Whitney et al. (2008a) also failed to find significant reductions in PC density between subjects with autism and matched controls. In contrast to previous studies, this group used calbindin-D28k as a marker of PCs, maintaining that this was a more reliable marker for PCs than the more commonly used Nissl staining (Whitney et al. 2008a, b).

There is evidence that connectivity between the cerebellum and other brain regions is impaired in subjects with autism. A diffusion tensor imaging study of children with autism found increased diffusivity of bilateral superior cerebellar peduncles, increased fractional anisotropy (FA) in the right middle cerebellar peduncle, and reversal of the asymmetry pattern of FA in inferior cerebellar peduncle (Sivaswamy et al. 2010). Importantly, the middle and inferior cerebellar peduncles contain afferent fibers of the cerebellum, the majority of which connect with the frontal lobe. Changes in diffusivity and FA indicate altered microstructural integrity and may be the result of altered myelination, axonal number, diameter, and orientation (Sivaswamy et al. 2010). A study using weighted MRI tractography identified reduced Purkinje cell fibers in the pathway that connects the cerebellar cortex and the right ventral dentate nucleus (VDN) in children with autism (Jeong et al. 2014). Moreover, there were reduced FA values on pathways connecting the cerebellar cortex with the left and right VDN as well as the right dorsal dentate nucleus (Jeong et al. 2014). An fMRI study of high-functioning children with autism found reduced cerebellar activation and increased activation of the premotor regions during a motor

task (Mostofsky et al. 2009). The authors conclude that the inability to recruit cerebellar regions suggests decreased functional connectivity between these areas (Mostofsky et al. 2009). Further evidence of altered connectivity between the cerebellum and the frontal cortex come from studies of cerebellar lesions. Congenital cerebellar abnormalities and cerebellar lesions are known to result in deficits of working memory (Ravizza et al. 2006) and executive function (Karatekin et al. 2000; Riva and Giorgi 2000; Tavano et al. 2007), roles associated with the dorsolateral prefrontal cortex.

Deficits in Specific Proteins in Autistic Cerebellum

A number of molecules associated with gamma-aminobutyric acid (GABA) signaling display altered expression in the cerebella of subjects with autism. Glutamic acid decarboxylase (GAD) is the rate-limiting enzyme in the conversion of glutamate to GABA. There are two isoforms of GAD, GAD 65 kDa protein (GAD65) and GAD 67 kDa protein (GAD67). In the cerebella of subjects with autism, there are significant reductions in GAD65 protein when compared with normal controls (Fatemi et al. 2002b). mRNA for GAD65 has also been found to be reduced in subpopulations of cells in cerebellar dentate nuclei of subjects with autism (Yip et al. 2009), verifying the earlier findings of Fatemi et al. (2002b). GAD67 mRNA has also been shown to be reduced in the cerebella of subjects with autism, specifically in Purkinje cells (Yip et al. 2007). In contrast, Yip et al. (2008) found upregulated expression of GAD67 mRNA in basket cells in the cerebella of subjects with autism, suggesting cell-specific differences in GAD expression (Yip et al. 2008).

In addition to GAD, reductions in $GABA_A$ and $GABA_B$ receptor subunits in the cerebella of subjects with autism have been documented (Fatemi et al. 2009a, b). $GABA_A$ receptors are ligand-gated ion Cl^- channels that mediate the fast inhibitory action of GABA, while $GABA_B$ receptors are G-protein-linked, metabotropic K^+/Ca^{2+} channels that produce slow, inhibitory signals. Reduced protein expression of $GABA_A$ receptor alpha 1 subunit (GABRα1), $GABA_A$ receptor beta 3 subunit (GABRβ3), $GABA_B$ receptor 1 (GABBR1), and $GABA_B$ receptor 2 (GABBR2) has been observed in the cerebella of subjects with autism (Fatemi et al. 2009a, b). The reduction of GABBR1 protein in cerebella of subjects with autism was matched by reduced expression of GABBR1 mRNA (Fatemi et al. 2010). Additional upregulation of mRNA for $GABA_A$ receptor alpha 2 subunit (GABRα2), $GABA_A$ receptor alpha 3 subunit (GABRα3), $GABA_A$ receptor alpha 4 subunit (GABRα4), $GABA_A$ receptor alpha 5 subunit (GABRα5), $GABA_A$ receptor beta 1 subunit (GABRβ1), GABRβ3, $GABA_A$ receptor gamma 2 subunit (GABRγ2), $GABA_A$ receptor gamma 3 subunit (GABRγ3), and $GABA_A$ receptor theta subunit (GABRθ) and downregulation of mRNA for $GABA_A$ receptor alpha 6 subunit (GABRα6) and $GABA_A$ receptor beta 2 subunit (GABRβ2) were also observed in cerebella of subjects with autism (Fatemi et al. 2010, 2014).

The Reelin signaling system is also impaired in the cerebella of subjects with autism (Fatemi et al. 2005). Reelin is a glycoprotein that during development is

involved in guiding neurons and radial glial cells to their correct positions in the developing brain (Forster et al. 2002; Luque et al. 2003). Altered expression of Reelin may contribute to disrupted corticogenesis and abnormal synaptic plasticity. Reduction in the Reelin 410 kDa and 180 kDa isoforms in the cerebella of subjects with autism have been documented (Fatemi et al. 2005). In contrast to this reduction of Reelin protein, mRNA for very low-density lipoprotein receptor (VLDLR), a receptor for Reelin, was significantly upregulated in the cerebella of subjects with autism (Fatemi et al. 2005), perhaps as a compensatory mechanism for reduced Reelin expression. Finally, a downstream molecule in the Reelin signaling system, disabled 1 (DAB1), showed reduced mRNA expression in the cerebella of subjects with autism, providing further evidence of Reelin signaling dysfunction (Fatemi et al. 2005).

There are multiple similarities between autism and fragile X syndrome (FXS) including repetitive behavior, decreased attention, poor eye contact (Hagerman 1996), and presence of seizures. Moreover, 2–3% of all subjects with autism are also comorbid for FXS (Hagerman et al. 2005). The multiple pathologies of FXS are caused by a loss in function of the fragile X mental retardation 1 (FMR1) gene and the absence of its protein product fragile X mental retardation protein (FMRP). FMRP expression has been shown to be significantly reduced in cerebellar vermis, in adults, but not children, with autism (Fatemi et al. 2011). This is the first demonstration of a reduction of FMRP in the brains of subjects with autism who do not have FXS. A subsequent study identified reduced expression of FMRP phosphorylated at serine 499 in cerebellar vermis of adults and children with autism (Rustan et al. 2013). Phosphorylated FMRP, represents an inactive form of FMRP that is associated with stalled, translationally inactive ribosomes (Ceman et al. 2003).

The absence of FMRP in subjects with FXS is theorized to be accompanied by unregulated signaling by metabotropic glutamate receptor 5 (mGluR5), ultimately leading to deficits associated with FXS (Krueger and Bear 2011). The dimeric (active) form of mGluR5 as well as total mGluR5 protein has been found to be increased in the cerebellar vermis of children, but not adults, with autism (Fatemi et al. 2011). Moreover, targets of FMRP-mGluR5 signaling display altered expression in the cerebellar vermis (Fatemi et al. 2013). Increased expression of Ras-related C3 botulinum toxin substrate 1 (RAC1), reduced expression of amyloid beta A4 precursor protein (APP) 120 kDa, and the reduction of the 66 kDa and 33 kDa species of striatal-enriched protein tyrosine phosphatase (STEP) has also been observed in cerebellar vermis of subjects with autism (Fatemi et al. 2013). RAC1, which modulates dendritic spine morphology, is overexpressed in Fmr1 KO mice and may contribute to impaired synaptic plasticity (Bongmba et al. 2011). APP is present both presynaptically and postsynaptically where it is associated with multiple targets including NMDA receptors and may play a role in NMDA signaling (Cousins et al. 2009; Innocent et al. 2012). A study has shown that genetic reduction of STEP improves cognition, synaptic plasticity, and NMDAR subunit expression in mouse models of Alzheimer's disease (Zhang et al. 2010). Taken together, these findings support the hypothesis that FMRP-mGluR5 signaling is disrupted in the

cerebella of subjects with autism. This could have profound consequences and help explain the overlap of symptoms between FXS and autism.

Mouse and *Drosophila* FMR1 knockouts have shown that the absence of FMR1 also impacts the presence of multiple $GABA_A$ receptor subunits (Adusei et al. 2010; Braat et al. 2015; El Idrissi et al. 2005; D'Hulst et al. 2006; Gantois et al. 2006; Hong et al. 2012). With regard to the cerebella of Fmr1 KO mice, reductions in mRNA for GABRα1, GABRα2, GABRα3, GABRβ1, and GABRβ2 have been observed (Braat et al. 2015; Hong et al. 2012). Interestingly, GABRβ3 is significantly reduced in cerebellar vermis of adults with autism (Fatemi et al. 2011). The reductions in $GABA_A$ subunits may be the result of reduced FMRP.

Markers of apoptosis, inflammation, and oxidative stress have also shown altered expression in autistic cerebellum. Significant increases in a number of proapoptotic proteins including p53, cathepsin D, and caspase 3 have been identified in the cerebella of subjects with autism (Sheikh et al. 2010a, b). In contrast, Araghi-Niknam and Fatemi (2003) found that the antiapoptotic protein B-cell CLL/lymphoma 2 (BCL2) was reduced in the cerebella of subjects with autism when compared with controls, a finding which has since been replicated (Sheikh et al. 2010a). Nonsignificant reductions in PTEN have been observed in the cerebella of both children and adults with autism (Fatemi et al. unpublished observations). Genetic studies have linked PTEN to autism (Varga et al. 2009; Redfern et al. 2010). PTEN has also been shown to modulate p53 expression in animal models (Cipriano et al. 2010; Zheng et al. 2010). Glial fibrillary acidic protein (GFAP), an indicator of astroglial activation, has also been shown to be elevated in the cerebella of subjects with autism (Laurence and Fatemi 2005; Vargas et al. 2005). Moreover, microglial activation has been documented in the cerebella of subjects with autism as measured by an increase in major histocompatibility complex II marker HLA-DR (Vargas et al. 2005). Deficits in the glutathione antioxidant system have been identified in the cerebella of subjects with autism (Chauhan et al. 2012; Gu et al. 2013; Rose et al. 2012). Chauhan et al. (2012) identified reduced expression of the oxidized (GSH) form of glutathione along with increased expression of the reduced (GSSG) form. Moreover, in the cerebellum of subjects with autism, total glutathione (tGSH) was reduced as was the ratio of GSH/GSSG, suggesting redox imbalance (Chauhan et al. 2012). The reductions of GSH and GSH/GSSG ratio in cerebella of subjects with autism were subsequently verified by Rose et al. (2012). Glutamate cysteine ligase (GCL), glutathione peroxidase (GPx), and glutathione S-transferase (GST) are enzymes which display reduced activities in cerebella of subjects with autism, suggesting impaired activity (Gu et al. 2013). Finally, increases in markers of oxidative stress have been observed in the cerebella of subjects with autism (Rose et al. 2012; Sajdel-Sulkowska et al. 2008, 2009). Increased expression of 3-nitrotyrosine (3-NT) (Sajdel-Sulkowska et al. 2008, 2009; Rose et al. 2012), a marker of oxidative protein modification, and 8-oxo-deoxyguanosine (8-oxo-dG) (Rose et al. 2012), a marker of oxidative DNA damage, have been observed in the cerebella of subjects with autism. Taken together, these studies provide evidence of dysregulation of apoptosis, inflammation, and oxidative stress which could contribute to the cerebellar pathology of autism

Ataxia

Ataxia is defined as a loss of motor coordination, especially with reference to gait. Pathology of the cerebellum, brain stem, and spinal cord all contribute to the development of ataxia. There are multiple forms of cerebellar ataxia including spinocerebellar ataxias (SCAs) which are dominantly inherited (reviewed by Paulson 2009; Didonna and Opal 2016), recessive-inherited ataxias including ataxia telangiectasia and Friedreich ataxia, X-linked [the most common being fragile X-associated tremor/ataxia syndrome (FXTAS)], and mitochondrial disorders (reviewed by Manto and Marmolino 2009; Didonna and Opal 2016). Cerebellar stroke patients often display ataxia (Picelli et al. 2017; Stoodley et al. 2016). Patients with lesions in lobules III–VI display higher ataxia scores than those with lesions in the posterior cerebellum (Stoodley et al. 2016). A separate study found that 1 week following stroke, injuries to V, VI, VIIA crus I, VIIA crus II, VIIB, VIIIA, and VIIIB lobules as well as the middle cerebellar peduncle were associated with scores on the International Cooperative Ataxia Rating Scale (ICARS) (Picelli et al. 2017). Injuries to VI, VIIA crus I, VIIA crus II, VIIB, VIIIA, and VIIIB lobules and middle cerebellar peduncle were associated with higher ICARS score 3 months after injury (Picelli et al. 2017).

SCAs have a prevalence of 1–4 per 100,000 (Manto 2005; Ruano et al. 2014). Currently, 49 SCAs have been described (neuromuscular.wustl.edu/ataxia/domatax.html), displaying extensive variability in phenotype (Didonna and Opal 2016; Paulson 2009), and commonly characterized by progressive degeneration of the cerebellum often with accompanying degeneration of the brain stem and spinal cord (Taroni and DiDonato 2004). Expansions within many of the causative genes (i.e., SCA3, SCA6, etc.) have been identified, and these expansions increase when passed on to the next generation, often producing more severe symptoms and earlier onset (Kawaguchi et al. 1994; Zhuchenko et al. 1997; Manto and Marmolino 2009; Paulson 2009). Some SCAs are considered pure cerebellar ataxias as degeneration is largely confined to the cerebellum (i.e., SCA5, SCA6, SCA11), while others have more pervasive degeneration in other brain regions or other parts of the central nervous system (i.e., SCA3, SCA7) (Paulson 2009). Deficits in executive function, memory, attention, and Theory of Mind have been identified in subjects with SCAs (Argyropoulos et al. 2020; Burk et al. 2001, 2003; Globas et al. 2003; Kawai et al. 2004; Garrard et al. 2008; Hoche et al. 2016, 2018). These impairments mirror deficits in autism and provide further evidence of the cerebellar involvement in processing cognitive and emotional functions.

FXTAS is a late-onset neurodegenerative disorder observed in individuals with FMR1 premutation, that is, individuals with 55–199 CGG repeats in the 5′ untranslated region of the gene (Hessl and Grigsby 2016). FXTAS is present in 45% of male premutation carriers and 11–18% of female carriers by age 50 (Rodriguez-Revenga et al. 2009). FXTAS premutation carriers display higher total scores on Autism-Spectrum Quotient (AQ) questionnaires when compared with controls as well as on subdomains of attention switching, social skills, communication, and imagination (López-Mourelo et al. 2017). Interestingly, FXTAS

premutation carriers also displayed higher scores on subdomains of communication and imagination versus non-FXTAS premutation carriers, suggesting that they display a broader autistic phenotype (López-Mourelo et al. 2017). White matter abnormalities have been observed in the cerebella of subjects diagnosed with FXTAS including the middle cerebellar peduncle (Brunberg et al. 2002; Filley et al. 2015). Moreover, cerebella of subjects with FXTAS display reduced expression of mGluR5 and excitatory amino acid transporter 1 (EAAT1) indicating abnormal glutamatergic signaling which could potentially contribute to the severity of FXTAS (Pretto et al. 2014).

Studies have shown that some subjects with congenital ataxia also show cerebellar hypoplasia, a finding similar to subjects with autism (Steinlin et al. 1998; Wassmer et al. 2003; Åhsgren et al. 2005; Vedolin et al. 2013). Additionally, Åhsgren et al. (2005) found that 16 of 32 study subjects with congenital ataxia also displayed symptoms of autistic spectrum disorder. Haas et al. (1996) found cerebellar hypoplasia in a group of pediatric autism patients when compared with controls. These subjects also displayed ataxia as measured by the difficulty of walking in a straight line (Haas et al. 1996). Irregular gait has also been shown to be displayed by adults with autism (Hallet et al. 1993). A study of gait function in newly diagnosed children with autism found that these children were less able to walk in a straight line, less coordinated, and showed variable or inconsistent movements when compared with a control group (Rinehart et al. 2006).

Conclusions and Future Directions

The cerebellum has roles in multiple domains impaired by autism including emotional processing, executive function, working memory, motor control, and language. In the cerebella of subjects with autism, there is extensive pathology including vermal hypoplasia, changes in gray and white matter and in Purkinje cell density and area, and disrupted connections to the frontal cortices. Markers of GABAergic function (GAD65/GAD67, $GABA_A$, and $GABA_B$ receptors), proper brain development (Reelin), apoptosis (p53, PTEN, Bcl-2), inflammation, and oxidative stress (GFAP, 3-NT, 8-oxo-dG, GSH, GSSG, GCL, and GPx) have been shown to display altered expression in autism. Finally, SCAs provide further evidence of the cerebellum's influence in multiple domains including both movement and cognition. These observed changes further underline the importance of the cerebellum to the pathology of autism. Future postmortem and animal model studies are required to fully elucidate the role of cerebellar pathology in cognitive domains of autism.

Cross-References

► Approach to the Differential Diagnosis of Cerebellar Ataxias
► Cerebro-cerebellar Connections

▶ GABA and Synaptic Transmission in the Cerebellum
▶ Lesion-Symptom Mapping of the Human Cerebellum
▶ X-Linked Ataxias

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