A theory inspired proposal for a novel medical treatment in autism. The cerebellar model of autism and the hypothesis of dorsal stream dysfunction: evidence from idiopathic and syndromic cases.

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Abstract

The cerebellum figures prominently in the pathophysiology of idiopathic autism. Many syndromic comorbid cases and animal studies also highlight cerebellar involvement. The role of the cerebellum is implicated in cognitive and affective disorders. However, there remains a profound gap in understanding the route from genes, the effect of mutations on Purkinje cells and ultimately the behavioural phenotype. Given that conditions like autism are disorders of consciousness it is likely that progress will be made beyond the data generating enterprise, by improved theoretical models of the mind-body gap. A way forward is the proposal of consciousness as embodiment of a process of world discovery through motor efference copy. The cerebellum and basal ganglia are essential to a component theory of motor efference copy, providing a heuristic for understanding the structure of cortical dorsal and ventral stream pathways of a sensory modality. This then, further suggests that autism results from a selective dorsal stream dysfunction with all the attendant and hierarchical features that follow such a model and lead to both high level social and attentional deficits as well as lower level motor and restrictive interests. The paper aims to present evidence for dorsal stream dysfunction and how it may relate to a primary cerebellar pathology. The involvement of the cerebellum in most if not all syndromic cases of comorbid ASD is then presented. Finally, it is shown how such insights can be used to propose a general medical intervention based on the use of cerebellar rTMS across the disorder spectrum.

1. Introduction

The cerebellum is a structure at the base of the brain with complex processing capabilities. This region is typically recognized for its role in motor function. Ataxic syndromes are defined by a lack of coordination of muscle movements that typically includes gait abnormalities, speech dysarthria and head and truncal titubation. However, recent research suggests the posterior cerebellum and expanded hemispheres play a critical role in cognition. (J. D. Schmahmann and Sherman 1998). This includes the non-motoric ability to shift attention, spatial awareness and perspective taking, which can account for higher level processes such as empathic understanding abstraction of language abilities and general social interactions.

Historically, the main focus of neuroscientific research into cognition was centred on neocortical grey matter of the cerebrum and the prefrontal cortex in particular. However, recent evidence from human cases of pathological brain processes, post mortem findings from psychiatric literature and animal models suggest a far more prominent role for the cerebellum in cognition and disease than previously appreciated.

The enigmas posed by modern neuropsychological descriptions of mental disease may be solved by exploration of paradigms that bridge the mind-body gap and that will ultimately both inform and be informed by clinical case studies. Autism spectrum disorder is a case in point that is defined clinically by impairments in social interaction and repetitive stereotyped behaviours. However, an expanding literature reveals a number of neurocognitive deficits that appear at its core fundamental to understanding the disease process. These include marked sensory aberrations, motor incoordination, attentional impairments, altered spatial awareness (Baum, Stevenson, and Wallace

2015; Greenfield et al. 2015). The latter study showed an aberrant interplay between conflicting proprioceptive and visual input in a virtual version of a rubber hand illusion task. The most well-replicated pathophysiology implicating the cerebellum has never been formally integrated into diagnostic classifications. In fact, the criticism surrounding the recent release of DSM V statistical manual refers to the lack of innovation in biological markers. This in turn is likely the result of a lack of consensus on the mind-body problem i.e being informative of the relative importance of pathophysiological findings.

It is the aim of this paper to use a developmental model of spatial cognitive function based on a component motor theory of reafferent algorithms (C. Vakalopoulos 2005; Costa Vakalopoulos 2005). The model proposes the idea of an organism that discovers and gradually builds a literal picture of the world through physical interactions with objects in its environment. The feedback an infant and toddler receive through their actions are coded according to irreducible components of their activities i.e. (i) force they apply and (ii) proprioceptive information received. This feedback is the basis of organizing principles that structure sensory hierarchies into dorsal and ventral streams and that are 'embodied' by action. Applied forces uniquely categorize information as ventral stream recognition pathways, there being no proprioceptive reafferent component as spatial localization is not generally required for identification. The proprioceptive component algorithm underlies the function of dorsal stream pathways involving cortical areas such as the parietal and dorsolateral prefrontal cortex and although it defines the dorsal stream, reafferent algorithms of force also constitute a separate element of the same pathway.

Visuomotor integration of perceptual information is processed in the cerebellum and through a mechanism of motor efference copy organizes spatial attentional abilities. The emergence of spatial awareness and the ability to shift the focus of attention is synonymous with the acquisition of these algorithms (C. Vakalopoulos 2005; Costa Vakalopoulos 2005). Any disruption of this process at

critical stages of development will portend the hierarchically-based syndrome that describes the features of autism spectrum disorders. The model makes a clear statement that an individual has no phenomenal awareness until it can interact with the world in a meaningful way i.e. conscious awareness is acquired and is an attribute of applied motor algorithms to coincident sensory data.

2. Cerebellum and spatial cognition

The cerebellum is implicated in cognitive function by its robust pathways to the cerebrum and that are relayed by deep cerebellar nuclei. They project not only to primary motor areas, but also form loops to regions of the parietal and frontal cortex that play a known role in cognition (Middleton and Strick 2000) . From the very same regions are reciprocal corticopontine projections (Figure 1) that ultimately transmit information to the cerebellum itself (J. D. Schmahmann and Pandya 1997). Phylogenetically, the expansion of the neocerebellum mirrors that of the neocortex and the range of cognitive functions higher primates and especially humans possess [\(Leiner, Leiner, and Dow 1989\)](#).

Figure 1: Summary of corticopontine projections. The yellow regions are not known to project to pons (J. D. Schmahmann and Pandya 1997).

Characteristically, corticopontine projections originate from areas including posterior parietal, superior temporal and DLPF cortices that are considered part of the ‘dorsal stream’ visual pathways. The dorsal stream refers to a pathway of information processing that is used during the processing of any visual task and which is essential to maintaining spatial attention and the execution of visuomotor tasks. It is involved in processing the relationship of an object in space relative to an individual. On the other hand, the ventral stream, a parallel visual pathway including the inferior temporal cortex, does not have any projections to the pons and thus cerebellum, and lacks cerebellar feedback. It is responsible for visual object recognition. This makes sense because recognition is independent of where its location is relative to the individual. The dorsal-ventral stream dichotomy of the visual system is now a well-accepted feature of cortical organization (Goodale and Milner 1992; Mishkin and Ungerleider 1982). A double dissociation is evident, where damage to the parietal cortex prevents appropriate reaching and grasping movements, but allows verbal descriptions of the same object. Conversely, damage to the inferior temporal cortex results in object agnosia or inability to name object, but remarkably effortless reaching and grasping by the same individual.

There are numerous studies showing a direct causal or presumed link between cerebellar dysfunction and certain restricted aspects of cognition. These tend to involve neglect of features in detection tasks with multiple objects and in particular the failure or marked slowing of covert attentional shifts as measured by reaction times (E. Courchesne et al. 1994). Changes in a number of executive functions including working memory, set shifting and even emotional dysregulation have been attributed to cerebellar damage in lesion studies (Baillieux et al. 2010; Jeremy D. Schmahmann 2004). A group of cerebellar patients with a variety of underlying causes showed

modest to moderate impairments in a range of cognitive tasks including visuospatial, sequencing, attention and executive (Tedesco et al. 2011). Deficits were most prominent in those patients with olivo-ponto-cerebellar atrophy and lesions of the posterior cerebellum. The posterior cerebellum is generally regarded as the critical area for cognitive functions (Grimaldi and Manto 2012). Although cognitive dysfunction is relatively broad, visuospatial abilities appear to be over-represented (M. Molinari et al. 2004a; Marco Molinari and Leggio 2007). The ability to rotate objects mentally and spatial sequencing deficits were offered as potential underlying mechanisms. These findings can present a more fundamental picture of the high-level impairments described as ‘theory of mind’ where manipulation of imagery and events are crucial in understanding other persons’ motives (Baron-Cohen, Leslie, and Frith 1985).

Rats having acquired procedural skills in a Morris Water Maze (MWM) prior to cerebellectomy can learn to find a hidden platform (Petrosini, Molinari, and Dell’Anna 1996). This suggests that the cerebellum is not directly implicated in the acquisition of allocentric spatial cues, a ventral stream function of the hippocampus, but is involved in dorsal stream execution of spatially related tasks¹. Aspiration of the posterior parietal cortex or hippocampus causes severe impairment of the MWM during both acquisition and retention phases (DiMattia and Kesner 1988). Rats after cerebellar lesions are perform similar to controls on the retention tasks. The difference in findings is consistent with the role of the cerebellum in the algorithmic expression by the parietal cortex of learned behaviours. A further case study implies a cognitive egocentric spatial dimension and not just motoric role for the cerebellum. fMRI showed activation of the left cerebellar hemisphere, vermis and right parietal cortex in a Landmark bisection judgment task, which is often used as a measure of unilateral neglect (Fink et al. 2000).

¹ Allocentric cues and dorsal stream execution of egocentric visuomotor tasks can obviously confound interpretation of studies assessing the relative roles of the hippocampus and posterior parietal cortex. For theoretical discussions regarding this issue see [32,33].

Cortico-cerebellar diaschisis is a loss of function in parietal cortex associated with cerebellar lesions due to disruption of long-range connections that demonstrates the importance of the cerebellum to cognition (Grealy and Lee 2011; Miller et al. 2010). Subjects with cerebellar lesions have deficits more commonly associated with parietal function, including disturbances of attention (Baillieux et al. 2010), ideomotor apraxia and right unilateral neglect (Silveri, Misciagna, and Terrezza 2001). The latter case study is particularly instructive as neglect most commonly involves the left hemispace associated with right parietal lesions. The right cerebellar lesion suggests widespread left frontoparietal and temporoparietal diaschisis to generate a clinically significant neglect in the right hemispace.

A summary of the roles of the cerebellum in behaviour with particular emphasis on cognition shows a marked overlap with deficient faculties in autism (Koziol et al. 2014). The findings also imply that the cortical effects of cerebellar pathophysiology are not limited to the visual system, but would affect spatial awareness and attentional attributes in all modalities. Thus, a cerebellar cause of dysfunction in distributed but parallel modal networks is easier to reconcile with the clinical findings in autism of pervasive attentional deficits. This concept is quite different from nodal abnormalities in emotional centres, such as the ventromedial cortex or amygdala and is secondarily associated with impaired cognitive mentalizing or neglect of socially relevant perceptual features.

3. Autism pathophysiology and dorsal stream function

3.1 Pathophysiology

A recent commentary highlights a disconnection between autism spectrum disorder as a clinical entity and the logical pathway that leads there from genetics and neuroanatomical findings (Kennedy, Paul, and Adolphs 2015). It refers to the meta-analysis of null findings for callosal size

in ASD in the same issue (Lefebvre et al. 2015). Implicit in the discussion are corticocentric biases toward connectionist theories. Concordant with this pervasive view is the emergence of theories like those based on subtle morphological changes in cortical minicolumns (Casanova et al. 2002). Limbic system models also figure prominently with neuroimaging studies showing decreased amygdala activation in theory of mind tasks (Baron-Cohen et al. 2000) and post mortem findings such as an increase in cell density and smaller neuronal size (Rapin and Katzman 1998). Such findings extend to other limbic areas including anterior cingulate, hippocampus and septum with often no abnormalities reported in the cortex, basal ganglia or hypothalamus (Margaret L. Bauman and Kemper 2005).

However, the most robust findings from post-mortem studies refer uniquely to the cerebellum with some showing 50 % loss of Purkinje cells in 90% of cases with core autistic diagnoses (Bailey et al. 1998). It is the most reproducible finding at autopsy and most autistic brains reported to date show significant decreases in Purkinje cells (Margaret L. Bauman and Kemper 2005; Ritvo et al. 1986). Purkinje cells are the sole output of the cerebellum. Loss primarily affects the cerebellar hemispheres (M. L. Bauman and Kemper 1996). A conspicuous exception to this was a stereological study using Calbindin-D28k, where only three of six cases showed lower than control Purkinje cell numbers and did not correlate with clinical severity (Whitney et al. 2008). 30 of 45 cases reviewed in a separate study found a decrease in the number of Purkinje cells and these recent studies are more representative of the autistic spectrum with a proportionately lesser number exhibiting mental retardation and epilepsy (Skefos et al. 2014). Density changes were most prominent in posterolateral hemispheres especially crus I and II. Even in this group the latter areas showed 20% reduction in Purkinje cell density. Purkinje cell density in lobule X did correlate with an ADI-R measure of patient social eye contact, but significance didn't survive correction.

Decreases in Purkinje cells have been found in children and adults with autism and those with and without a history of seizures or use of medications. The usual absence of glial hyperplasia suggests cerebellar lesions are acquired early in development and probably during embryonic stages.

Pathological findings extend to the cerebellar nuclei and inferior olive.

3.2 Autism as a disease of the cerebellum

The neglect of the cerebellum in theoretical models of autism is nothing less than a failure of an accepted paradigm for the mind-body gap. The gap between cerebellar neuropathology and cortical function can be filled by the concept of a reentrant component of motor efference copy that codes algorithms acquired neurodevelopmentally by dorsal stream networks and define spatial orientation and awareness (C. Vakalopoulos 2007; Costa Vakalopoulos 2013). This predicts that the putative cognitive consequences of cerebellar dysgenesis are more profound than late onset lesions and is proposed to underlie the hierarchical deficits demonstrated in ASD.

Modelling deficits stem from the role the cerebellum plays in dorsal stream function and rapid shifts in spatial attention required for analyzing complex gestures like emotional expression. It includes virtual shifts in imagery from memory in interpreting events during social interaction. Thus, the mind's eye roves in a spatial domain and is critical to social performance. Theory of mind is more akin to egocentric spatial transformations that enable an individual to take a different perspective. Inadequate extraction of information leads to abnormal responses in empathy, not a lack of capacity for emotional response per se. Recognition of emotional expression requires both extraction of subtle and complex facial information and gestures that are spatially integrated and an assessment of context through imagination to understand the significance of an event or response of an individual. Similar disability leads to poverty in the symbolic representation of language. Implicit

understanding of social constructs over time belies the actual complexity of the serial logic involved in extracting behavioural causal chains.

Consistent with a hierarchical view of autistic dysfunction a review of cortical lesions associated with impaired emotional empathy by Hillis (2014) included a case of extensive stroke of the bilateral cerebellum. The case study involved infarction of the posterior vermis, medial posterior parts of the cerebellar hemispheres and a small central lesion of the pons (Figure 2) (Roldan Gerschovich et al. 2011).

Figure 2. MRI T2, Coronal (left) and Axial (right) views of cerebellar infarction. From Roldan Gerschovich (2011).

The patient was severely impaired in theory of mind tasks and failed in reversal and extinction tasks (Table 1). This is consistent with the role of the posterior cerebellum in cognition. The findings are important because they mirror some of the features of inflexibility in autism spectrum disorders and are all the more extraordinary given adult cerebellar lesions are less than ideal in modelling ASD.

A.

<i>Test</i>	<i>Patient (Total score/max. score)</i>	<i>Controls [n=21] (Mean ± SD)</i>
Reading the Mind in the Eyes and Faces (<i>faces</i>)	11/20	17.9 ± 1.2
Reading the Mind in the Eyes and Faces (<i>eyes</i>)	13/36	27.5 ± 2.0
Faux Pas	7/10	9.5 ± 0.6

B.

<i>Test</i>	<i>Patient</i>	<i>Controls [n=21] (Mean ± SD)</i>
Iowa Gambling Task		
Total score [C+D] – [A+B] (<i>total/max. score</i>)	–26/+100	31.3 ± 12.6
Game of Dice Task		
Safe – Risk (<i>total/max. score</i>)	–14/+18	9.2 ± 6.1
Stimulus Reward Learning, Reversal Task		
Total Errors First Reversal	(<i>failed to reverse</i>) 17	9.1 ± 6.5
Commission Errors	11	4.2 ± 4.0
Omission Errors	6	2.9 ± 2.6
Stimulus Reward Learning, Extinction Task		
Total Errors in Extinction	(<i>failed to extinguish</i>) 22	7.9 ± 3.7
Perseveration Errors	14	4.7 ± 2.2
Attribution Errors	8	3.1 ± 2.3

Table 1. A. Theory of mind tests. B. Decision making tests. From Roldan Gerschovich (2011).

3.3 Significance of cortical findings

There has been considerable effort looking for cortical evidence of neuropathology that could underpin clinical aspects of autism. One study found a layer-specific decrease in neuron density and number in the fusiform gyrus (FG) of 7 autistic subjects, but this did not extend to the primary visual cortex or whole cortical grey matter (van Kooten et al. 2008). The FG is considered part of a network of face processing areas and the study was suggested as an explanation of the selectively poor facial recognition abilities of autistic subjects. Another study of autism found reduced numbers of neurons in the amygdala and in particular the lateral nucleus, but no change in mean neuron size (Schumann and Amaral 2006). Radiological findings vary considerably with increased, decreased and no change of amygdala volume in ASD and any discrepancy was attributed to larger volumes in a younger population (Schumann et al. 2004). Theories of amygdala dysfunction are attractive because of its role in fear processing and social behaviour. Likewise, another study demonstrated reduced volume in autism of the orbitofrontal cortex, an emotional centre of the brain (Hardan et al.

2006). However, a study looking at neuron numbers in the prefrontal cortex using stereological methods showed an overall 67% increase in ASD in children aged 2-16 years (Eric Courchesne et al. 2011). The increase in neuron number was irrespective of a corresponding increase in brain weight. As is discussed in the section on syndromic autism this finding has important mechanistic implications.

The problem with this approach is the incohesive and narrow focus of explanations in a complex and hierarchically organized disorder. Behavioural studies associated with focal lesions, although suggest important roles in dimensions like emotional empathy (Hillis 2014), they do not resemble the full syndrome of autism. A good example of the limited power of such explanations is an animal model of neonatal lesions of the monkey amygdala on fear conditioning (Kazama et al. 2012). Adult monkeys learned fear responses, albeit delayed, and showed flexibility including reversal of learning. Contrast this with the adult cerebellar patient and scores in table 1. Areas critical in affective perspective-taking include at least, the medial prefrontal cortex, anterior insula, anterior cingulate, anterior temporal cortex and amygdala.

More extensive lesions of the frontal cortex and medial temporal lobe (Baron-Cohen et al. 2000) do however, share some features with autism. A study of two adult patients who had sustained bilateral prefrontal lesions as a young infant or early childhood demonstrated poor social judgment and disinhibited behaviour but not other core features of autism (Price et al. 1990).

The review by Hillis (2014) did support a more pervasive role in perspective taking and other ‘mentalizing’ for the temporo-parietal junction (TPJ), an area that is strongly associated with spatial awareness. 3 patients with left TPJ infarcts and either right sided extinction, neglect or aphasia performed at chance level on false-belief tasks in addition to gaze direction processing deficits (Samson et al. 2004). A recent study of brain responses using fMRI to socially awkward situations

showed normal activation of brain regions commonly associated with social perception and cognition in both clinical and control groups including dorsal and ventral medial prefrontal cortex (Pantelis et al. 2015). Hypoactivation of right rTPJ and posterior superior temporal sulcus (rSTS) alone differentiated the ASD cohort. A preliminary finding of the study was the positive correlation of coactivity between rSTS and rTPJ and left orbitofrontal and left temporal pole. This could signify a disengagement of cortical nodes associated with empathy secondary to a failed cognitive mentalizing of scenarios that might lead to their normal activation i.e. scanning imagery from memory and relating them to an egocentric context could in turn lead to appropriate emotional responses to an event. It explains an overlapping activation of the same defined regions of interest (ROIs) in a first-order false belief task of a high functioning autistic (HFA) cohort (Dufour et al. 2013). Normal activity extended to STS and TPJ in this verbal theory of mind study that is passed by HFA subjects.

The studies imply a task-related functional deficit rather than a primary cortical pathophysiology. This does not imply that degenerative involvement of the cerebellum does not induce indirect changes in cortical organization or that the disease process itself does not directly impact on cortical pathophysiology adding to a non-specific cognitive burden, especially in low-functioning individuals, but is consistent with a primary cerebellar deficit. This will become more obvious when considering syndromic autism and associated mental retardation. Another study actually found cerebellar activation in a visual perspective task in addition to TPJ, but no involvement of the medial prefrontal cortex (Aichhorn et al. 2006). The authors though, simply attributed this to an increase of visual elements on the other perspective condition, which may have been unwarranted. It does highlight a reluctance to see an important connection between the cerebellum and temporoparietal regions in formulating spatial theories of cognitive function.

Post mortem findings in autism outside the cerebellum are often tempered by inconsistency. It is plausible that changes in cortical structures reflect a generalized primary disease process, but may contribute only indirectly if at all, to core features of ASD. Accordingly, primary limbic dysfunction does not underlie ASD and any changes in cortical morphology or functional status are either incidental and/or follow-on effects. Consistent with the latter thesis, amygdala volume in a group of 17 adult subjects with Asperger syndrome did not correlate positively with emotional and social understanding as it did in controls, but did show a negative association with narrow interest patterns (Dziobek et al. 2006).

There is an age-related decrease in total grey matter volume in a group of children with autism (8-12 years old) as compared to controls (Hardan et al. 2009). The decrease correlated with symptom severity. However, another volumetric study showed increase in size of the right posterior superior temporal gyrus (RpSTG) in 18 boys with high-functioning autism and a mean age of just 13.7 years (Jou et al. 2010). The RpSTG is a visual motor area and often implicated in unilateral neglect, a spatial attentional deficit syndrome. Volumetric findings overall suggest an initial gain of function related to the disease process, c.f. syndromic autism discussed below. Subsequent cortical volume decrease over time indexes dimensional severity of symptoms, but does not explain early manifestations of the disease.

An alternative and complimentary model of long term cortical atrophy relates to crossed cerebello-cerebral diaschisis. A prospective study of premature infants with isolated cerebellar hemisphere injury on neonatal MRI revealed decreased cortical grey and white matter in specific regions as measured by follow-up volumetric MRI (Limperopoulos et al. 2010). The findings extended beyond sensorimotor cortex and included dorsolateral prefrontal, premotor and midtemporal areas. Although, the parieto-occipital area did not show parallel changes as would be predicted, the authors noted the segmentation in this region of analysis might have been too large.

3.3.1 Facial recognition of emotions and social constructs

Failure of appropriate social interaction and communication has led to the idea that ASD is associated with deficits in facial recognition of emotions (Adolphs, Sears, and Piven 2001). The study of HFA based this interpretation on abnormal judgments of trustworthiness and approachability to unfamiliar faces, which were more positive than in normal subjects. The judgments were in fact in between those of normal and patients with bilateral amygdala damage, but apart from 2 of the ASD cohort they all fell within an appropriate negative rating score. More revealing is that in spite of variability, on tasks that involved face identity and simple emotional recognition the mean performance was within the norm, but differed from the bilateral amygdala subjects.

Although outcomes can depend on subgroups and in particular, whether controls are matched for verbal ability, the findings replicated a study by Grossman et al. (2000), which also showed no deficits in recognition of simple emotions but did show deficits during more demanding judgments that involved interference from incongruous words. So what explains the subtle nature of the impairment of social understanding given intact visual discrimination. A clue is available from another study that showed impaired delayed matching of facial emotions in autistic subjects, but who performed normally for facial identity (Celani, Battacchi, and Arcidiacono 1999). This suggests target exposure time was too brief for the autistic subjects to scan and register in real time and/or in working memory. So it may not be recognition per se that is impaired, but the ability to scan subtle information rapidly and manipulate information in a virtual space. Consistent with the latter interpretation subjects were also impaired in a sorting task of emotional expressions based on preference. The task does not index recognition directly, but judgment evokes context and in turn, requires virtual shifts in attention in an imaginary space. Further, the autistic group performed

equally poorly on delayed matching for happy and sad expressions, unlike bilateral amygdala patients. The model of impaired virtual spatial shifts in imagination can explain poverty in recounting autobiographical memory, future self-concepts and self-consciousness (Lind 2010).

Autistic children are capable of accurately labelling even ambiguous expressions of affect in pictures, but have much more difficulty in understanding socially constructed emotions (Capps, Yirmiya, and Sigman 1992). A substantial number of HFA confounded the emotions sadness with embarrassment and happiness with pride, which almost never occurred in normal reports. An understanding of pride and embarrassment requires attribution to the mental state of an audience, at least developmentally before they conform to normative behavioural patterns. Although a much smaller majority than controls appropriately labelled a picture example as “embarrassing”, more than a third offered a less socially informed label of “confused”. This interpretation is supported by a study which showed a comparative lack of attention to others and insensitivity to praise, but derived personal pleasure from completing puzzles as gauged by smiling (Kasari et al. 1993). Complex social emotions require imaginary perspective-taking which in turn, relies at its most fundamental on a process of egocentric spatial transformations. This is a dorsal stream property of cognition. The ventral stream property of recognition is facilitated by adequate perspective-taking. This does not mean that autistics have no capacity for spatial transformative cognition, but it is markedly slowed and might even exhibit enhanced performance when tasks entail restricted visuospatial engagement. A model of dorsal stream dysfunction underlies resistance to change, failure at complex social interchange and behavioural stereotypy.

Further recognition studies, offering a similar interpretation, show tasks involving intramodal (gestural and facial) and intermodal (facial and vocalizations) dimensional shifts in facial identity, emotional expressions and objects are impaired in HFA (Davies et al. 1994; Hobson 1986). The

deficit is none the less relative not absolute, depending on task difficulty and whether an object association is overlearned. When autistic subjects are asked to match faces or affects during a simultaneous display of target and test items, they show modest or no deficits in performance relative to controls and an object condition (Braverman et al. 1989). There was a correlation in another study between errors for facial expression and mismatch labels for an emotion with set-shifting ability on the Wisconsin Card Sorting Test (WCST), a measure of executive function (Grossman et al. 2000). Performance was however, normal on the distracting word condition. Mismatch errors was non-significantly correlated with perseverative errors, the most obvious impaired variable of WCST in autism (Ozonoff, Pennington, and Rogers 1991). So impulse control and frontal executive liability to distraction do not appear to underlie performance differences, but are better explained by impaired attentional shifts.

3.4 Vision fails to modulate proprioceptive feedback

The subtitle of this section suggests a reverse consequence of the proposed cerebellar model of a neurodevelopmental disorder. It aims to explain several clinical features and anomalous experimental findings of autistic adaptation. Pathognomonic repetitive behaviours like hand-flapping, toe-walking and rocking are best explained by compensatory proprioceptive self-stimulation. The calming effects of Temple Grandin's squeeze machine (Grandin 2008) may be looked upon in a similar way. So how do these behavioural signs of autism relate to cognitive deficiencies in ASD? Recent experimental work offers a clue.

In a study of HFA comparable acquisition and adaptation to throwing balls at visual targets while wearing prism goggles to controls was viewed as evidence for the generation of normal predictive internal models (Larson, Bastian, Donchin, Shadmehr, & Mostofsky, 2008). However, a defining study in the field showed that individuals with classic autism demonstrated adaptation with the right

hand in a reaching study while inducing prism-induced lateral displacement of the visual field (Masterton and Biederman 1983). Unlike the control groups, older and younger normal and retarded subjects, only the autistic group showed transfer of adaptation to the non-adapted left hand. The use of an alternative strategy, proprioception over visual control, was interpreted by the authors as a visual perceptual deficit or 'lag' rather than a preference for proprioception per se.

Extensive damage to bilateral posterior parietal cortex (PPC) in a patient IG with bilateral optic ataxia was unable to make corrective on-line reaching movements to an unexpected shift of the target (Pisella et al. 2004). IG achieved the target position by a secondary movement after initial reach to previous target position was completed. Her adaptation to prisms, measured by the negative aftereffect, was similar to controls. However, like the autistic group in the above study the transfer of adaptation to the unexposed limb was much greater. The authors concluded that visuo-motor inaccuracy in patient IG is not an impediment in itself to adaptation, which they ascribed to the role of an intact cerebellum. A similar patient JJ with bilateral parietal cortex damage and Balint's syndrome, however did reveal impaired adaptation for both right and left hands (Newport and Jackson 2006).

Cerebellar patients showed impaired prism adaptation as measured by negative aftereffect, but not other groups including dementia, cerebral hemisphere and Parkinson's patients (Weiner, Hallett, and Funkenstein 1983). Ablation of cerebellar areas that receive visual mossy fibre input from corticopontine projections disrupts prism adaptation in monkeys, but not more anterior lesions (Baizer, Kralj-Hans, and Glickstein 1999). Posterior inferior cerebellar artery (PICA) territory involving the posterior cerebellum but not superior cerebellar artery infarcts (SCA) impaired prism adaptation while throwing (T. A. Martin et al. 1996). SCA, but not PICA infarcts caused severe ataxia. Similarly, dentato-thalamic lesions did not impede adaptation, but were associated with

ataxia. These results suggest motor abnormalities do not impair adaptation to prisms, but is consistent with the notion that motor reafference directly transforms visual cortical areas.

Similar deficits are observed with focal olivocerebellar lesions (T. A. Martin et al. 1996) and for reacquisition of prism adaptation after muscimol injections into ventral premotor cortex of monkeys (Kurata and Hoshi 1999). Transection of upper thoracic and cervical nerve roots did not prevent prism adaption, but did depend on voluntary and not passive movements (Bossom and Ommaya 1968). Climbing fibres from the principal olive (PO) project to the cerebellar hemispheres including the posterior cognitive regions crus 1 and 2, the same regions that have afferent mossy fibre input from the visual cortex. There is no spinocerebellar input to PO but the nucleus receives a motor efference copy from extensive motor and premotor cortical areas (figure 3) via the parvocellular red nucleus (D. R. Humphrey, Gold, and Reed 1984; Oka, Jinnai, and Yamamoto 1979; Sasaki et al. 1977; Voogd and Glickstein 1998).

Figure 3. Distribution of climbing fibre responses in the cerebellar cortex which were evoked by stimulation of the lateral (A), intermediate (B) and medial (C) part of the precentral motor cortex of Rhesus monkeys (Sasaki et al. 1977). These areas substantially overlap with visual mossy fibre projections.

Many of the prism studies show adaptation for the exposed arm only, but when more complex body movements are implicated this can generalize from walking to reaching and is also impaired by cerebellar lesions in human patients (Morton and Bastian 2004). 4 of 5 of controls that showed generalization also had a non-significant rightward visual shift of the straight ahead direction suggesting an incipient but fundamental visual spatial transformation in process and that was not explained by proprioceptive compensatory effects. There was no correlation between adaptation in cerebellar patients to walking and generalization, unlike controls. That visuomotor adaptation is accompanied by changes in visuospatial perception and facilitated by motor efference copy is further suggested by early inverting lens experiments where trial and error from awkward initial coordinating movements led to “reconstruction of the visual field” after 4 days (Stratton 1896). The assumption then is that the measured visual shift with further training would match those angles found in generalizing movements rather than as the authors claim of an effect chiefly on motor output (Morton and Bastian 2004).

The study by Stratton (1896) can inform modern studies of visual aberrations in autism. He found that adaptation to an inverting lens initially involved the shift of proprioceptive attribution of his feet and hands to the inverted position as seen, but not of the shoulders or head, which could not be observed i.e. they remained in the correct orientation. This occurred prior to reinversion of the image while still wearing the lens. What this means is that in order to maintain visual coherence there was a shift in proprioception of the interacting body parts and this was induced by the primacy of vision. What perhaps is not so obvious is an insight gained by the experimental results that vision itself must be dominantly conferring proprioceptive information of correct limb position, which in turn suggests that proprioceptive information is an inherent part of the structure of the visual percept and induced change is not just a corollary of eye position.

Autistic subjects were unable to effectively adjust reaching speed to catch a ball rolling down either a steep or low ramp (Whyatt and Craig 2013). Nor did they show deceleration around corners during a digitized trace task (Figure 4). Both these studies suggest an impairment in the visual prediction of kinematics of the tasks. In other words, autistic visual perception does not contain a sufficiently flexible code or algorithm in executing anticipatory visuomotor transformations. The inverse situation is found in Parkinson's disease, where kinematic cues are used to initiate fluent movements.

Figure 4. Example summary graph for deceleration patterns when approaching a single corner section of the track task. Combined analysis of performance on all corner sections highlights significantly shorter phases of deceleration in the ASD group than both the receptive language ($p < 0.05$) and non-verbal ($p < 0.01$) control groups, from Whyatt & Craig (2013).

3.4.1 Rubber hand illusion

There is a dominance of proprioceptive over visual information even in adults with HFA when experimenters attempt to induce a sense of hidden limb position to a visible rubber version of a hand (Paton, Hohwy, and Enticott 2012). Visual induction of proprioceptive drift while integrating unseen touch of the real hand is impaired.

Another paper showed a similar delay in proprioceptive drift in children with ASD and the ADOS score for lack of empathy negatively correlated with proprioceptive drift (figure 5).

Figure 5. Relation between total proprioceptive drift following 6 minutes of synchronous brushing and impairment in empathy, as measured by the ADOS, in participants with ASD (Cascio et al. 2012).

Conversely, the study also found that, at least initially, asynchronous stimulation did cause greater proprioceptive drift in ASD than controls (Cascio et al. 2012). It suggests a fundamental difference in processing information and the difficulties in segregating information of relative timeframes between the presentation of multisensory inputs even at 500 msec offsets. This was corroborated by increased subjective endorsement by ASD group only, although this was not replicated in the previous study, probably due to methodological differences. Thus, it remains plausible that in spite of offset subjects with ASD experienced these perceptual inputs simultaneously and this reflects impaired timing of events, a known function of the cerebellum. Compared to Parkinson's, cortical and peripheral neuropathy patients, those with cerebellar lesions only were less accurate with time duration judgments of difference, considered a purely perceptual deficit (Ivry and Keele 1989). Auditory deviance detection that was associated with a violation of temporal regularity induced a

significantly smaller P3b ERP measure from a centroparietal locus in cerebellar patients compared to controls (Kotz, Stockert, and Schwartze 2014).

The counterintuitive finding of Cascio et al. (2012) may reveal profound insights into the nature of aberrant perception in autism reflecting on distortions in spatial awareness and the rapid shifts in attention. Another study of neck vibration showing a failure to correct stance using vision (Morris et al. 2015) confirms the excessive reliance on real-time proprioceptive information to establish a stable sense of postural orientation.

3.5 Caveats and Gender inequalities

Rates of autism in males far exceeds those found in females and a limitation of the current paper is in addressing this specific issue. The fact that Rett syndrome and comorbid ASD is almost exclusively female in aetiology suggests common upstream confluence, which can be modelled on dorsal stream dysfunction. The higher penetrance of mutations in males however, has often been attributed to hormonal differences during critical stages of cerebellar development and neurosteroids are produced in the embryonic Purkinje cell (Dean and McCarthy 2008; Tsutsui 2006). In fact, support of for this hypothesis comes from heterozygous mutant *reeler* mice where males display selective loss in Purkinje cells and partial rescue by oestradiol treatment (Biamonte et al. 2009). The oestrogen antagonist tamoxifen in fact, potentiates cell loss in heterozygote mutant and wild type female mice. However, both testosterone and oestradiol levels are actually raised in heterozygous male *reeler* mice and an androgen receptor antagonist did not alter Purkinje cell levels. This suggests that in this model at least 'maleness' as measured by gonadal hormone effects is far too simplistic a model.

3.6 Summary

The evidence suggests that the qualitative differences in visual perceptual processing between ASD and normal controls are due to an inherent impairment of visually-guided adjustments of the body during active engagement with its environment. This in turn, is consistent with the concept that the algorithmic dimension deficient in the visuomotor transformations of ASD is a proprioceptive one of cerebellar origin, rather than the more immediate interpretation of spared proprioceptive capacity because of an increased reliance on intact peripheral somatosensory input. This interpretation is consistent with a demonstrated deficit in proprioceptive modulation of stance by children with ASD during a standing on one leg with eyes closed task (Weimer et al. 2001). Children with ASD also outperformed when learning from errors sensed through proprioception, but conversely were impaired relative to controls when adapting to errors using visual information (Marko et al. 2015). Smaller anterior cerebellar volume extending to lobule VI and VIII in the autistic probands correlated with decreased sensitivity to visual error agrees with a particular predictive proprioceptive insensitivity of visual processing. The studies also suggest exaggerated proprioceptive sensitivity, probably as a result of overcompensation for aberrant central component efferent copies that renders responses to visual cues unreliable. None the less, another hand illusion study demonstrated a categorical lack of over-reliance on proprioception (Greenfield et al. 2015) and as the Weimer study shows it is likely that visual cues interfere with proprioceptive adaptation in controls rather than true superior performance in ASD.

There thus, exists a fundamental distortion of the proprioceptive predictive structure of the visual dorsal stream rather than a loss of peripheral proprioceptive information per se. What this subtle distinction further entails for the structure of phenomenal aspects of any sensory modality is that deficits in spatial awareness observed in ASD are a consequence of a dysfunctional component efference copy that specifies the acquired knowledge of spatial engagement with one's surroundings

used in making further predictions. The most obvious candidate in the process of neurodevelopmental disabilities characterizing ASD remains the cerebellum where the necessary visual algorithms for spatial location of the body are derived. The idea of a deficit in component copy of motor efference can also be extended to an understanding of ‘proprioceptive’ self-stimulation or stimming as suggested above. The current discussion harks back to the impenetrability of a complex disorder like ASD reflecting a lack of solutions to the mind-body problem and that any visually-guided reaching act entails a code for appropriate changes in joint positions ‘built’ within the structure of the visual phenomenology itself.

4. Restrictive behaviours and spatial cognition in autism

Are there tasks which reveal an upper limit of cognitive function that may also inform wide ranging behavioural deficits in ASD? There is now good evidence of primary cognitive dysfunction in ASD resulting from impaired abilities in mental object rotation and perspectival flexibility (Grandin and Panek 2013). These two tasks were performed at chance level by the autistic author and professor Temple Grandin. They highlight the spatial nature of autistic cognitive deficits. Mental rotation of objects is also impaired in patients with cerebellar lesions (M. Molinari et al. 2004b).

The size of the cerebellum in ASD predicted exploratory activity and stereotypy, the presence of which was dissociated from full scale IQ suggesting behavioural specificity (Pierce and Courchesne 2001). Further, family genetic studies have shown the same genetic liability for idiopathic autism independently of IQ (Starr et al. 2001). These studies suggest selective cognitive deficits underlying autistic behaviour. A visual discrimination study of moving dots corroborates a selective dorsal stream deficiency in an ASD cohort that differed in motion, but not form coherence thresholds (Spencer et al. 2000). A more pervasive dorsal stream deficit is also supported by the finding that autistic subjects manifest dyspraxia that extends beyond basic motor skills implicating deficits in

cognitive transformations of the posterior parietal cortex and premotor frontal areas (Dziuk et al. 2007). Dyspraxia scores correlated directly with each ADOS score for social interaction, communication and repetitive behaviours.

Figure 6 demonstrates poor exploration of rectangular and oval containers on the right relative to normal subjects. The image portrays a more basic level deficit than usually attributed to poor social function in ASD. A model of impaired spatial manipulation of concrete imagery is proposed to explain more complex deficits in theory of mind and social lack of empathy, which are higher level cognitive and behavioural constructs.

Figure 6. (A) T₁-weighted magnetic resonance image with tracings showing midsagittal vermal lobules I–V and VI–VII for a 6-year-old autistic boy and his matched normal control subject. (B) Close-up of midsagittal vermis slice. Note the hypoplasia in the autistic child in comparison to his matched control subject. (C) Exploration maps for the autistic and matched control subjects (corresponding cerebella for each child shown in A and B). Lines depict patterns of movement across the entire session. Note the varied exploration pattern of the normal child in comparison to

the near absent exploration of the autistic child (Pierce and Courchesne 2001).

Importantly the finding does not generalize to other brain structures. Right caudate volume was significantly larger in autistic subjects than in controls (Hollander et al. 2005). In contrast to cerebellar volume, right caudate and total putamen volumes correlated positively with repetitive behavior scores.

Traditionally studies cited normal even enhanced visuospatial abilities in the context of impaired executive function, first and especially second order theory of mind tasks and emotion perception (Ozonoff, Pennington, and Rogers 1991). The spatial tasks that autistic subjects perform better on, Embedded Figures Test, Block Design and Object Assembly use focal features. They would likely, not tax capacity to rapidly shift attention, reducing the need for conjoint assessment of features and manipulation within working memory. Conversely, in a task that was grouped under executive function the 'Tower of Hanoi', planning requires the simultaneous assessment of size and spatial location held in working memory and was markedly impaired in ASD relative to controls. Thus, spatial tasks parallel performance in emotion recognition abilities where ambiguity is explained by judgments based on shifts in spatial attention and virtual manipulation of objects in space, implicating convergence on frontoparietal networks and not primary limbic dysfunction.

4.1 Summary of a dorsal stream theory of autism

The variable support for higher end social theories in ASD on the one hand, and the integration of cognitive findings and stereotyped behaviours on the other, can be modelled on dorsal stream capacity limitations. Two broad areas of dysfunction are invoked (i) real time and (ii) imagery or virtual:

- (i) Rapid shifts in attention are required for configural extraction of information especially when these are subtle and briefly expressed as in emotional gestures or expressions.

Profound instances of a failure to shift attention can lead to hyposensitivity to environmental events akin to neglect or extinction of stimuli commonly reported in right parietal stroke patients. Accordingly, stereotypical behaviour reflects a compromised dorsal stream network when extracting information from a complex setting. This leads to an apparent preference for activities with easily predictable outcomes. Paradoxically, it can also be an explanation of an exaggerated responsiveness or hypersensitivity to stimuli where spatial shifts of awareness are also a means attentional disengagement.

- (ii) Impaired conceptual abstraction where recall of associations itself requires virtual spatial shifts of attention and egocentric perspectives. Even as interpreting events becomes implicit there is an initial serial imagery, which places information in context leading to certain conclusions or outcomes and that eventually become automatic. A failure of manipulation, including comparative strategies, of online and offline data, which necessarily entails segregated spatial contexts can also lead to the concreteness and even oddness of language. The normal use of language is symbolic precisely because it assumes an explicit understanding of the connection of events as recalled images. The symbolic character of language is diminished by its inability to evoke virtual egocentric transformations from memory that could provide context. Conversely, the concreteness or inappropriateness of autistic language is underscored by these difficulties in imagination. It is thus, by no means inconsistent with the precocious technical proficiency in certain aspects of language use sometimes exhibited by HFA, such as reading.

5. Syndromic Autism

An expanding literature on syndromic autism offers new insights into ASD. Although only representing between about 15-20% of diagnosed ASD, the specific disease entities usually have a known genetic abnormality that lead to animal models. A detailed study of the large number of genetic mutations associated with ASD is impressive for the confluence of biochemical deviation and an overlapping neuropathology. The incidence of comorbid ASD varies, but often ranges from 20-40%. Despite generalized tissue involvement in genetically defined syndromes including non-focal brain abnormalities they can be quite informative in theory because of a limited number of cases in each disease actually manifesting comorbid autistic behaviours. The cerebellum is almost universally implicated in the disease process.

Biochemically, syndromic autism often manifests as a gain in function with dysregulation of RAS/ERK or PI3K/Akt and upregulated mTOR in various conditions including neurofibromatosis type 1 (NF1), tuberous sclerosis, Angelman syndrome (LaSalle, Reiter, and Chamberlain 2015; Sun et al. 2015) and PTEN hamartoma tumour syndrome. Absence of fragile X mental retardation protein (fmrp), which normally sequesters mRNAs results in increased translation of proteins. Rett syndrome is marked by a loss of methyl-CpG-binding protein, a component of transcription repressor complexes. Thousands of genes are thought to be upregulated, but the effects of gene deletion and overexpression have complex effects (figure 7).

Figure 7. Intracellular signalling cascade for cell proliferation is often associated with a gain of function in genetic diseases associated with comorbid ASD.

5.1 Tuberous sclerosis complex

Tuberous sclerosis complex, which results from mutations of genes for either TSC1 or TSC2, causes benign tumours to grow throughout the body including the brain. A French study found an incidence of tuberous sclerosis of 1.1% in a group of 175 autistic patients (Fombonne et al. 1997). Like many genetic diseases tuberous sclerosis can be associated with autistic regression (Humphrey, Neville, Clarke, & Bolton, 2006). Temporal, but not cerebellar tubers have been positively correlated with the presence of autism and more global cognitive impairment compared to those patients without autistic symptoms (Bolton and Griffiths 1997; Jeste et al. 2008). The classic study by Bolton and Griffiths (1997) actually shows how prior biases can inform research interpretation. 9 of 18 patients with tuberous sclerosis were diagnosed with ASD, 8 of which had temporal lobe involvement and none of the non ASD group had temporal tubers. However, given the subregional importance of temporal lobe involvement it is difficult to draw conclusions as this was not specified in the study. Further, after frontal lobe involvement, the next most commonly located tubers were in the parietal lobe. The authors grouped parietal and occipital lesions together for a comparative control as these cortical regions were considered not to be implicated in the pathogenesis of autism.

It is also possible that the association of temporal cortex specifically, and cortical tubers in general, with autistic features represents a marker of severity of disease and thus, likely cerebellar involvement, which may not be so obvious on neuroimaging. Thus, the ratio of cerebellar tubers

was 3:1 for ASD and non-ASD cases in the study by Bolton and Griffiths (1997). Consistent with this interpretation a study found no significant correlation between number and site of tubers and factors including autism (Wong and Khong 2006). Two other studies, however did reveal an association between cerebellar tubers and autistic symptomatology even after controlling for number and location of cortical tubers (Eluvathingal et al. 2006; Weber et al. 2000). The former study was based on patients with intractable epilepsy and use measures based on the Vineland Adaptive Behavior Scale (VABS) and the Gilliam Autism Rating Scales (GARS). In the latter study the significant measure was the Childhood Autism Rating Scale (CARS).

Purkinje cell loss is present in up to half of post-mortem cases of tuberous sclerosis and loss was confirmed in a mouse model of TSC2 deletion (Figure 8) (Reith et al. 2013). Conversely, the cortex surrounding tubers in other parts of the brain is characteristically normal with orderly lamination (Richardson 1991).

Figure 8. Calbindin staining at 3 months of age shows loss of Purkinje cells in the Tsc2f/- (Reith et al. 2013).

5.2 Rett syndrome

Rett syndrome is an X-linked dominant disorder more common in females. Absence of MeCP2 protein leads to activation of 85% of affected genes (Chahrour et al. 2008). Early on in the course it may be indistinguishable from infantile autism (Gillberg, Opitz, and Reynolds 1986). It was originally listed in DSM IV as one of five autism-related conditions prior to the discovery of a genetic cause. It has been removed altogether from DSM V and autistic features generally manifest early and are transient as profound mental retardation becomes progressive. It is characterized by severe cognitive deficits, impaired social communication, stereotypical hand movements, which manifest after a period of normal motor and language development (Percy 2011). Rett syndrome demonstrates marked and progressive cerebellar degeneration as revealed by imaging (Murakami et al. 1992). Cerebellar atrophy with marked loss of Purkinje cells was present at autopsy in five patients (Oldfors et al. 1990).

Microscopic findings resemble those in idiopathic cases of ASD. Although there can be a generalized reduction in brain volume there is only a modest if no loss in pyramidal cortical neurons, but loss of dendritic arbours and spines (Belichenko et al. 1994). Cortical atrophy correlates with a decrease in cell size and increased cell-packing density including in medial temporal lobe structures such as hippocampus and amygdala (Bauman, Kemper, & Arin, 1995). Similarly, in 7-9 week-old heterozygous and homozygous MeCP2B mouse mutants, normal lamination and no loss of neocortical neurons was apparent in spite of reduced thickness (Metcalf et al. 2006). In the three brains of girls with Rett syndrome there was a widespread loss of Purkinje cells predominantly in cerebellar hemispheres (Bauman et al., 1995). A lack of gliosis and retrograde inferior olivary degeneration suggested an early developmental lesion.

5.2.1 MeCP2 duplication syndrome

A study by Ramocki et al. (2009) looking at cases of MeCP2 duplication from 8 families (9 males) claims 100% penetrance of autism in boys based on ADI-R and 88% using ADOS. Most cases show severe progressive mental retardation, absence of speech and spasticity with cause of death typically a respiratory infection (Van Esch 2012). Seizure onset is variable in up to half of cases. MeCP2 was initially identified as a transcription repressor, however nearly two thirds of genes are upregulated in a mouse duplication model appearing to cause disease by a gain of function (Ben-Shachar et al. 2009). A reverse trend was found in null mice. Downstream effects include upregulation of G protein-coupled receptor 26 and downregulation of low-density lipoprotein-related protein 1B, a mooted tumour suppressor. Neuroradiological evidence from one study shows both cerebral white matter and marked time-dependent cerebellar atrophy (Reardon et al. 2010). These gross cerebellar changes appeared only after age 9 (Figure 9). However, a single post mortem study of a child of five showed extensive Purkinje cell loss in the context of normal findings in the cerebral cortex (Lubs et al. 1999).

Figure 9. Views of the cerebellum of case III2 (family 1), demonstrating normal left and right cerebellar hemispheres at age 7 years and significant right and left cerebellar hemisphere atrophy by age 14 years (Reardon et al. 2010).

5.3 Fragile X

Fragile X is the commonest cause of inherited intellectual disability. It is due to a mutation of the FMR1 gene, the syndrome manifesting with >200 CGG repeats. Inactivation by methylation of the promoter region results in a reduction of the fragile X mental retardation protein (FMRP). FMRP is a dendritic RNA-binding protein so that up to 3% of RNAs are excessively translated, a separate mechanism to one's discussed above leading to a gain of function. Diagnostic criteria for autistic disorder was met by 30% of 63 males in a study of fragile X syndrome, with another 30% having a comorbid pervasive developmental disorder (Harris et al. 2008).

Comparable to idiopathic cases size of posterior cerebellar vermis is negatively correlated with repetitive behaviour and communication deficits (Mazzocco et al. 1997). Cerebellar size partially accounted for reduced performance in visuo-spatial tasks (Mostofsky et al. 1998). A separate study of females with fragile X syndrome showed increase activation of anterior prefrontal cortex, but failed to show the expected increase in superior and inferior parietal cortex during a numerical version of the Stroop task (Tamm et al. 2002).

In a series of post-mortem cases of fragile X there was extensive loss of Purkinje cells (Figure 10) (Greco et al. 2011).

Figure 10. A. Purkinje cell counts in the cerebellum. Purkinje cell (PC) counts in: (A) superior lobule; (B) posterior lobule; (C) inferior lobule; and (D) lateral cortex, in the three fragile X cases and age-matched controls (Greco et al. 2011).

Conversely, there was focal thickening of the hippocampal CA1 (Figure 11).

Figure 11. Hippocampal formation. Images of the hippocampal formation at the level of the lateral

geniculate body from (A) patient 1 and (C) patient 3 show abnormal expansion of CA1 by increased numbers of pyramidal neurons. These are compared with the more usual hippocampal microarchitecture that shows a thinner linear band of neurons in CA1, as seen in (B) a 62-year-old male control. Haematoxylin and eosin, original magnification $\times 10$; scale bar = 1 mm. Arrow indicates bulge/expansion composed of increased numbers of pyramidal cells in (A) patient 1 and (C) patient 3 (Greco et al. 2011).

Only the cerebellum and superior temporal gyrus showed a decrease in size in at least one review of neuroanatomical studies of fragile X, while the thalamus, caudate, amygdala and hippocampus were all increased in size (Hessl, Rivera, and Reiss 2004). A voxel-based morphometry study in older male premutation carriers revealed widespread cortical grey matter loss in a symptomatic group for tremor/ataxia syndrome and a profound reduction in the vermis and hemispheres of the anterior and superior posterior lobes of the cerebellum (Hashimoto et al. 2011). Loss in the left amygdala in this study correlated with obsessive compulsive symptoms and depression. However, in the asymptomatic group grey matter reduction was only significant in the anterior vermis. An overall emerging picture is one of a selective vulnerability of Purkinje cells especially during embryonic stages to gain of function genetic mutations in syndromic autism and thus suggests a causal role in ASD. At least some of the cortical changes would follow from this primary pathology or result from secondary causes.

Table 2. Neuroanatomic abnormalities in fragile X patients (Hessl, Rivera, and Reiss 2004).

5.4 Joubert syndrome

Joubert syndrome is partly defined by cerebellar abnormalities including hypoplasia. Between 25-40% of cases may have a comorbid diagnosis of ASD (Alvarez Retuerto et al. 2008; Ozonoff et al. 1999). It is considered a ciliopathy with a mooted upregulation of mTOR (Boehlke et al. 2010). Failure of decussation of the superior cerebellar peduncles and corticospinal tracts are hallmarks of the disorder (Figure 12), but do not extend to other neural pathways (Poretti, Boltshauser, and

Doherty 2014). These findings remarkably, were uniform across the 6 patients in the study given the heterogeneity in the underlying genetic causes.

Figure 12. Cerebellar hypoplasia with mainly vermis involvement. A: Axial T2-weighted image in a child with Joubert syndrome shows the molar tooth sign with elongated, thickened, and horizontally orientated superior cerebellar peduncles (arrows) and a deepened interpeduncular fossa. B: Midsagittal T2-weighted image of the same patient demonstrates severe hypoplasia of the cerebellar vermis with dysplasia of the vermian remnants (arrows), shortening of the ponto-mesencephalic isthmus and enlargement of the fourth ventricle with upwards displacement of the fastigium (asterisk) (Poretti, Boltshauser, and Doherty 2014).

5.5 Neurofibromatosis

A prevalence of 25% comorbid ASD in NF1 was established in a recent epidemiological study (Garg et al. 2013). Cerebellar hypoplasia in NF1 appears to have been underestimated (Toelle et al. 2015) and another study showed a strong association between gait width and spatial working memory (Champion et al. 2014). NF1 deletion in precursor cells of mouse cerebellar neural progenitors resulted in impaired proliferation and migration of granule cells (Sanchez-Ortiz et al. 2014). Neurofibromin is a RAS GTPase-activating protein that reduces ERK activity. Mouse models of NF1 show a smaller cerebellum, but enlarged cerebral cortex and corpus callosum (Y. Wang et al. 2012).

5.6 Myotonic Dystrophy type 1

Myotonic dystrophy type 1 (DM1) is an autosomal dominant disorder caused by the expansion of a CTG triplet repeat within the 3' untranslated region of the myotonic dystrophy protein kinase (DMPK) gene (Brook et al. 1992). In one study of fifty-seven children with DM1 49% had comorbid autism spectrum disorder (Ekström et al. 2008). Of the total cohort 85% had mental retardation. The mechanism resulting in cortical abnormalities is considered to be due to RNA gain-of-function (Ranum and Day 2004). However, in other ways DM1 appears an anomaly to the usual dominant manifestation of cerebellar pathophysiology. No loss of Purkinje or granule cells has been described (Itoh et al. 2010). The CTG repeats in granule cells of the cerebellum were the shortest (Jinnai et al. 2013). However, long CTG repeats were found in the basilar pons and the long CTG repeats in the dentate nucleus, cerebellar peduncle and white matter were attributed to glial cells.

Voxel-based morphometry revealed grey matter loss of the right cerebellum (lobules VII, VIII and Crus), the left posterior cingulate, left supramarginal gyrus, left pre and post-central gyrus, bilaterally in the precuneus (Serra et al. 2015). These cortical areas are intimately connected to the cerebellum. Consistent with the reductions cognitive function in this cohort of largely adult-onset DM1 was largely restricted to visuospatial tasks. These findings confirmed an earlier study, which showed grey matter (GM) reductions in both hemispheres involving frontal and parietal, but not temporal cortex (Minnerop et al. 2011), although another study does extend findings of GM loss to the superior and middle temporal gyrus (Antonini et al. 2004). White matter changes in the cortex were more pronounced, but unlike the previous study the pons, middle cerebellar peduncles and the cerebellar peduncles were also implicated. However, further studies of cerebellar structure in DM1 are required to be confident of its involvement and primacy in comorbid ASD.

5.7 Sanfilippo syndrome

Mucopolysaccharidosis type III (MPS III), or Sanfilippo syndrome is a lysosomal storage disease results in the accumulation of the glycosaminoglycan heparan sulphate due to a failure of degradation. Each subtype IIIA-D is characterized by a deficiency of a different enzyme affecting the same catabolic pathway. The central nervous system is mainly affected with somatic symptoms generally being mild (Coleman and Gillberg 2012). It is often associated with developmental delay, hyperactivity and autism spectrum disorder (Wijburg et al. 2013). The two sibling cases of MPS IIIA (the most frequent subtype) showed normal development up to 1 year of age before the onset of a progressive neurocognitive, behavioural and motor decline (Sharkia et al. 2014). MRIs at 11-12 years showed parieto-occipital atrophy, thin corpus callosum and diffuse white matter hypomyelination. There was no discussion of cerebellar findings. However, autopsies of two cases with MPS III subtypes A and C revealed storage disease in cortical neurons and Purkinje cells (J. J. Martin et al. 1979). A canine model of MPS IIIA (sulphamidase) clearly demonstrated a time-dependent loss of Purkinje cells with only ~12% remaining after 40 months (Figure 13) and their replacement by Bergmann glia coinciding with the onset of ataxic symptoms (Hassiotis, Jolly, and Hemsley 2014). This can in principle model autistic regression seen in several syndromic cases.

Figure 13. Morphology of Purkinje cells (PKC) in hematoxylin and eosin stained sections of

cerebellar cortex (A–F) and PKC counts (G). (A) shows a high-powered image of a PKC in a symptomatic MPS IIIA dog aged 30.9 months (mo). Note the accumulation of translucent, highly eosinophilic inclusions (arrowhead) in the distended PKC, which displaces the nucleus (star). (B) PKC in the brain of an unaffected dog aged 33 months. Note the prominent nucleolus (black arrow). (C) Cerebellar cortex of MPS IIIA dog aged 40.9 months reveals a lack of PKC and disorganization of the PKC layer interface (arrow). (D) Same brain area in an unaffected animal aged 39 months, with distinct molecular layer (ML), granule cell layer (GCL) and PKC layer. Arrows depict gaps in the Purkinje cell layer (Hassiotis et al. 2013).

A ‘designer’ knockout (KO) mouse strain defined as MPS IIIE with a milder phenotype than MPS IIIA mice and is predictive of a human equivalent. Neuropathological changes are largely restricted to the cerebellum and cell death was exclusively of Purkinje cells highlighting their exquisite susceptibility (Kowalewski et al. 2015). The major neurological finding in these mice, ataxia is consistent with the anterior-to-posterior gradient of decreasing cell loss found.

5.8 Smith-Lemli-Opitz (SLOS)

Children with SLOS syndrome have an inborn error of cholesterol metabolism. There is a failure in the final step of cholesterol biosynthesis resulting from a deficiency of the enzyme 7-dehydrocholesterol reductase. Cholesterol plays an important role in embryogenesis and together with the accumulation of its precursors leads to a phenotype that includes congenital malformations, motor delay with hypotonia and mental retardation (Kelley and Hennekam 2000). Studies have shown that up to 88% of children have comorbid ASD, making it the most frequently associated genetic syndrome (Sikora et al. 2006; Tierney et al. 2001).

Case studies have shown complete agenesis of the cerebellar vermis with patchy Purkinje cell loss in lateral hemispheres (Fierro et al. 1977) and hypoplasia of the vermis on MRI (Caruso et al. 2004) with marked reduction in cerebellar activity as shown by SPECT (Koutsouraki et al. 2007).

5.9 Other genetic disorders comorbid with ASD

Other genetic mutations associated with high prevalence of ASD include CHARGE, which presents with cerebellar hypoplasia due to dysregulated FGF (Yu et al. 2013) and the metabolic syndromes: phenylketonuria (PKU) and adenylosuccinate lyase deficiency (ADSL) (Edery et al. 2003; Ghaziuddin and Al-Owain 2013). Cerebellar hypoplasia can be marked in ADSL, although atrophy may extend to cerebrum and corpus callosum, and hyperphenylalaninemia is especially toxic (Poretti, Boltshauser, and Doherty 2014; Van den Berghe, Vincent, and Jaeken 1997; Wen et al. 1980). The list of genetics mutations with comorbid ASD is too extensive to discuss in detail here. However, in any genetic condition associated with comorbid ASD one can be reasonably confident in predicting known or as yet unrecorded cerebellar pathology.

Although some of these diseases are quite rare and the effects can be non-specific damage to CNS they do help unlock causal structures in ASD. What remains to be demonstrated is whether syndromic autism directly covaries with cerebellar involvement. The evidence challenges proponents of a non-specificity of neuroanatomical findings (Lefebvre et al. 2015).

6. Very low birth weight

Preterm infants <27 weeks are at least 3 times more likely to be diagnosed with ASD in one cohort of 2-11 year olds and there was an association with intracranial haemorrhage (Kuzniewicz et al. 2014). Using the Modified Checklist for Autism (M-CHAT), a positive screening measure for 26% ex-preterm toddlers with a birth weight <1500 g was found in one study compared to 5.7% in a random sample (Limperopoulos et al. 2008). The prevalence was still 16% in infants <28 weeks when developmental impairment as a confound was removed and 10% in a further subgroup without cognitive impairment (Kuban et al. 2009). Core items of the M-CHAT include joint attention, interest in other children, responding to being called by name and imitating. Extreme prematurity is a major risk factor for cerebellar lesions (figure 15) and is related to poorer outcome

(Messerschmidt et al. 2008).

Figure 14. Follow-up brain MRIs (coronal spoiled gradient recalled T1-weighted) of infants with isolated cerebellar hemorrhagic injury on neonatal cranial ultrasound. A, Complete absence of the left cerebellar hemisphere with preservation of the right cerebellar hemisphere and vermis. B, Absence of the inferior cerebellar vermis and inferior portions of both cerebellar hemispheres. C, Near-total cerebellar destruction with only a small amount of superior cerebellar vermis present (Limperopoulos et al. 2007).

Compared to controls, cerebellar injury resulted in 37% positive screen on M-CHAT and between 37-48% incidence of impairments in expressive language, delayed receptive language, cognitive deficits and motor disabilities (Limperopoulos et al. 2007). The incidence in preterm controls was 0% for all measures. Preterm infants with combined cortical and cerebellar haemorrhagic injury did not exhibit an increased risk of neurodevelopmental deficits, but did show worse motor abilities. Positive screening on M-CHAT and Social Communication Questionnaire (SCQ) and impaired socialization (VABS) were associated largely with involvement of the vermis. Questions have been raised about specificity of M-CHAT in very low birth weight infants.

7. Sporadic cases

De novo mutations using whole-exome sequencing were recently identified in the gene coding for activity-dependent neuroprotective protein (ADNP) as a causative factor in ASD, potentially

accounting for 0.17% of all cases (Helsmoortel et al. 2014; Vandeweyer et al. 2014). ADNP is a transcriptional factor and 10 out of 11 cases were considered gain-of-function mutations with the excess mutant protein possibly unable to bind to the autoregulatory promoter. All had facial dysmorphic features and variable intellectual disability characteristic of syndromic ASD. Immunohistology of the normal rat showed that ADNP was widely expressed by neurons in the brain, with the highest expression in the cerebellum and strongly in the brainstem including deep cerebellar nuclei (Gennet et al. 2008). *Engrailed 2* is a homeobox transcription factor similar to ADNP and is in a chromosomal region with linkage to ASD (Gharani et al. 2004). Ectopic overexpression of *en-2* in Purkinje cells late in embryogenesis and the early post-natal period of transgenic mice cause their loss by more than a third (Baader et al. 1998) supporting a unique sensitivity of Purkinje cells to gain-of-function mutations. Gain-of-function mutations are presumably better models of idiopathic, HFA. Indeed, in a study of 2588 autistic cases from simplex and multiplex families the size of copy number variant CNV deletions varied negatively with non-verbal IQ, but did not affect autism severity (Girirajan et al. 2013). Half of the larger events were *de novo*. Conversely, CNV duplications size did vary directly with autistic symptoms, but not with NVIQ. The authors failed to account for why an increase in gene dosage impairs neurodevelopmental processes, but is consistent with a linear gain in function and a negative correlation with Purkinje cell function and/or survival.

A targeted sequencing study demonstrated recurrent disruptive *de novo* mutations in 6 genes that were thought to contribute to 1% of sporadic ASD (O’Roak et al. 2012). Apparently, no dysmorphic features or comorbidities were present. Chromodomain helicase DNA binding protein 8 (CHD8) and phosphatase and tensin homolog (PTEN) mutations were associated with macrocephaly consistent with gain-of-function. Heterozygous CHD8 knockout of induced pluripotent stem cells revealed a transcriptome profile enriched in the expression of genes related to neurodevelopment, β -catenin/Wnt signalling (P. Wang et al. 2015). Gene dysregulation in this instance is effectively a

model of indirect gain-of-function². Non-verbal IQ varies from profound disability to average demonstrating variable penetration (O’Roak et al. 2012). One of the six genes mutations, dual-specificity tyrosine-(Y)-phosphorylation regulated kinase (DYRK1A) represents a loss of function and the cases are typically microcephalic. It maps onto a Down syndrome critical region (van Bon et al. 2016). The mutations result in cortical atrophy and corpus callosum hypoplasia, but otherwise normal brain architecture, making it more difficult to interpret a differential causal role in autistic symptoms for any specific region. None the less, midbrain and hindbrain regions are disproportionately reduced.

Out of 13 patients with developmental verbal dyspraxia and mutations in Foxp2, 3 had a diagnosis of ASD and one other met partial criteria (Feuk et al. 2006). Forkhead box p2 gene codes for a transcription factor located on human 7q31 and chromosome 7 has been linked to ASD susceptibility (Ashley-Koch et al. 1999). Others have suggested Foxp2 is not a major susceptibility gene especially its common variants (Newbury et al. 2002). A missense knock-in mutation in mice does cause impaired vocalization and Purkinje cell dendritic thinning (Fujita et al. 2008). However, a synonymous missense mutation in the KE family was not associated with ASD suggesting either more extensive mutations of the gene or inclusion of other loci.

A study using induced pluripotent stem cells (modeling first trimester telencephalic development) from four probands with idiopathic ASD showed a selective hyperproliferative capacity of GABAergic neurons (Mariani et al. 2015). Head circumference was positively correlated with ASD symptoms and RNA interference showed that transcription factor FOXP1 is part of the causal chain in upregulated cellular events, but also a hint at a shared pathophysiological mechanism within idiopathic and between idiopathic and syndromic cases in spite of a polymorphic underlying genetic aetiology. There was no equivalence though of macrocephaly in asymptomatic fathers supporting dysregulation of a subpopulation of GABAergic neurons i.e. loss of Purkinje cells in the

² Gene dysregulation is complex with both up- and down-regulated transcripts. Gain-of-function here refers to both phenotypic macrocephaly associated with cortical neural proliferation and a presumed converse loss of Purkinje cells.

cerebellum, that is of greater developmental importance in ASD symptom dimensions.

Distal deletions of chromosome 1q typically present with microcephaly, hypoplasia of the corpus callosum, psychomotor retardation and can manifest autistic features (Perrone et al. 2012).

However, they often involve several genes in addition to cholinergic muscarinic M3 receptor. A case of a 3¹/₂ year-old with a diagnosis of autistic disorder had an interstitial 473 kb deletion at 1q43 region and was restricted to a single gene for the M3 subtype (Petersen et al. 2013). This unique case demonstrates the likely importance of M3 receptor haploinsufficiency in autistic symptoms associated with 1q43 terminal deletions. M1 receptor subtype is predominantly expressed in the cortex and striatum, but not the cerebellum (Bakker et al. 2015). M1 and M3 are the only muscarinic subtypes with intracellular transduction through Gq/11 receptor. Unlike M1, M3 subtype is the predominant muscarinic receptor of the cerebellum. Activation of M3, but not M1 appears to be the primary mechanism for LTP suppression of parallel fibre-Purkinje cell synapses (Rinaldo and Hansel 2013). M3 is also found in certain limbic regions such as the amygdala and hippocampus, but has a low expression (Levey et al. 1994). Thus, the effects of M3 on cognitive function as observed in ASD, could be largely dependent on cerebellar dysfunction rather than direct effects on memory as the authors postulated. M1 receptor is much more heavily expressed in limbic regions than M3 and is important for memory.

7.1 Evolutionary biology

The massive expansion of the human brain up to its current size occurred roughly 200 000 years ago. There has been little further increase in brain size in the last 150 000 years. Although ample speculation exists as to the underlying reasons for this, ultimately multiple causes are likely to be responsible. The current analysis would suggest that autism could well present a bottleneck in human evolution of brain size not previously anticipated. Although many syndromic and sporadic cases discussed result from known and specific gene disruptions, regulatory regions in DNA non-coding sequences have been given greater prominence in theoretical discourse on the evolution of

phenotypes (Carroll 2008). There is a relative constancy of the genome and protein function, even from distant relatives. Regulatory sequences include human accelerated regions (HARS) typified by the neuro-developmental enhancer of the *Wnt* receptor *Frizzled 8*, which showed increase in neocortical size with human as compared to chimpanzee derived transgenic mouse models (Boyd et al. 2015; Franchini and Pollard 2015). Novel non-coding sequence mutations could account for a significant proportion of the *idiopathic* majority of the autistic spectrum. Preliminary evidence from two studies detected smaller, multiple CNVs in putative regulatory regions near known autism risk genes of simplex probands (Turner et al. 2016; Yuen et al. 2016).

The cerebral neocortex and cerebellum show phylogenetic coordination during growth (Hofman 2014). Thus, hyperproliferative mutations in non-coding regulatory regions leading to neocortical expansion, synonymous with increased head circumference in ASD, are presumably associated with a concomitant loss of selectively vulnerable Purkinje cells. The intriguing implications of such a model may also explain the evolutionary pressure for adaptation causing a relatively high prevalence of the disorder in the population. This model speculates that the reciprocal effect on heterologous brain components found in autism is a major roadblock to the continued evolutionary expansion of the neocortex.

8. A proposal for medical intervention using repetitive transcranial magnetic stimulation (rTMS).

Support for a prospective major effect size for TMS intervention in ASD comes from two incidental studies. Firstly, transcranial direct current stimulation (tDCS) applied to the cerebellum of normal subjects resulted in faster visuomotor adaptation to load changes than did a similar protocol directly to the primary motor cortex (Galea et al. 2011). tDCS of primary motor cortex did not in itself affect adaptation, but did increase maladaptive retention shown by maintenance of errors during deadaptation. The second study was a recent mouse model of high frequency cerebellar rTMS altering dendritic and spine morphology of Purkinje cells and in a further lesion experiment induced climbing fibre reinnervation of Purkinje cells (Morellini et al. 2015). Stimulation enhanced

performance in the probe test for the Morris water maze, a test of spatial memory for a submerged platform.

Extrapolating from these findings, transcranial stimulation of the cerebellum should prove more effective in adaptive cognitive abilities related to parietal and dorsolateral cortical function than direct cortical application of the technique. Improvement in cognitive manipulations of spatial awareness should lead to follow-on effects in social skill and language abilities. Studies of rTMS in autism are few and none have addressed its application to the structure most commonly implicated in pathophysiology, the cerebellum. There is a powerful theoretical precedent for medical intervention targeting the cerebellum to improve core features of ASD. The proposed intervention should in principle, be causal independent.

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