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The cerebellum and motor dysfunction in neuropsychiatric disorders

E Gowen[1] and **RC Miall**[2]

[1]Faculty of Life Sciences, University of Manchester, UK

[2]School of Psychology, University of Birmingham, UK

Abstract

The cerebellum is densely interconnected with sensory-motor areas of the cerebral cortex, and in man, the great expansion of the association areas of cerebral cortex is also paralleled by an expansion of the lateral cerebellar hemispheres. It is therefore likely that these circuits contribute to non-motor cognitive functions, but this is still a controversial issue. One approach is to examine evidence from neuropsychiatric disorders of cerebellar involvement. In this review, we narrow this search to test whether there is evidence of motor dysfunction associated with neuropsychiatric disorders consistent with disruption of cerebellar motor function. While we do find such evidence, especially in autism and schizophrenia, we caution that the restricted set of motor symptoms does not suggest global cerebellar dysfunction. Moreover, these symptoms may also reflect involvement of other, extra-cerebellar circuits and detailed examination of specific sub groups of individuals within each disorder may help to relate such motor symptoms to cerebellar morphology.

Introduction

The cerebellum has long been known to be a critical structure for the coordination and control of movement. However, both recent and quite early evidence indicates that the cerebellum also plays a role in cognitive and emotional functions (1–6; see 7 for a comprehensive review of early work). It is also increasingly clear that there are extensive connections between the cerebellum and frontal associative areas of the cerebral cortex that fall well outside the classical sensory-motor circuit (8). [NEW REF: Ramnani et al 2006] These findings have raised questions as to whether through these connections the cerebellum contributes directly to the behavioural and cognitive symptoms of psychiatric disorders such as autistic spectrum disorder (ASD), schizophrenia, and depression. There is also a suggested link between cerebellar abnormality and dyslexia, with motor deficits potentially linked to differential development of the anterior cerebellum, as well as with attention deficit hyperactivity disorder (ADHD). Interestingly, symptoms and signs characteristic of these conditions such as personality change, mood disorder, executive dysfunction and language and reading deficits have been reported in cerebellar pathology.

However, as the cerebellum has been traditionally and strongly linked with motor control (13–18), one might then expect signs of compromised motor control in these psychiatric disorders, if generalized cerebellar dysfunction contributed to their pathology. Indeed, clumsiness and abnormal motor behaviour has been well documented in disorders such as

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autism and Aspergers' syndrome (Asperger, 1944, translated in (19), 20–22), in dyslexia (23,24) and in schizophrenia (25–27). It is clear that the cerebellum is functionally heterogeneous, with cerebellar zones selectively interconnecting with many cerebral subsystems (47). Thus one might not be surprised to find the developmental disorders that affect different cerebral systems also affect the cerebellum. We attempt a more specific argument, however, addressing whether motor dysfunction is common across neuropsychiatric disorders, over and above the possible role of the cerebellum to the cognitive and psychiatric aspects of each disorder. Consequently, this review will examine this issue, presenting evidence for and against motor symptoms that are consistent with cerebellar dysfunction. We also review recent anatomical and functional imaging papers that have looked for cerebellar involvement in these disorders.

Motor functions of the cerebellum

Deficiency in cerebellar motor control can manifest as inaccuracies of visually guided movement (28–31), speeded complex movement (13,32), loss of muscle tone (12), timing (33–35) and loss of prediction and coordination (36–40). Clinically, these features are apparent as dysmetria (inaccurate movement), dysdiadochokinesis (inability to execute rapidly alternating movements), hypotonia (reduced muscle tone) and dyscoordination or ataxia (inability to perform smoothly coordinated voluntary movement) (13,41). The topography of the cerebellar cortex with respect to motor control and non-motor function is perhaps surprisingly unclear. Somatotopic maps of the proximal and distal musculature are seen in the anterior and posterior lobes (42,43), and lesions of these lateral areas lead to distal motor dysfunction (44,45). Likewise, the vermis and paravermal cortex are closely interconnected to spinal, vestibular and brainstem systems controlling balance, medial musculature, eye movements and gait (45–46). However the lateral hemispheres have expanded dramatically in primates, and the cerebello-cerebral connections and roles of these lateral areas are yet to be fully determined. In general, one can see a separation of information from the lateral cerebellar cortex through the dorsal portions of the lateral nucleus to motor and premotor cerebral areas, and a ventral stream linking to non-motor areas (47). While the motoric symptoms of cerebellar dysfunction are indisputable, the exact function or functions of the cerebellum in motor control are still very uncertain. Key ideas are its role in associative sensory-motor learning, timing, error detection and correction, and coordination of different effectors. While the consensus is that the cerebellum is closely concerned with motor control and sensory-motor integration, there are also claims that its function is largely sensory (Bower 1997) or in state estimation (Paulin, 1993, 2005). Theoretical work has provided a detailed account of how the cerebellum may control aspects of movement and timing, suggesting that it provides predictive estimates of future motor commands in terms of their timing and sensory consequences that allow detection and correction of errors (16, 48–51).

These characteristic findings of movement disturbances allowed Dow and Moruzzi (41) and subsequent researchers to develop test batteries such as the Assessment Battery for Children (52), the Bruininks-Oseretsky test (53) a subcomponent of the National Evaluation Scale for Schizophrenia (54) and The Test of Motor Impairment – Henderson Revision (55) to specifically detect cerebellar dysfunction. Subsequently, these test batteries have been

applied to various neuropsychiatric disorders such as autism, Asperger's syndrome and schizophrenia and have provided indirect and qualitative behavioural evidence for abnormal cerebellar motor control. In the following sections we examine whether these qualitative reports are supported by quantitative behavioural and imaging evidence data. We have restricted our focus to Autism Spectrum Disorder, schizophrenia and depression, and also include developmental dyslexia, as together these have attracted the majority of interest both in terms of cerebellar involvement and motor research.

Autistic Spectrum Disorder (ASD)

Currently, it is unclear what are the precise distinguishing features between autism and Aspergers' syndrome, and this is compounded by the possibility that different subgroups may be present within each disorder (56). As different diagnostic criteria are employed, this has led to overlap between the two disorders, rendering it difficult to evaluate whether the prevalence and characteristics of motor deficits differ between autism and Aspergers' syndrome. A number of studies indicate that autism and Aspergers' syndrome cannot be differentiated according to motor abnormalities (57,58), but others indicate that differences may be apparent on a finer level (59–61). This is an area that requires extensive and consistent research and one that is beyond the scope of the current review. Consequently, we have used the term ASD to cover both autism and Aspergers' syndrome.

There have been a number of qualitative reports suggesting impairments of prediction and coordination in ASD, particularly balance (5–59,62,63) and speeded complex and visually guided movements (tested as manual dexterity or ball skills) (58,59,64,65). Heightened interest in motor control abnormalities associated with ASD has increasingly led to the use of quantitative studies of matched groups. With regard to speeded complex movements and muscle tone, there is little evidence of either dysdiadochokinesis or hypotonia (66–67). This negative result is supported by the observation that movement preparation but not movement execution is impaired in individuals with ASD (60). Such findings may relate to the developmental nature of ASD, as hypotonia resulting from cerebellar lesions is most severe during the early acute stage but subsides with time (32). Few studies have specifically investigated dysmetria or used combined eye–hand tracking tasks where the cerebellum is known to play a role (30,31,68). One rather general sensory-motor test that does involve eye-hand coordination and employs cerebellar resources (29) is the Annett peg-board test in which participants rapidly move a row of small pegs from one side of a board to holes in the other side. Completion times and errors (dropped pegs) are normally recorded. However, results with ASD participants are mixed, with reports of slower completion times compared to controls (69) or of no differences (63). Recently, using a functionally related visually guided pointing task, we observed that ASD participants were both slower and less accurate, suggesting poorer visual guidance of movement (66). In addition, during a reach to grasp task, ASD individuals were able to synchronise reaching and grasping components but displayed an increased peak velocity and decreased duration compared to controls (70), which the authors suggested represented a strategy to avoid disruptive visual feedback mechanisms. Interestingly, a low IQ group performing the same task demonstrated inability to synchronise reaching and grasping components, suggesting that they were unable to use

predictive mechanisms of control. These results emphasise the presence of different subgroups and that impairments in visual feedback and/or predictive mechanisms may exist.

Postural stability requires intact anticipatory and sensory processes and the cerebellar vermis is believed to use vestibular, proprioceptive and visual inputs to coordinate muscle timing so that the centre of gravity stays within the limits of stable upright standing (36,71). ASD participants consistently display impaired balance during eyes open and eyes closed conditions, suggesting deficits of both visual and proprioceptive integration (66,72). Posturography investigations of cerebellar patients suggest that different lesions result in varying degrees and direction of sway, as well as affecting the ability to use visual compensation (73). Future examination of such sway characteristics may reveal whether balance abnormalities in ASD are related to diffuse or local damage. Direct evidence for reduced anticipatory function in ASD children has been demonstrated during bimanual load lifting in the form of absent anticipatory muscular events and absent anticipatory motor cortex activity using electromyographic and electroencephalogram recordings respectively (67,74). Gripping an object also requires predictive control so that load force changes can be anticipated and grip force altered accordingly to prevent gripped objects from slipping (75,76). However, we observed (66) that ASD subjects were equally able to predict this load change despite being poorer at a visually guided task. As our subjects had average/high ability this complements the findings of (70), suggesting that they were able to use some predictive control. However, we only tested grip force of the dominant hand (66), and it has been demonstrated that impairments in predictive grip force are restricted to the hand ipsilateral to the cerebellar lesion (39) so some differences might be seen in the non-preferred hand.

There are very few studies that have directly looked at timing ability in ASD. We used a synchronisation and continuation interval timing task where subjects tapped in time with an external beep, or produced a remembered sequence of beeps (66). In contrast to the continuation task, Asperger participants tended to display greater absolute error in the synchronisation task, caused mainly by an underestimation the target interval. These findings are reminiscent of abnormal conditioned eye-blink responses observed in autistic subjects, characterised by earlier acquisition and extinction and by shorter response latencies (Sears). Eye blink conditioning is known to rely on cerebellar structures such as the anterior interpositus nucleus and H-VI lobules (Steinmetz). Timing deficits are frequently associated with cerebellar lesions using perceptual and motor interval tasks in the sub-second range (33; Mangels, Nichelli) and during conditioned eye blink responses (Woodruff). It is unclear whether such findings arise from impairments in one area within the cerebellum that is specialised for timing computations, a localized timing system distributed throughout the cerebellum where temporal information is computed within structures involved for a particular task, or a distributed network that involves structures outside the cerebellum (Ivry 35). The former has been suggested by Ivry and colleagues (33), as lateral cerebellar lesions impaired a central timing process, whereas medial lesions impaired implementation. Consequently, the timing deficits observed in our Asperger participants could arise from either impoverished sensory input to the cerebellum, damage to a specialised timing module within the cerebellum, localised cerebellar damage for sensorimotor integration, or an inability to execute the correct motor response despite intact timing signals. As simple motor

execution appears unaffected in ASD and our participants performed within normal limits on the continuation task, this suggests that the observed timing deficits were due to either poor sensory input or reduced sensorimotor integration. Future work comparing sensory function with motor and perceptual timing tasks could help elucidate the origin of subnormal ASD timing and whether any functionally identifiable ASD subgroups exists.

Overall, behavioural findings indicate that individuals with ASD display impairments in visually guided movements, prediction and coordination (balance) and timing but show intact motor execution. As we have suggested (66) a common theme appears to be the integration of sensory input (vision, proprioception, audition) with a motor response, a function well suited to the cerebellum. However, future work needs to distinguish whether this results from impaired integration or from disrupted sensory input. Furthermore, studies need to control for IQ levels as this does appear to have an impact on motor control (66,70,72).

A cerebellar contribution towards these motor signs is supported by post-mortem evidence revealing Purkinje cell loss, hypo- and hyper-plasia in the vermis and in the hemispheres (77,78). It should be noted that many existing post-mortem reports of ASD brains suffer from much inter-subject variability and low subject numbers, and of course lack functional or behavioural correlates, so the increasing spatial resolution of modern MR imaging is likely to provide the most convincing evidence of structural change. Hypo- and hyper-plasia of the cerebellar vermis and hemispheres has also been demonstrated using anatomical or structural MRI (79,80 and others see 78). In man, the cerebellar vermis and lateral hemispheres are much more heavily connected with prefrontal areas, via the ventral dentate nucleus and thalamus, than in non-human primates (81). Reduced exploratory behaviour in autistic children has been correlated with hypoplasia of vermal lobules VI-VII and frontal lobe suggesting a direct link between structural abnormalities and autistic signs (82).

There is now a number of growing functional imaging studies, that complement the structural abnormalities mentioned above with patterns of abnormal activation in tasks aimed to test cognitive and motor functions. Allen & Courchesne (83) reported increased cerebellar activation in a button pressing task, and reduced activation in a visual attention task. With a similar motor task and the same subject groups, it was further shown that a correlation between structural and functional changes existed in the autistic group (84). With a more complex motor sequence learning task, changes in prefrontal and parietal cortex have been seen (85), with greater variability in peak activation loci, and suggested a developmental process in which the abnormal cerebello-cerebral pathways contribute to abnormal fronto-parietal function. Finally, electrophysiological methods have detected differential evoked responses in autism in a spatial attention task (86), that is consistent with abnormal cerebellar modulating influence on fronto-parietal systems. However, it should be emphasised that the role of the cerebellum in attention shifting remains under debate as the original evidence linking the cerebellum to attention (Allen et al 1997;Akshomoff and Cour 1992) has not been replicated in subsequent cerebellar studies (Schoch; Ravizza 2001). Instead it has been suggested that the apparent deficits of attention in cerebellar patients may be due to either redirection of attention resources to an impaired motor response, small

group sizes, extra-cerebellar involvement or a cerebellar contribution to response reassignment rather than attention shifting (Bischoff-Grethe;(Schoch).)

Developmental dyslexia

The cerebellar deficit hypothesis in developmental dyslexia has been predominantly championed by Nicolson and colleagues. They suggest that the full range of difficulties encountered by dyslexics such as reading, writing and spelling can be explained by cerebellar dysfunction (24). Specifically, hand writing impairment may be directly attributed to poor motor coordination, whereas impoverished reading and spelling skills may arise through delayed and less fluent articulation and automatising that may take up more resources such as working memory, leading to difficulties in language acquisition and phonological awareness. In a series of studies examining large cohorts of dyslexic children, they demonstrated time estimation deficits (87), impaired postural stability, hypotonia and slower toe tapping speed (23,88). Recently, supportive evidence from an extensive study examining dyslexic balancing skills has highlighted that instability is a common finding in dyslexia and is correlated to impaired literacy and cognitive ability (90). The same group has also shown that adult dyslexic individuals exhibit slower processing speed on the Annett's peg-board test (91) and impaired implicit motor learning (92) both of which were correlated with literacy skills.

Such indirect behavioural evidence has now been supported by structural, functional and post-mortem results that indicate both anterior and posterior cerebellar abnormalities (93, see 94 for review). Recent work by this group comparing automatic and manual estimation of grey and white matter volumes in the cerebellum confirms the differential development of the anterior cerebellum, but also suggests that changes here and in the cerebral cortex are correlated to whole brain volume changes (95). Likewise, greater cerebellar symmetry in dyslexic adults correlates with phonological processing deficits (96), which reflects the greater cerebral symmetry seen in dyslexic subjects. There is also evidence of altered symmetric cerebellar metabolism in the dyslexic cerebellum that correlates to both peg moving performance and phonological scores (96). Nicholson and colleagues (89) have also demonstrated functional activation reductions in the right anterior cerebellar cortex in dyslexic adults that can be associated with their deficits in a motor sequence learning task, supporting the link between disturbed cerebellar function, motor deficits, and dyslexia. However, the links between developmental disruption of the cerebellum and dyslexic reading and language skills are often blurred by the diverse phenomenology of dyslexia and the strongly confounding effects of IQ or attention deficit hyperactivity disorder (97). Cerebellar involvement is perhaps more clearly suggested by evidence of dyslexic symptoms after acquired lesions (98,10,11). Furthermore, the relationship between these structural and behavioural findings is unclear and one criticism against the cerebellar deficit hypothesis is the absence of consistent motor deficits found in all dyslexic subjects. In order to allay such criticism, future imaging work is required to demonstrate that specific structural and functional abnormalities can relate to different aspects of cognitive or motor impairment.

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Schizophrenia

The involvement of the cerebellar vermis in schizophrenia has been proposed for some time (99). More recently, several authors (100–102) have suggested the disorder to be a consequence of disruption to the cortico-cerebellar-thalamic-cortical circuits, whereby the fluidity and synchrony of thought is modified by the cerebellum in a similar manner to movement control. This “poor mental coordination” is referred to as cognitive dysmetria. Qualitative reports and assessments have frequently documented motor abnormalities in patients with schizophrenia (often classed as neurological, non-localising soft signs in the schizophrenia literature) (27,103–109, see 25 for a review). Indeed, employing a meta-analysis examining neurocognitive deficits, Heinrichs and Zakzanis (104) observed that motor abnormalities exhibited the second highest effect size. Importantly, it appears that first episode, drug naïve patients exhibit motor control abnormalities in excess of healthy controls (Dazzan) and there is little relationship between the level/duration of anti-psychotic treatment and motor abnormalities (Bombin, although see Boks et al), highlighting that these signs are most probably not a consequence of anti-psychotic medication.

In contrast to ASD studies, schizophrenic patients exhibit deficits in both simple and complex movement execution such as rapid alternating movement, finger tapping and fine manual dexterity (Purdue pegboard test, similar to Annett peg-board test but requires assembly of collars and washers onto pegs). Some authors have reported correlations between these finding and social functioning (110), whereas others have found relatively weaker correlations between motor and executive impairments (111). Furthermore, the extent of these motor abnormalities vary with the clinical course of schizophrenia within individuals (103) and have been correlated to smaller cerebellar volumes (103,105). In turn, smaller cerebellar volumes, particularly of the vermis have been associated with cognitive and psychotic symptoms (112,113).

It has been suggested that these motor abnormalities may arise from deficient predictive control mechanisms whereby the predicted sensory outcome of one’s movement does not match with the actual sensory afference (114–117). Consequently, schizophrenic individuals demonstrate difficulties in recognising their actions as their own and perceiving the consequences of their actions (118,119). This may extrapolate to difficulties in distinguishing the origins of their perceptions, and thus links schizophrenic hallucinations to a failure to predict action outcomes (114). However, evidence suggests that some predictive processes may be spared and that impairments may be more apparent during sequencing of motor actions (120). Such effects may be related to incorrect timing judgements as schizophrenic patients show increased binding between a movement and a previous causal action i.e. they underestimate the temporal interval between events leading to heightened but incorrect associations (121). Furthermore, underestimation of short temporal durations has been observed (122) which is similar to our findings in individuals with ASD. Importantly, these results could not be explained by levels of intelligence or working memory and as the tasks did not require a motor response this suggested a deficit of specialised cerebellar timing processes.

In line with these timing and prediction deficits, postural stability appears affected in schizophrenia (123–125) although these findings suffer from the use of qualitative recording methods, (123,124) and lack of suitable IQ matching with control subjects (123–125). Furthermore, it is possible that the co-morbidity of alcohol abuse in schizophrenia contributes to the reported balance disturbances (126). There is, of course, a strong impact of alcohol abuse on the anterior cerebellar lobe as well as on many other brain regions (127). Studies that have attempted to control for this factor indicate that balance ability is not related to prior alcohol abuse (123–125). Interestingly, eye closure does not appear to affect balance in schizophrenic patients to any greater degree than in controls, suggesting a visual, rather than proprioceptive impairment (125). Increased postural sway in individuals with schizophrenia has been correlated to both the degree of cognitive impairment and cerebellar tissue loss: those patients who demonstrated cerebellar signs (predominantly increased postural sway) were more likely to exhibit greater deficits in memory, visuospatial, attention and motor skills, combined with cerebellar hypoplasia (123). As only 32 out of the 155 patients demonstrated cerebellar signs it should be emphasised that, as with autism and dyslexia, different subgroups of schizophrenic patients may exist.

Konarski *et al.*, (2) have recently reviewed structural and functional imaging evidence for cerebellar involvement in schizophrenia, and argue that there is converging evidence for this role, despite a tendency for it to have been overlooked in previous research. However, rather few studies have tested functional activation differences during performance of motor tasks. Reduced cerebellar activation during a motor sequence task has been reported (128). A contrast between schizophrenic and control subjects in a joystick movement task with PET scanning reported no differential cerebellar activity (129), but did see cerebral differences (in the insular cortex and right angular gyrus); in contrast, hyper-activation of anterior cerebellum in a very similar task was seen (130), when contrasting passivity status across schizophrenic sub-groups.

Mood and bipolar disorder

There are limited reports linking the cerebellum to depression and bipolar disorder. Beyer and Krishnan (131) review studies of volumetric differences, mainly in bipolar depression and report mixed evidence for cerebellar atrophy in comparison with schizophrenic or control groups. Strakowksi, DelBello and Adlert (132) review evidence of a functional neuroanatomical basic for bipolar disorder, and provide some support for structural change in the cerebellar vermis, that progresses with repeated episodes of mood disturbance (133). Using magnetic resonance spectroscopy, Cecil *et al* (134) found reduced levels of N-acetylaspartate (NAA) in the cerebellar vermis, while increased glucose metabolism has been found in the cerebellum and posterior cortex (lingular gyrus and cuneus) across all mood subgroups (135). Even fewer studies appear to have examined motor control in individuals with bipolar disorder. Qualitative studies have observed dysdiadochokinesis in individuals with bipolar disorders compared to healthy control participants, but this finding has been related to impairments in attentional set shifting resulting from DLPFC dysfunction (136,137).

A further problem with assessing the role of the cerebellum in such disorders is the widespread use of therapeutic drugs such as lithium and antidepressants (Maj; Silverstone and Silverstone), since long term usage is known to lead to changes in cerebellar structure and consequently cerebellar signs such as ataxia, gait instability, dysmetria, dysdiadochokinesis and hypotonia (Adityanjee). For example, vermal hypoplasia (Mills) and cerebellar volume (Loeber) have been correlated to duration of antidepressant exposure. Future studies need to examine drug naïve patients and investigate correlations between drug level/exposure and cerebellar signs before any firm conclusions regarding the role of the cerebellum in bipolar motor deficits can be drawn.

ADHD

The evidence for a cerebellar contribution to ADHD in adults is quite limited, but from developmental studies using anatomical imaging, it has been suggested that there is involvement of quite diverse cerebello-thalamo-striato-cortical systems [NEW REFS Schneider et al., 2006, Carmona et al, 2005], with hypoplasia of the posterior cerebellar vermis {NEW REF Berquin et al, 1998]. However, a recent meta-analysis of functional imaging studies [NEW REF Dickstein et al, 2005] reports limited functional differences in the cerebellum, with greater evidence for fronto-striatal and fronto-parietal dysfunction, consistent with executive and attentional networks. This is reflected in behavioural studies where evidence for cerebellum specific motor dysfunction is sparse and any motor abnormalities have been related to dysfunction of frontal-striatal-basal ganglia networks rather than to the cerebellum (Dickstein). Generally, motor control in ADHD has not been extensively or quantitatively studied, although qualitative studies point to clumsiness (Karatekin), slower repetitive actions such as finger tapping (Dickstein, Rubia) and poorer manual dexterity and balance (Piek et al 1999;Raberger). In addition, ADHD individuals demonstrate impairments in time reproduction and perception tasks (see Toplak for an extensive review). Observations that time perception is preferentially impaired for durations greater than one second (Radanovich) lead the authors to suggest deficits in frontal lobe working memory processes as opposed to the cerebellum which contributes to sub-second timing functions (Mangels, Lewis & Miall, 2006). Of note was the bimodal distribution of results with half the group performing normally (Radanovich), highlighting the existence of subgroups.

Examination of motor control is complicated by both the nature of ADHD, as motor deficits may arise due to poor attention to the task, and by the high degree of co-morbidity between ADHD and developmental coordination disorder (DCD) (Pyck and Dyck 2004), defined as motor coordination that is significantly lower than the child’s mental and intellectual ability. With regard to the former, motor and timing abnormalities appear to persist despite normal performance on other attention demanding tasks (Piek et al 1999) and also during increased motivational state (Van Meel), although other work has demonstrated poor time judgment only during low arousal states (Shaw and Brown). It is difficult to judge whether observed motor deficits in ADHD should be considered separate to or as a continuation with DCD. Using the Purdue peg-board task Pitcher et al. (REF) demonstrated that participants with a combined diagnosis of ADHD and DCD performed significantly worse than those with just ADHD, who did not differ from controls. This indicates that DCD may be a dissociable

disorder. Such concerns may also trouble studies of ASD and dyslexia as DCD is also frequently present (Gillberg, 2003; Pyck and Dyck 2004) leading to the suggestion (Pyck) that one link between ADHD, autism and DCD may be the degree to which the cerebellum is affected. Alternatively, the range of executive and motor signs has hypothesised to be a continuation of different abnormalities within the cortico-striato-thalamo-cortical loops (Castellanos). Once again quantitative and detailed assessment combined with assessment of comorbid disorders and neuroimaging is required to understand these relationships further.

Summary

With the exception of depression and bipolar disorders there appears to be some quantitative behavioural evidence that individuals with ASD, schizophrenia and dyslexia display signs of cerebellar motor dysfunction. Although, it is difficult to compare the three disorders as the same tests have not been applied to each, it does appear that they display a preponderance of balance and timing deficits, indicating a global functional deficit is unlikely. Both are key signs in cerebellar pathology (33,73,138) but can also involve many other neural areas (71,139–141) that may also be abnormal in neuropsychiatric disorders. A higher proportion of imaging studies report changed activation or structure within the vermis than in other cerebellar areas, which would complement the observations of balance dysfunction (36,71). Different timing processes may be localised to a variety of areas both within and outside the cerebellum (33,40142,143, Mangels) highlighting that future studies should adopt more specific timing paradigms in order to localise deficits. In contrast to ASD, schizophrenic and dyslexic individuals show signs of hypotonia and dysdiadochokinesis suggesting that motor execution deficits may play more of a role. Whether this indicates that cerebellar dysfunction may be more widespread, or whether there may be greater involvement of higher cortical areas, remains to be discovered. Of potential significance are the observations of different types of impaired eye blink conditioning in ASD, dyslexia and ADHD (Sears/Coffin/Nicolson). In ASD eye blink conditioning was associated with earlier acquisition and extinction and shorter response latencies, in dyslexia there was an absence of conditioning and in ADHD an inability to sustain the learned response occurred. This suggests that for each condition different cerebellar networks are affected. An intriguing possibility is that the form of cerebellar involvement and its onset may give rise to different disorders.

A related issue is the degree to which cerebellar damage alone is responsible for these motor impairments. The cerebellum receives extensive input from areas that are involved in motor control such as the basal ganglia, SMA, parietal cortex, motor and premotor cortex (8) rendering it difficult to judge whether motor impairments arise from deficits in cerebellar circuitry or from inaccurate afferent connections. Consequently, it is unclear as to whether sensory, integration or motor impairments (or all three) contribute towards the motor deficits. There is burgeoning work demonstrating sensory alterations in those with schizophrenia and autism in terms of enhanced tactile sensation (144), enhanced visual processing (145,146), increased global motion thresholds (147,148) and weak context suppression (149, see 150 for a review). What is unclear is the impact of these sensory differences on motor coordination. Altered sensory input to the cerebellum may prevent normal motor coordination which would appear as cerebellar motor deficits and may give

rise to the altered structural and functional cerebellar findings; future work should aim to correlate sensory deficits to motor deficits.

What does appear clear is the vast heterogeneity of findings within each disorder suggesting interplay of differentially affected regions compounded by variables such as developmental experience, drug exposure and experimental procedures. It may be that a balance exists in the degree and location of impairment between cerebellar, cortical and striatal circuits that determines the final cognitive and motor clinical picture. Therefore it is important to identify different subgroups in each of the disorders we have discussed, using well matched control groups and a variety of quantitative motor and cognitive measures in order to explore correlations. In addition, careful consideration should be paid to the presence of co morbidity within ASD, dyslexia and ADHD and the impact of drugs on the motor findings owing to the high prevalence of medicated patients. Future studies are required to correlate motor, sensory and cognitive deficits together with fMRI, in order to define linkages, subgroups and whether the cerebellum contributes on a local or global scale to these subgroups.

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