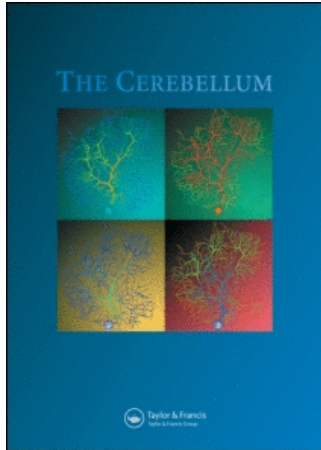


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ORIGINAL ARTICLE

The cerebellum and motor dysfunction in neuropsychiatric disorders

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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, schizophrenia and dyslexia, 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.

Key words: *Movement, cognitive, imaging, psychiatric*

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 (8,9). 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 (3,5,10–13).

However, as the cerebellum has been traditionally and strongly linked with motor control (14–19), 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 autism and Asperger's syndrome (Asperger, 1944, translated in [20], 21–23), in dyslexia (24,25) and in schizophrenia (26–28). It is clear that the cerebellum is functionally heterogeneous, with cerebellar zones selectively interconnecting with many cerebral subsystems (29). 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 (30–33), speeded complex movement (14,34), loss of muscle tone (13), timing (35–37) and loss of

prediction and coordination (38–42). 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) (14,43). 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 (44,45), and lesions of these lateral areas lead to distal motor dysfunction (46,47). Likewise, the vermis and paravermal cortex are closely interconnected to spinal, vestibular and brainstem systems controlling balance, medial musculature, eye movements and gait (29,47). 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 (48). 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 (49,50) or in state estimation (51,52). 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 (17,53–56).

These characteristic findings of movement disturbances allowed Dow and Moruzzi (43) and subsequent researchers to develop test batteries such as the Assessment Battery for Children (57), the Bruininks-Oseretsky test (58) a subcomponent of the National Evaluation Scale for Schizophrenia (59) and The Test of Motor Impairment – Henderson Revision (60) 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. We have restricted our focus to Autism Spectrum Disorder, schizophrenia and depression,

and also include developmental dyslexia and ADHD, 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 Asperger's syndrome, and this is compounded by the possibility that different subgroups may be present within each disorder (61). 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 Asperger's syndrome. A number of studies indicate that autism and Asperger's syndrome cannot be differentiated according to motor abnormalities (62,63), but others indicate that differences may be apparent on a finer level (64–66). 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 Asperger's syndrome.

There have been a number of qualitative reports suggesting impairments of prediction and coordination in ASD, particularly balance (62–64,67,68) and speeded complex and visually guided movements (tested as manual dexterity or ball skills) (63,64,69,70). 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 (71,72). This negative result is supported by the observation that movement preparation but not movement execution is impaired in individuals with ASD (65). 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 (34). Few studies have specifically investigated dysmetria or used combined eye-hand tracking tasks where the cerebellum is known to play a role (32,33,73). One rather general sensory-motor test that does involve eye-hand coordination and employs cerebellar resources (31) 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 (74) or of no differences (68). 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 (71). In addition, during a reach to grasp task, ASD individuals were able to synchronize reaching and grasping components but displayed an increased peak velocity and decreased duration compared to controls (75), 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 synchronize reaching and grasping components, suggesting that they were unable to use predictive mechanisms of control. These results emphasize 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 (38,76). ASD participants consistently display impaired balance during eyes open and eyes closed conditions, suggesting deficits of both visual and proprioceptive integration (71,77). 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 (78). 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 (72,79). 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 (80,81). However, we observed (71) 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 (75), suggesting that they were able to use some predictive control. Alternatively, as we only tested grip force of the dominant hand (71), and it has been demonstrated that impairments in predictive grip force are restricted to the hand ipsilateral to the cerebellar lesion (41) some differences might have been apparent 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 (71). 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, characterized by earlier acquisition and extinction and by shorter response latencies (82). Eye blink conditioning is known to rely on cerebellar structures such as the anterior interpositus nucleus and H-VI lobules (83). Timing deficits are frequently associated with cerebellar lesions using perceptual and motor interval tasks in the sub-second range (35,84,85) and during conditioned eye blink responses (86). It is unclear whether such findings arise from impairments in one area within the cerebellum that is specialized 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 (37). The former has been suggested by Ivry and colleagues (35), 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 specialized timing module within the cerebellum, localized 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 exist.

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 (71) 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 (71,75,77).

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 (87,88). 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 (88,90 and others see 88). 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 (91). 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 (92).

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 (93) 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 (94). With a more complex motor sequence learning task, changes in prefrontal and parietal cortex have been seen (95), with greater variability in peak activation loci, suggested to represent 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 (96) that is consistent with abnormal cerebellar modulating influence on fronto-parietal systems. However, it should be emphasized that the role of the cerebellum in attention shifting remains under debate as the original evidence linking the cerebellum to attention (1,97) has not been replicated in subsequent cerebellar studies (98,99). 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 (99,100)

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 (25). 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 automatizing 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 (101), impaired postural stability, hypotonia and slower toe tapping speed (25,102). 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 (103). The same group has also shown that adult dyslexic individuals exhibit slower processing speed on the Annett peg-board test (104) and impaired implicit motor learning (105) 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 (106, see 107 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 (108). Likewise, greater cerebellar symmetry in dyslexic adults correlates with phonological processing deficits (109), 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 (109). Nicholson and colleagues (110) 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 ADHD (111). Cerebellar involvement is perhaps more clearly suggested by evidence of dyslexic symptoms after acquired lesions (11,12,112). 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.

Schizophrenia

The involvement of the cerebellar vermis in schizophrenia has been proposed for some time (113).

More recently, several authors (114–116) 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-localizing soft signs in the schizophrenia literature) (28,117–122, see 26 for a review). Indeed, employing a meta-analysis examining neurocognitive deficits, Heinrichs and Zakzanis (118) 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 (123) and there is little relationship between the level/duration of anti-psychotic treatment and motor abnormalities (26, although see 124), 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 (125), whereas others have found relatively weaker correlations between motor and executive impairments (126). Furthermore, the extent of these motor abnormalities vary with the clinical course of schizophrenia within individuals (117) and have been correlated to smaller cerebellar volumes (117,119). In turn, smaller cerebellar volumes, particularly of the vermis have been associated with cognitive and psychotic symptoms (127,128).

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 (129–132). Consequently, schizophrenic individuals demonstrate difficulties in recognizing their actions as their own and perceiving the consequences of their actions (133,134). This may extrapolate to difficulties in distinguishing the origins of their perceptions, and thus links schizophrenic hallucinations to a failure to predict action outcomes (129). However, evidence suggests that some predictive processes may be spared and that impairments may be more apparent during sequencing of motor actions (135). 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 (136). Furthermore, underestimation of short temporal durations has been observed (137) 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 specialized cerebellar timing processes.

In line with these timing and prediction deficits, postural stability appears affected in schizophrenia (138–140) although these findings suffer from the use of qualitative recording methods, (138,139) and lack of suitable IQ matching with control subjects (138–140). Furthermore, it is possible that the comorbidity of alcohol abuse in schizophrenia contributes to the reported balance disturbances (141). There is, of course, a strong impact of alcohol abuse on the anterior cerebellar lobe as well as on many other brain regions (142). Studies that have attempted to control for this factor indicate that balance ability is not related to prior alcohol abuse (138–140). 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 (140). 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 (138). As only 32 out of the 155 patients demonstrated cerebellar signs it should be emphasized 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 (143). A contrast between schizophrenic and control subjects in a joystick movement task with PET scanning reported no differential cerebellar activity (144), 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 (145), 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

(146) review studies of volumetric differences, mainly in bipolar depression and report mixed evidence for cerebellar atrophy in comparison with schizophrenic or control groups. Strakowski, DelBello and Adlert (147) review evidence of a functional neuroanatomical basis for bipolar disorder, and provide some support for structural change in the cerebellar vermis, that progresses with repeated episodes of mood disturbance (148). Using magnetic resonance spectroscopy, Cecil et al. (149) 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 (150). 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 dorsolateral prefrontal cortex dysfunction (151,152).

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 (153,154), 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 (155). For example, vermal hypoplasia (156) and cerebellar volume (157) 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 (158,159), with hypoplasia of the posterior cerebellar vermis (160). However, a recent meta-analysis of functional imaging studies (161) 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 more frequently related to dysfunction of frontal-striatal-basal ganglia networks rather than to the cerebellum (162). Generally, motor control in ADHD has not been extensively or quantitatively studied, although qualitative studies point to

clumsiness (163), slower repetitive actions such as finger tapping (162,164) and poorer manual dexterity and balance (165,166). In addition, ADHD individuals demonstrate impairments in time reproduction and perception tasks (see 167 for an extensive review). Observations that time perception is preferentially impaired for durations greater than one second (168; although see 167 evidence for sub-second impairments) suggests deficits in frontal lobe working memory processes as opposed to the cerebellum which contributes to sub-second timing functions (84,169). Of note was the bimodal distribution of results with half the group performing normally (168), 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) (170), 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 (165) and also during increased motivational state (171), although other work has demonstrated poor time judgment only during low arousal states (172). 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. (173) 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 (170,174) leading to the suggestion (170) that one link between ADHD, autism and DCD may be the degree to which the cerebellum is affected. Alternatively, it has been hypothesized that the range of executive and motor signs could be a continuation of different abnormalities within the cortico-striato-thalamo-cortical loops (175). Once again quantitative and detailed assessment combined with assessment of co-morbid disorders and neuroimaging is required to understand these relationships further.

Conclusion

With the exception of depression, bipolar disorders and ADHD 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. Abnormal timing has also been a consistent and quantitatively examined feature of ADHD. Both balance and timing are key signs in cerebellar pathology (35,78,176) but can also involve many other neural areas (169,177,178) 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 (38,76). Different timing processes may be localized to a variety of areas both within and outside the cerebellum (36,42,84,179,180) highlighting that future studies should adopt more specific timing paradigms in order to localize 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 (82,181,182). 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 (8,9) 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 (183), enhanced visual processing (184,185), increased global motion thresholds (186,187) and weak context suppression (188, see 189 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 cerebellar and extra-cerebellar 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 ultimately whether specific cerebellar regions are associated with the different motor, sensory and cognitive findings.

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References

1. Allen G, Buxton RB, Wong EC. Attentional activation of the cerebellum independent of motor involvement. *Science*. 1997;275:1940-43.
2. Konarski JZ, McIntyre RS, Grupp LA, Kennedy SH. Is the cerebellum relevant in the circuitry of neuropsychiatric disorders? *J. Psychiatry Neurosci*. 2005;30:178-86.
3. Leroi I, O'Hearn E, Marsh L, et al. Psychopathology in patients with degenerative cerebellar diseases: A comparison to Huntington's disease. *Am J Psychiatry*. 2002;159:1306-14.
4. Schmahmann JD. An emerging concept. The cerebellar contribution to higher function. *Arch Neurol*. 1991;48:1178-87.
5. Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. *Brain*. 1998;121(Pt 4):561-79.
6. Schmahmann JD. Disorders of the cerebellum: Ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome. *J Neuropsychiatry Clin Neurosci*. 2004;16:367-78.
7. Schmahmann JD. Rediscovery of an early concept. In: Schmahmann JD, editor. *The cerebellum and cognition*. San Diego: Academic Press; 1997. pp 3-27.
8. Ramnani N. The primate cortico-cerebellar system: Anatomy and function. *Nat Rev Neurosci*. 2006;7(7):511-22.
9. Ramnani N, Behrens TE, Johansen-Berg H, et al. The evolution of prefrontal inputs to the cortico-pontine system: Diffusion imaging evidence from Macaque monkeys and humans. *Cereb Cortex*. 2006;16(6):811-8.
10. Akshoomoff NA, Courchesne E, Townsend J. Attention coordination and anticipatory control. *Int Rev Neurobiol*. 1997;41:575-98.
11. Moretti R, Bava A, Torre P, et al. Reading errors in patients with cerebellar vermis lesions. *J Neurol*. 2002;249:461-8.

12. Scott RB, Stoodley CJ, Anslow P, Paul C, Stein JF, et al. Lateralized cognitive deficits in children following cerebellar lesions. *Dev Med Child Neurol.* 2001;43:685–91.
13. Wassmer E, Davies P, Whitehouse WP, Green SH. Clinical spectrum associated with cerebellar hypoplasia. *Pediatr Neurol.* 2003;28:347–51.
14. Holmes G. The symptoms of acute cerebellar lesions due to gunshot injuries. *Brain.* 1917;40:461–535.
15. Holmes G. The cerebellum of man. *Brain.* 1939;62:1–30.
16. Eccles JC, Ito M, Szentagothai J. The cerebellum as a neuronal machine. New York: Springer; 1967.
17. Ito M. The cerebellum and neural control. New York: Raven Press; 1984.
18. Stein JF, Glickstein M. The role of the cerebellum in the visual guidance of movement. *Physiol Rev.* 1992;72:967–1017.
19. Thach WT, Goodkin HP, Keating JG. The cerebellum and the adaptive coordination of movement. *Ann Rev Neurosci.* 1992;15:403–42.
20. Frith U. Autism and Asperger's syndrome. Cambridge: Cambridge University Press; 1991.
21. Kanner L. Autistic disturbances of affective contact. *Nervous Child.* 1943;2:217–50.
22. Bauman ML. Motor dysfunction in autism. In: Joseph AB, Young RR, editors. *Movement disorders in neurology and neuropsychiatry.* Boston MA: Blackwell Scientific; 1992. pp 658–61.
23. Wing L. Asperger's syndrome: A clinical account. *Psychol Med.* 1981;11:115–29.
24. Fawcett AJ, Nicolson RI. Performance of dyslexic children on cerebellar and cognitive tests. *J Mot Behav.* 1999;31:68–78.
25. Nicolson RI, Fawcett AJ, Dean P. Developmental dyslexia: The cerebellar deficit hypothesis. *Trends Neurosci.* 2001;24:508–11.
26. Bombin I, Arangon C, Buchanan RW. Significance and meaning of neurological signs in schizophrenia: Two decades later. *Schizophr Bull.* 2005;31:962–77.
27. Kraepelin E. *Dementia praecox and paraphrenia.* Edinburgh, UK: E&S Livingstone; 1919.
28. Owens DG, Johnstone EC, Frith CD. Spontaneous involuntary disorders of movement: their prevalence, severity, and distribution in chronic schizophrenics with and without treatment with neuroleptics. *Arch Gen Psychiatry.* 1982;39:452–61.
29. Dichgans J, Diener HC. Clinical evidence for functional compartmentalization of the cerebellum. In: Bloedel JR, Dichgans J, Precht W, editors. *Cerebellar functions.* Berlin/Heidelberg: Springer-Verlag; 1984. pp 126–47.
30. Bonnefoi-Kyriacou B, Legallet E, Lee RG, Trouche E. Spatio-temporal and kinematic analysis of pointing movements performed by cerebellar patients with limb ataxia. *Exp Brain Res.* 1998;119:460–6.
31. Miall RC, Christensen LO. The effect of rTMS over the cerebellum in normal human volunteers on peg-board movement performance. *Neurosci Lett.* 2004;371:185–9.
32. Miall RC, Reckess GZ, Imamizu H. The cerebellum coordinates eye and hand tracking movements. *Nat Neurosci.* 2001;4:638–44.
33. van Donkelaar P, Lee RG. Interactions between the eye and hand motor systems: Disruptions due to cerebellar dysfunction. *J Neurophysiol.* 1994;72:1674–85.
34. Johnson DS, Montgomery EB. Chapter 44: Pathophysiology of cerebellar disorders. In: Watts R, Koller W, editors. *Movement disorders: Neurological principles and practice.* New York: McGraw-Hill; 1997. pp 587–610.
35. Ivry RB, Keele SW, Diener HC. Dissociation of the lateral and medial cerebellum in movement timing and movement execution. *Exp Brain Res.* 1988;73:167–80.
36. Ivry R, Keele SW. Timing functions of the cerebellum. *J Cogn Neurosci.* 1989;1:136–52.
37. Ivry RB, Spencer RM. The neural representation of time. *Curr Opin Neurobiol.* 2004;14:225–32.
38. Diener HC, Dichgans J, Guschlbauer B, Bacher M, Langenbach P. Disturbances of motor preparation in basal ganglia and cerebellar disorders. *Prog Brain Res.* 1989;80:481–8.
39. Muller F, Dichgans J. Dyscoordination of pinch and lift forces during grasp in patients with cerebellar lesions. *Exp Brain Res.* 1994;101:485–92.
40. Nowak DA, Hermsdorfer J, Marquardt C, Fuchs HH. Grip and load force coupling during discrete vertical arm movements with a grasped object in cerebellar atrophy. *Exp Brain Res.* 2002;145:28–39.
41. Serrien DJ, Wiesendanger M. Role of the cerebellum in tuning anticipatory and reactive grip force responses. *J Cogn Neurosci.* 1999;11:672–81.
42. Theoret H, Haque J, Pascual-Leone A. Increased variability of paced finger tapping accuracy following repetitive magnetic stimulation of the cerebellum in humans. *Neurosci Lett.* 2001;306:29–32.
43. Dow RS, Moruzzi, editors. *The physiology and pathology of the cerebellum.* Minneapolis: University of Minnesota Press; 1958.
44. Grodd W, Hulsmann E, Lotze M, Wildgruber D, Erb M. Sensorimotor mapping of the human cerebellum: fMRI evidence of somatotopic organization. *Hum Brain Mapp.* 2001;13(2):55–73.
45. Manni E, Petrosini L. A century of cerebellar somatotopy: A debated representation. *Nat Rev Neurosci.* 2004;5(3):241–9.
46. Bastian A, Thach W. Structure and function of the cerebellum. In: Manto M, Pandolfo M, editors. *The cerebellum and its disorders.* New York: Cambridge University Press; 2002. pp 49–68.
47. Schoch B, Dimitrova A, Gizewski ER, Timmann D. Functional localization in the human cerebellum based on voxelwise statistical analysis: A study of 90 patients. *Neuroimage.* 2006;30(1):36–51.
48. Dum RP, Strick PL. An unfolded map of the cerebellar dentate nucleus and its projections to the cerebral cortex. *J Neurophysiol.* 2003;89(1):634–9.
49. Bower JM. Control of sensory data acquisition. *Int Rev Neurobiol.* 1997;41:489–513.
50. Bower JM. Is the cerebellum sensory for motor's sake, or motor for sensory's sake: The view from the whiskers of a rat? *Prog Brain Res.* 1997;114:463–96.
51. Paulin MG. The role of the cerebellum in motor control and perception. *Brain Behav Evol.* 1993;41:39–50.
52. Paulin MG. Evolution of the cerebellum as a neuronal machine for Bayesian state estimation. *J Neural Eng.* 2005;2(3):S219–34.
53. Kawato M, Gomi H. A computational model of four regions of the cerebellum based on feedback-error-learning. *Biol Cybern.* 1992;68:95–103.
54. Kawato M, Kuroda T, Imamizu H, Nakano E, Miyauchi S, Yoshioka T. Internal forward models in the cerebellum: fMRI study on grip force and load force coupling. *Prog Brain Res.* 2003;142:171–88.
55. Miall RC, Weir DJ, Wolpert DM, Stein JF. Is the cerebellum a Smith Predictor? *J Motor Behav.* 1993;25:203–16.
56. Nixon PD. The role of the cerebellum in preparing responses to predictable sensory events. *Cerebellum.* 2003;2:114–22.
57. Henderson SE, Sugden D, editors. *The movement assessment battery for children.* London: The Psychological Corporation; 1992.
58. Bruininks RH, editor. *The Bruininks-Oseretsky test of motor proficiency.* Circle Pines, MN: American Guidance Service; 1978.

59. Buchanan RW, Heinrichs DW. The Neurological Evaluation Scale (NES): A structured instrument for the assessment of neurological signs in schizophrenia. *Psychiatry Res.* 1989;27:335–50.
60. Stott DH, Moyes FA, Henerson SE. Manual: Test of motor impairment (Henderson revision). Guelph, Canada: Brook International; 1984.
61. Frith U. Emanuel Miller lecture: Confusions and controversies about Asperger syndrome. *J Child Psychol Psychiatry.* 2004;45:672–86.
62. Ghaziuddin M, Butler E, Tsai L, et al. Is clumsiness a marker for Asperger syndrome? *J Intellect Disabil Res.* 1994;38(Pt 5):519–27.
63. Manjiviona J, Prior M. Comparison of Asperger syndrome and high-functioning autistic children on a test of motor impairment. *J Autism Dev Disord.* 1995;25:23–39.
64. Ghaziuddin M, Butler E. Clumsiness in autism and Asperger syndrome: A further report. *J Intellect Disabil Res.* 1998;42(Pt 1):43–8.
65. Rinehart NJ, Bradshaw JL, Moss SA, et al. A deficit in shifting attention present in high-functioning autism but not Asperger's disorder. *Autism.* 2001;5:67–80.
66. Nayate A, Bradshaw JL, Rinehart NJ. Autism and Asperger's disorder: Are they movement disorders involving the cerebellum and/or basal ganglia? *Brain Res Bull.* 2005;67:327–34.
67. Gillberg C. Asperger syndrome in 23 Swedish children. *Dev Med Child Neurol.* 1989;31:520–31.
68. Weimer AK, Schatz AM, Lincoln A, et al. "Motor" impairment in Asperger syndrome: Evidence for a deficit in proprioception. *J Dev Behav Pediatr.* 2001;22:92–101.
69. Green D, Baird G, Barnett AL, et al. The severity and nature of motor impairment in Asperger's syndrome: A comparison with specific developmental disorder of motor function. *J Child Psychol Psychiatry.* 2002;43:655–68.
70. Miyahara M, Tsujii M, Hori M, et al. Brief report: Motor incoordination in children with Asperger syndrome and learning disabilities. *J Autism Dev Disord.* 1997;27:595–603.
71. Gowen E, Miall RC. Behavioural aspects of cerebellar function in adults with Asperger syndrome. *Cerebellum.* 2005;4:279–89.
72. Schmitz C, Martineau J, Barthelemy C, et al. Motor control and children with autism: Deficit of anticipatory function? *Neurosci Lett.* 2003;348:17–20.
73. Miall RC, Imamizu H, Miyauchi S. Activation of the cerebellum in co-ordinated eye and hand tracking movements: An fMRI study. *Exp Brain Res.* 2000;135(1):22–33.
74. Hardan AY, Kilpatrick M, Keshavan MS, et al. Motor performance and anatomic magnetic resonance imaging (MRI) of the basal ganglia in autism. *J Child Neurol.* 2003;18:317–24.
75. Mari M, Castiello U, Marks D, et al. The reach-to-grasp movement in children with autism spectrum disorder. *Philos Trans R Soc Lond B Biol Sci.* 2003;358:393–403.
76. Ouchi Y, Okada H, Yoshikawa E, et al. Brain activation during maintenance of standing postures in humans. *Brain.* 1999;122(Pt 2):329–38.
77. Minshew NJ, Sung K, Jones BL, et al. Underdevelopment of the postural control system in autism. *Neurology.* 2004;63:2056–61.
78. Diener HC, Dichgans J. Chapter 9: Cerebellar and spinocerebellar gait disorders. In: Bronstein A, Brandt T, Woollacott M, editors. *Clinical disorders of balance, posture and gait.* London, Sydney, Auckland: Arnold; 1996. pp 138–55.
79. Martineau J, Schmitz C, Assaiante C, et al. Impairment of a cortical event-related desynchronisation during a bimanual load-lifting task in children with autistic disorder. *Neurosci Lett.* 2004;367:298–303.
80. Flanagan JR, Wing AM. The role of internal models in motion planning and control: Evidence from grip force adjustments during movements of hand-held loads. *J Neurosci.* 1997;17:1519–28.
81. Johansson RS, Westling G. Roles of glabrous skin receptors and sensorimotor memory in automatic control of precision grip when lifting rougher or more slippery objects. *Exp Brain Res.* 1984;56:550–64.
82. Sears LL, Finn PR, Steinmetz JE. Abnormal classical eye-blink conditioning in autism. *J Autism Dev Disord.* 1994;24:737–51.
83. Steinmetz JE. Brain substrates of classical eyeblink conditioning: A highly localized but also distributed system. *Behav Brain Res.* 2000;110:13–24.
84. Mangels JA, Ivry RB, Shimizu N. Dissociable contributions of the prefrontal and neocerebellar cortex to time perception. *Brain Res Cogn Brain Res.* 1998;7:15–39.
85. Nichelli P, Alway D, Grafman J. Perceptual timing in cerebellar degeneration. *Neuropsychologia.* 1996;34:863–71.
86. Woodruff-Pak D, Papka M, Ivry R. Cerebellar involvement in eyeblink classical conditioning in humans. *Neuropsychology.* 1996;10:443–58.
87. Bailey A, Luthert P, Dean A, et al. A clinicopathological study of autism. *Brain.* 1998;121(Pt 5):889–905.
88. Courchesne E. Brainstem, cerebellar and limbic neuroanatomical abnormalities in autism. *Curr Opin Neurobiol.* 1997;7(2):269–78.
89. Abell F, Krams M, Ashburner J, et al. The neuroanatomy of autism: A voxel-based whole brain analysis of structural scans. *Neuroreport.* 1999;10:1647–51.
90. Murakami JW, Courchesne E, Press GA, et al. Reduced cerebellar hemisphere size and its relationship to vermal hypoplasia in autism. *Arch Neurol.* 1989;46:689–94.
91. Ramnani N, Behrens TE, Johansen-Berg H, Richter MC, Pinski MA, Andersson JL, et al. The evolution of prefrontal inputs to the cortico-pontine system: diffusion imaging evidence from Macaque monkeys and humans. *Cereb Cortex.* 2006;16(6):811–8.
92. Pierce K, Courchesne E. Evidence for a cerebellar role in reduced exploration and stereotyped behavior in autism. *Biol Psychiatry.* 2001;49:655–64.
93. Allen G, Courchesne E. Differential effects of developmental cerebellar abnormality on cognitive and motor functions in the cerebellum: An fMRI study of autism. *Am J Psychiatry.* 2003;160:262–73.
94. Allen G, Muller RA, Courchesne E. Cerebellar function in autism: Functional magnetic resonance image activation during a simple motor task. *Biol Psychiatry.* 2004;56:269–78.
95. Muller RA, Kleinhans N, Kemmotsu N, et al. Abnormal variability and distribution of functional maps in autism: An FMRI study of visuomotor learning. *Am J Psychiatry.* 2003;160:1847–62.
96. Townsend J, Westerfield M, Leaver E, et al. Event-related brain response abnormalities in autism: Evidence for impaired cerebello-frontal spatial attention networks. *Brain Res Cogn Brain Res.* 2001;11:127–45.
97. Akshoomoff NA, Courchesne E. A new role for the cerebellum in cognitive operations. *Behav Neurosci.* 1992;106:731–8.
98. Ravizza SM, Ivry RB. Comparison of the basal ganglia and cerebellum in shifting attention. *J Cogn Neurosci.* 2001;13:285–97.
99. Schoch B, Gorissen B, Richter S, et al. Do children with focal cerebellar lesions show deficits in shifting attention? *J Neurophysiol.* 2004;92:1856–66.
100. Bischoff-Grethe A, Ivry RB, Grafton ST. Cerebellar involvement in response reassignment rather than attention. *J Neurosci.* 2002;22:546–53.

101. Nicolson RI, Fawcett AJ, Dean P. Time estimation deficits in developmental dyslexia: evidence of cerebellar involvement. *Proc Biol Sci.* 1995;259:43–7.
102. Fawcett AJ, Nicolson RI, Dean P. Impaired performance of children with dyslexia on a range of cerebellar tasks. *Ann Dyslexia.* 1996;46:259–83.
103. Stoodley CJ, Fawcett AJ, Nicolson RI, Stein JF. Impaired balancing ability in dyslexic children. *Exp Brain Res.* 2005;167:370–80.
104. Stoodley CJ, Stein JF. A processing speed deficit in dyslexic adults? Evidence from a peg-moving task. *Neurosci Lett.* 2006;399:264–7.
105. Stoodley CJ, Harrison EP, Stein JF. Implicit motor learning deficits in dyslexic adults. *Neuropsychologia.* 2006;44:795–8.
106. Eckert MA, Leonard CM, Richards TL, Aylward EH, Thomson J, Berninger VW. Anatomical correlates of dyslexia: Frontal and cerebellar findings. *Brain.* 2003;126(2):482–94.
107. Eckert MA. Neuroanatomical markers for dyslexia: A review of dyslexia structural imaging studies. *Neuroscientist.* 2004;10(4):362–71.
108. Eckert MA, Leonard CM, Wilke M, Eckert M, Richards T, Richards A, Berninger V. Anatomical signatures of dyslexia in children: Unique information from manual and voxel based morphometry brain measures. *Cortex.* 2005;41(3):304–15.
109. Rae C, Harasty JA, Dzendrowskyj TE, et al. Cerebellar morphology in developmental dyslexia. *Neuropsychologia.* 2002;40:1285–92.
110. Nicolson RI, Fawcett AJ, Berry EL, et al. Association of abnormal cerebellar activation with motor learning difficulties in dyslexic adults. *Lancet.* 1999;353:1662–7.
111. Ramus F, Pidgeon E, Frith U. The relationship between motor control and phonology in dyslexic children. *J Child Psychol Psychiatry.* 2003;44(5):712–22.
112. Akshoomoff NA, Courchesne E, Press GA, Iragui V. Contribution of the cerebellum to neuropsychological functioning: Evidence from a case of cerebellar degenerative disorder. *Neuropsychologia.* 1992;30:315–28.
113. Snider SR. Cerebellar pathology in schizophrenia – cause or consequence? *Neurosci Behav Rev.* 1982;6:47–53.
114. Andreasen NC, O’Leary DS, Cizadlo T, et al. Schizophrenia and cognitive dysmetria: A positron-emission tomography study of dysfunctional prefrontal-thalamic-cerebellar circuitry. *Proc Natl Acad Sci USA.* 1996;93:9985–90.
115. Andreasen NC, Nopoulos P, O’Leary DS, Miller DD, Wassink T, Flaum M. Defining the phenotype of schizophrenia: Cognitive dysmetria and its neural mechanisms. *Biol Psychiatry.* 1999;46:908–20.
116. Schmahmann JD. The role of the cerebellum in affect and psychosis. *J Neurolinguistics.* 2000;13:189–214.
117. Bachmann S, Bottmer C, Schroder J. Neurological soft signs in first-episode schizophrenia: A follow-up study. *Am J Psychiatry.* 2005;162:2337–43.
118. Heinrichs RW, Zakzanis KK. Neurocognitive deficit in schizophrenia: A quantitative review of the evidence. *Neuropsychology.* 1998;12:426–45.
119. Keshavan MS, Sanders RD, Sweeney JA, et al. Diagnostic specificity and neuroanatomical validity of neurological abnormalities in first-episode psychoses. *Am J Psychiatry.* 2003;160:1298–304.
120. Quitkin F, Rifkin A, Klein D. Neurological signs in schizophrenia and character disorders. *Arch Gen Psychiat.* 1976;33:845–53.
121. Schroder J, Niethammer R, Geider FJ, et al. Neurological soft signs in schizophrenia. *Schizophr Res.* 1991;6:25–30.
122. Venkatasubramanian G, Latha V, Gangadhar BN, et al. Neurological soft signs in never-treated schizophrenia. *Acta Psychiatr Scand.* 2003;108:144–6.
123. Dazzan P, Murray RM. Neurological soft signs in first-episode psychosis: A systematic review. *Br J Psychiatry Suppl.* 2002;43:s50–7.
124. Boks MP, Liddle PF, Burgerhof JG, et al. Neurological soft signs discriminating mood disorders from first episode schizophrenia. *Acta Psychiatr Scand.* 2004;110:29–35.
125. Lehoux C, Everett J, Laplante L, et al. Fine motor dexterity is correlated to social functioning in schizophrenia. *Schizophr Res.* 2003;62:269–73.
126. Sullivan EV, Fama R, Shear PK, et al. Motor sequencing deficits in schizophrenia: A comparison with Parkinson’s disease. *Neuropsychology.* 2001;15:342–50.
127. Nopoulos PC, Ceilley JW, Gailis EA, Andreasen NC. An MRI study of cerebellar vermis morphology in patients with schizophrenia: Evidence in support of the cognitive dysmetria concept. *Biol Psychiatry.* 1999;46:703–11.
128. Wassink TH, Andreasen NC, Nopoulos P, Flaum M. Cerebellar morphology as a predictor of symptom and psychosocial outcome in schizophrenia. *Biol Psychiatry.* 1999;45:41–8.
129. Frith CD, Blakemore S, Wolpert DM. Explaining the symptoms of schizophrenia: Abnormalities in the awareness of action. *Brain Res Brain Res Rev.* 2000;31:357–63.
130. Haggard P, Martin F, Taylor-Clarke M, Jeannerod M, Franck N. Awareness of action in schizophrenia. *Neuroreport.* 2003;14:1081–5.
131. Lindner A, Their P, Kircher TT, Haarmeier T, Leube DT. Disorders of agency in schizophrenia correlate with an inability to compensate for the sensory consequences of actions. *Curr Biol.* 2005;15:1119–24.
132. Shergill SS, Samson G, Bays PM, Frith CD, Wolpert DM. Evidence for sensory prediction deficits in schizophrenia. *Am J Psychiatry.* 2005;162:2384–6.
133. Blakemore SJ, Wolpert D, Frith C. Why can’t you tickle yourself? *Neuroreport.* 2000;11:R11–R6.
134. Franck N, Farrer C, Georgieff N, et al. Defective recognition of one’s own actions in patients with schizophrenia. *Am J Psychiatry.* 2001;158:454–9.
135. Delevoeye-Turrell Y, Giersch A, Danion H. Abnormal sequencing of motor actions in patients with schizophrenia: Evidence from grip force adjustments during object manipulation. *Am J Psychiatry.* 2003;160:134–41.
136. Franck N, Posada A, Pichon S, et al. Altered subjective time of events in schizophrenia. *J Nerv Ment Dis.* 2005;193:350–3.
137. Elvegag B, McCormack T, Gilbert A, Brown GD, Weinberger DR, Goldberg TE. Duration judgements in patients with schizophrenia. *Psychol Med.* 2003;33:1249–61.
138. Ho BC, Mola C, Andreasen NC. Cerebellar dysfunction in neuroleptic naive schizophrenia patients: Clinical, cognitive, and neuroanatomic correlates of cerebellar neurologic signs. *Biol Psychiatry.* 2004;55:1146–53.
139. Kinney DK, Yurgelun-Todd DA, Woods BT. Neurologic signs of cerebellar and cortical sensory dysfunction in schizophrenics and their relatives. *Schizophr Res.* 1999;35:99–104.
140. Marvel CL, Schwartz BL, Rosse RB. A quantitative measure of postural sway deficits in schizophrenia. *Schizophr Res.* 2004;68:363–72.
141. Deshmukh A, Rosenbloom MJ, Pfefferbaum A, Sullivan EV. Clinical signs of cerebellar dysfunction in schizophrenia, alcoholism, and their comorbidity. *Schizophr Res.* 2002;57:281–91.
142. Fadda F, Rossetti ZL. Chronic ethanol consumption: from neuroadaptation to neurodegeneration. *Prog Neurobiol.* 1998;56(4):385–431.
143. Kumari V, Gray JA, Honey GD, Soni W, Bullmore ET, Williams SC, Ng VW, Vythelingum GN, Simmons A, Suckling J, Corr PJ, Sharma T. Procedural learning in

- schizophrenia: A functional magnetic resonance imaging investigation. *Schizophr Res.* 2002;57(1):97–107.
144. Farrer C, Franck N, Frith CD, Decety J, Georgieff N, d'Amato T, Jeannerod M. Neural correlates of action attribution in schizophrenia. *Psychiatry Res.* 2004;131(1):31–44.
 145. Spence SA, Brooks DJ, Hirsch SR, Liddle PF, Meehan J, Grasby PM. A PET study of voluntary movement in schizophrenic patients experiencing passivity phenomena (delusions of alien control). *Brain.* 1997;120(11):1997–2011.
 146. Beyer JL, Krishnan KR. Volumetric brain imaging findings in mood disorders. *Bipolar Disord.* 2002;4:89–104.
 147. Strakowski SM, DelBello MP, Adler CM. The functional neuroanatomy of bipolar disorder: A review of neuroimaging findings. *Mol Psychiatry.* 2005;10:105–16.
 148. DelBello MP, Strakowski SM, Zimmerman ME, Hawkins JM, Sax KW. MRI analysis of the cerebellum in bipolar disorder: A pilot study. *Neuropsychopharmacology.* 1999;21(1):63–8.
 149. Cecil KM, DelBello MP, Sellars MC, Strakowski SM. Proton magnetic resonance spectroscopy of the frontal lobe and cerebellar vermis in children with a mood disorder and a familial risk for bipolar disorders. *J Child Adolesc Psychopharmacol.* 2003;13(4):545–55.
 150. Ketter TA, Kimbrell TA, George MS, Dunn RT, Speer AM, Benson BE, Willis MW, Danielson A, Frye MA, Herscovitch P, Post RM. Effects of mood and subtype on cerebral glucose metabolism in treatment-resistant bipolar disorder. *Biol Psychiatry.* 2001;49(2):97–109.
 151. Dickstein DP, Garvey M, Pradella AG, et al. Neurologic examination abnormalities in children with bipolar disorder or attention-deficit/hyperactivity disorder. *Biol Psychiatry.* 2005;58:517–24.
 152. Negash A, Kebede D, Alem A, et al. Neurological soft signs in bipolar I disorder patients. *J Affect Disord.* 2004;80:221–30.
 153. Maj M. The effect of lithium in bipolar disorder: A review of recent research evidence. *Bipolar Disord.* 2003;5:180–8.
 154. Silverstone PH, Silverstone T. A review of acute treatments for bipolar depression. *Int Clin Psychopharmacol.* 2004;19:113–24.
 155. Adityanjee, Munshi KR, Thampy A. The syndrome of irreversible lithium-effectuated neurotoxicity. *Clin Neuropharmacol.* 2005;28:38–49.
 156. Mills NP, DelBello MP, Adler CM, et al. MRI analysis of cerebellar vermal abnormalities in bipolar disorder. *Am J Psychiatry.* 2005;162:1530–2.
 157. Loeber RT, Gruber SA, Cohen BM, et al. Cerebellar blood volume in bipolar patients correlates with medication. *Biol Psychiatry.* 2002;51:370–6.
 158. Schneider M, Retz W, Coogan A, et al. Anatomical and functional brain imaging in adult attention-deficit/hyperactivity disorder (ADHD) – A neurological view. *Eur Arch Psychiatry Clin Neurosci.* 2006;256(Suppl. 1):i32–41.
 159. Carmon S, Vilarroya O, Bielsa A, Tremols V, et al. Global and regional gray matter reductions in ADHD: A voxel-based morphometric study. *Neurosci Lett.* 2005;389(2):88–93.
 160. Berquin PC, Giedd JN, Jacobsen LK, Hamburger SD, et al. Cerebellum in attention-deficit hyperactivity disorder: A morphometric MRI study. *Neurology.* 1998;50(4):1087–93.
 161. Dickstein SG, Bannon K, Xavier Castellanos F, Milham MP. The neural correlates of attention deficit hyperactivity disorder: An ALE meta-analysis. *J Child Psychol Psychiatry.* 2006;47(10):1051–62.
 162. Dickstein DP, Garvey M, Pradella AG, et al. Neurologic examination abnormalities in children with bipolar disorder or attention-deficit/hyperactivity disorder. *Biol Psychiatry.* 2005;58:517–24.
 163. Karatekin C, Markiewicz SW, Siegel MA. A preliminary study of motor problems in children with attention-deficit/hyperactivity disorder. *Percept Mot Skills.* 2003;97:1267–80.
 164. Piek JP, Skinner RA. Timing and force control during a sequential tapping task in children with and without motor coordination problems. *J Int Neuropsychol Soc.* 1999;5:320–9.
 165. Piek JP, Pitcher TM, Hay DA. Motor coordination and kinaesthesia in boys with attention deficit-hyperactivity disorder. *Dev Med Child Neurol.* 1999;41:159–65.
 166. Raberger T, Wimmer H. On the automaticity/cerebellar deficit hypothesis of dyslexia: Balancing and continuous rapid naming in dyslexic and ADHD children. *Neuropsychologia.* 2003;41:1493–7.
 167. Toplak M, Dockstader C, Tannock R. Temporal information processing in ADHD: Findings to date and new methods. *J Neurosci Methods.* 2006;151:15–29.
 168. Radonovich KJ, Mostofsky SH. Duration judgments in children with ADHD suggest deficient utilization of temporal information rather than general impairment in timing. *Child Neuropsychol.* 2004;10:162–72.
 169. Lewis PA, Miall RC. Distinct systems for automatic and cognitively controlled time measurement: Evidence from neuroimaging. *Curr Opin Neurobiol.* 2003;13:250–5.
 170. Piek JP, Dyck MJ. Sensory-motor deficits in children with developmental coordination disorder, attention deficit hyperactivity disorder and autistic disorder. *Hum Mov Sci.* 2004;23:475–88.
 171. van Meel CS, Oosterlaan J, Heslenfeld DJ, et al. Motivational effects on motor timing in attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry.* 2005;44:451–60.
 172. Shaw G, Brown G. Arousal, time estimation and time use in attentional-disordered children. *Develop Neuropsychol.* 1999;16:227–42.
 173. Pitcher TM, Piek JP, Hay DA. Fine and gross motor ability in males with ADHD. *Dev Med Child Neurol.* 2003;45:525–35.
 174. Gillberg C, Kadesjo B. Why bother about clumsiness? The implications of having developmental coordination disorder (DCD). *Neural Plast.* 2003;10:59–68.
 175. Castellanos FX, Sonuga-Barke EJ, Milham MP, et al. Characterizing cognition in ADHD: Beyond executive dysfunction. *Trends Cogn Sci.* 2006;10:117–23.
 176. Sullivan EV, Deshmukh A, Desmond JE, et al. Cerebellar volume decline in normal aging, alcoholism, and Korsakoff's syndrome: Relation to ataxia. *Neuropsychology.* 2000;14:341–52.
 177. Jancke L, Loose R, Lutz K, Specht K, Shah NJ. Cortical activations during paced finger-tapping applying visual and auditory pacing stimuli. *Brain Res Cogn Brain Res.* 2000;10:51–66.
 178. Rao SM, Harrington DL, Haaland KY, Bobholz JA, Cox RW, Binder JR. Distributed neural systems underlying the timing of movements. *J Neurosci.* 1997;17:5528–35.
 179. Jueptner M, Flerich L, Weiller C, et al. The human cerebellum and temporal information processing – results from a PET experiment. *Neuroreport.* 1996;7:2761–5.
 180. Penhune VB, Zattore RJ, Evans AC. Cerebellar contributions to motor timing: A PET study of auditory and visual rhythm reproduction. *J Cogn Neurosci.* 1998;10:752–65.
 181. Coffin JM, Baroody S, Schneider K, et al. Impaired cerebellar learning in children with prenatal alcohol exposure: A comparative study of eyeblink conditioning in children with ADHD and dyslexia. *Cortex.* 2005;41:389–98.

182. Nicolson RI, Daum I, Schugens MM, et al. Eyeblink conditioning indicates cerebellar abnormality in dyslexia. *Exp Brain Res.* 2002;143:42–50.
183. Blakemore SJ, Tavassoli T, Calo S, et al. Tactile sensitivity in Asperger syndrome. *Brain Cogn.* 2006;61:5–13.
184. O’Riordan MA, Plaisted KC, Driver J, et al. Superior visual search in autism. *J Exp Psychol Hum Percept Perform.* 2001;27:719–30.
185. Mottron L, Dawson M, Soulieres I, et al. Enhanced perceptual functioning in autism: An update, and eight principles of autistic perception. *J Autism Dev Disord.* 2006;36:27–43.
186. Bertone A, Mottron L, Jelenic P, et al. Motion perception in autism: A “complex” issue. *J Cogn Neurosci.* 2003;15: 218–25.
187. Pellicano E, Gibson L, Maybery M, et al. Abnormal global processing along the dorsal visual pathway in autism: A possible mechanism for weak visuospatial coherence? *Neuropsychologia.* 2005;43:1044–53.
188. Dakin S, Carlin P, Hemsley D. Weak suppression of visual context in chronic schizophrenia. *Curr Biol.* 2005;15: R822–4.
189. Dakin S, Frith U. Vagaries of visual perception in autism. *Neuron.* 2005;48:497–507.