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Eye movements, sensorimotor adaptation and cerebellar-dependent learning in autism: toward potential biomarkers and subphenotypes

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Abstract

Because of the wide range of symptoms expressed in individuals with autism spectrum disorder (ASD) and their idiosyncratic severity, it is unlikely that a single remedial approach will be universally effective. Resolution of this dilemma requires identifying subgroups within the autism spectrum, based on symptom set and severity, on an underlying neuro-structural difference, and on specific behavioral dysfunction. This will provide critical insight into the disorder and may lead to better diagnoses, and more targeted remediation in these subphenotypes of people with ASD. In this review, we discuss findings that appear to link the structure of the cerebellar vermis and plasticity of the saccadic eye-movement system in people with an autism spectrum disorder (ASD). Differences in cerebellar vermis structure in ASD could critically impact visuo-sensorimotor development in early infancy, which may in turn manifest as the visual orienting, communication and social interaction differences often seen in this population. It may be possible to distinguish a subpopulation of children with vermal hypoplasia, to establish whether this group manifests more severe deficits in visual orienting and in adaptation to persistent visual errors, and to establish whether this putative subphenotype of ASD is associated with a specific and distinct clinical symptom profile.

Eye movements

Eye movements and the neural mechanisms that control them have been a major component of neuroscience research for many decades. There are several benefits of studying eye movements if one is interested in uncovering the ways in which sensory information is processed to produce rapid, coordinated behaviors that are essential for everyday tasks. The rapid eye movements made when we look from one object to another, known as saccades, are an integral component mediating our interactions with both animate and inanimate objects; they are crucial for navigating, and also for orienting visual attention to spatial locations containing pertinent information. Saccades are defined by their characteristic rapidity, precision and accuracy. But precision and accuracy must be maintained in the face of changes in the mechanical properties of the eyes caused by growth and aging, fatigue of the musculature and degeneration of neurons that contribute to eye-movement control.

The core knowledge of the neural mechanisms that produce eye movements has been translated to the neurology clinic in several ways. The most prevalent is the assessment of function during a standard neurological examination in which patients track moving objects, look from one location to another and fixate stationary objects. Simple observation of these movements can demonstrate intact performance of three pairs of cranial nerves, the associated motor neuron pools, the pontine premotor regions and to some extent the vestibular apparatus. When these neural mechanisms fail, due to damage or disease or developmental disorder, the resultant changes in eye movements can suggest specific computational errors that may be responsible and highlight brain regions where these computations are thought to occur. Conversely, pathological differences in brain structural integrity may implicate specific eye-movement deficits that could in turn lead to informed hypotheses about potential underlying neuro-computational disorganization.

Plasticity of saccades

Movements planned and executed through the concerted actions of neuromuscular systems do not always produce the intended results. Simply put, sometimes executed eye movements will over- or undershoot the intended target locations. If such errors persist, the nervous

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system will attempt to adjust the motor output to reduce or eliminate discrepancies between desired and actual outcomes (this adjustment of motor output resulting from detection of sensory errors is known as sensorimotor adaptation). Dysfunction of the cerebellum can result in a failure to perceive errors or an inability to modulate motor commands and can have drastic behavioral consequences (disorientation, incoordination, ataxia, etc.; Horak *et al.*, 1989; Bastian *et al.*, 1996; Martin *et al.*, 1996; Takagi *et al.*, 1998; Baker *et al.*, 1999; Barash *et al.*, 1999; Deuschl *et al.*, 2000; Schmahmann, 2004).

Adaptation of the amplitude of saccadic eye movements has often been investigated by experimentally introducing a visual error at the end of saccades (McLaughlin, 1967; Miller *et al.*, 1981; Deubel *et al.*, 1986; Frens & Opstal, 1997; Phillips *et al.*, 1997; Straube *et al.*, 1997; Scudder *et al.*, 1998; Wallman & Fuchs, 1998; Noto *et al.*, 1999; Hopp & Fuchs, 2002, 2006; Robinson *et al.*, 2003; Alahyane & Pelisson, 2004, 2005; Takeichi *et al.*, 2005, 2007; Cecala & Freedman, 2008, 2009; Ethier *et al.*, 2008). This surreptitious introduction of visual error is accomplished using some variant of the task first introduced by McLaughlin (1967). Subjects start by fixating a visual target, generally in a central location and often referred to as the 'zero' target or T0. After this initial fixation, a second target (T1) is presented and subjects are instructed to look at this location as quickly and accurately as they can. After some baseline trials to determine how each subject performs this basic saccade task, adaptation trials begin. During these trials, when a subject initiates a saccadic eye movement to look to the T1 location, the target is turned off. A second target light (T2) is turned on, either at the same time that T1 is turned off or after a very brief delay. The T2 target can be either in between the T0 and T1 locations, or it can be beyond the T1 location. The first case simulates a large overshoot of the T1 location as the visual error after the initial saccade is back along the route that the eyes just followed. After a delay subjects typically make a second saccade (known as a corrective movement) to look at the T2 location. After repeated trials of this sort, the amplitude of saccades to the T1 target get progressively smaller (gain-down adaptation) thereby reducing the perceived visual error at the end of the primary movement. During adaptation trials in which the T2 target is positioned beyond the T1 position, the visual error at the end of the primary saccade is in the same direction as the just completed eye movement, as if the primary saccade fell short of the intended target. Over the course of repeated trials of this type, the amplitude of primary saccades to T1 will increase (gain-up adaptation), reducing the residual visual error (McLaughlin, 1967; Straube *et al.*, 1997; Noto *et al.*, 1999; Hopp & Fuchs, 2004; Panouilleres *et al.*, 2009; Schnier & Lappe, 2011). During saccadic adaptation, the motor output is altered despite unaltered sensory input; the location of the visual target that triggers the initial saccade (T1) is constant throughout adaptation, yet the amplitude of the movement to this target changes. This suggests that adaptation alters the transformation of sensory signals into motor commands.

A great deal of research makes it clear that the cerebellum is a key mediator of sensorimotor adaptation (Thach *et al.*, 1992; Barash *et al.*, 1999; Takeichi *et al.*, 2005; Fuchs & Soetedjo, 2006; Golla *et al.*, 2008; Donchin *et al.*, 2012; Block & Celnik, 2013; Panouilleres *et al.*, 2015). During saccadic adaptation, Purkinje cells in vermis lobules VI and VII and the deep cerebellar nucleus that they project to (caudal fastigial nucleus) are critical (Soetedjo *et al.*, 2008; Herzfeld *et al.*, 2015). For instance, there is a neurodegenerative disorder in humans known as spinocerebellar ataxia type 6 (SCA-6) that results in the death of cerebellar Purkinje cells (Koeppen, 2005; Xu-Wilson *et al.*, 2009). As P-cells are the output neurons of the cerebellar cortex, the function of the cerebellum is drastically altered in SCA-6. In these people, sensorimotor adaptation of saccade amplitude is significantly reduced compared to people without this disorder (Golla *et al.*, 2008; Xu-Wilson *et al.*, 2009). Other types of cerebellar lesion have also been shown to result in impaired saccade adaptation (Waespe & Baumgartner, 1992; Straube *et al.*, 2001; Golla *et al.*, 2008). In non-human primates, transient inactivation of the oculomotor cerebellum leads to dysmetric saccades (loss of accuracy) as well as increased variability in end point control (loss of precision; Robinson *et al.*, 1993; Takagi *et al.*, 1998, 2003; Quinet & Goffart, 2005; Guerrasio *et al.*, 2010; Kojima *et al.*, 2011). Direct stimulation of the posterior cerebellum using transcranial direct current techniques can increase cerebellar activity (Galea *et al.*, 2011; Schlerf *et al.*, 2012) which leads to more rapid sensorimotor adaptation (Jayaram *et al.*, 2012; Block & Celnik, 2013; Cantarero *et al.*, 2015) and can also enhance the rate of motor learning (Cantarero *et al.*, 2013a,b). Repetitive transcranial stimulation of the posterior cerebellum in humans has been shown to disrupt saccadic adaptation, and the disruption is correlated with the magnitude of the stimulation (Jenkinson & Miall, 2010).

There is a growing consensus that the cerebellum plays a critical role in motor learning of a variety of types including adaptation in of the vestibulo-ocular reflex (Belton & McCrea, 2000), eye-blink conditioning (Nagao *et al.*, 1984; Evinger & Manning, 1988), arm movements (Gilbert & Thach, 1977; Thach *et al.*, 1992; Martin *et al.*, 1996; Miall *et al.*, 1998; Norris *et al.*, 2004), pursuit eye movements (Ohtsuka & Enoki, 1998) and saccadic eye movements (see citations above and these reviews: Pelisson *et al.*, 2010; Shadmehr *et al.*, 2010). The seminal work of Marr (Marr, 1969) and Albus (Albus, 1971) suggested that motor learning is based on the output of Purkinje cells (P-cells) residing the cerebellar cortex, and in the case of saccades, in the oculomotor vermis (Kase *et al.*, 1980; Noda & Fujikado, 1987a,b). Purkinje cells have two different action potential waveforms. Simple spikes are produced by inputs from mossy fibers and activate P-cells via the parallel fiber network synapsing on the P-cell dendrites. In contrast, complex spikes are driven solely by climbing fiber inputs that originate in the inferior olive (IO). There continues to be discussion of the exact nature of the IO input, with some studies indicating that it provides a corrective error signal (Fuchs & Soetedjo, 2006; Soetedjo *et al.*, 2008; Herzfeld *et al.*, 2015) and others suggesting that it reinforces newly learned behaviors (Catz *et al.*, 2005). Theoretical frameworks that include cerebellar function generally involve some use of a comparison of expected results of movements (based on the self-generated motor commands) and actual results based on inflow of information from the senses ((Bell, 1982; Miall *et al.*, 1993; Wolpert *et al.*, 1995; Miall & Wolpert, 1996; Bell *et al.*, 1997; Blakemore *et al.*, 1998; Baddeley *et al.*, 2003; Miall *et al.*, 2007; Tian *et al.*, 2009; Shadmehr *et al.*, 2010), and see (von Holst & Mittelstaedt, 1971) for an early description of this concept). Detailed description of these models is beyond the scope of the current review, but what is clear from both the experimental and theoretical work is that in order to generate precise, accurate saccadic eye movements and to adjust their amplitude as a result of imposed visual errors, normal function of the Purkinje cells in the cerebellar vermis lobes VI–VII, and neurons the fastigial nucleus are paramount. Disordered activity leads to loss of accuracy, precision and dynamic modification.

Development of cerebellum in autism

Several studies have demonstrated a reduction in the size (hypoplasia) of the cerebellar vermis in subjects with an ASD (Gaffney

et al., 1987; Courchesne *et al.*, 1988; Bauman, 1991; Hashimoto *et al.*, 1993, 1995; Bauman & Kemper, 2005) and lobes VI and VII appear to be particularly altered compared to neurotypical subjects (Courchesne *et al.*, 1988, 1994b)). However, findings are not always consistent, and other studies have suggested no hypoplasia of the vermis in ASD (Holttum *et al.*, 1992; Kleiman *et al.*, 1992; Manes *et al.*, 1999; Scott *et al.*, 2009). A meta-analysis (Stanfield *et al.*, 2008) did find evidence supporting the notion that lobes VI and VII as well as lobes I-V of the vermis are reduced in ASD. There is also some evidence that the structure of the cerebellum at the cellular level may also be altered in people with autism. For instance, reduced density of P-cells and granular cells in both the cerebellar hemispheres and vermis has been observed in ASD (Bauman, 1991; Bailey *et al.*, 1998; Kemper & Bauman, 2002), but based on these postmortem analyses, this appears to be the case in only about 50% of autism cases. In a careful study of both the volume and area of the cerebellum in three subgroups of ASD individuals (low-functioning autism—LFA, high-functioning autism—HFA and Asperger's syndrome—ASP), Scott and colleagues (Scott *et al.*, 2009) did report vermal hypoplasia in ASD compared to TD control subjects (although no differences in area were observed). Interestingly, and perhaps surprisingly, the difference in vermis volume was found to be due to a marked hypoplasia in the HFA group. No significant hypoplasia was observed in either the LFA or ASP groups.

After birth, the size of the cerebellum and brainstem increases as infants develop in both ASD and control groups (Hashimoto *et al.*, 1995). This pattern of development suggests that the differences in vermal size in autism are not due to progressive degeneration and that after birth development is not different than TDs (Hashimoto *et al.*, 1995). Rather it suggests that neocerebellar hypoplasia in autism might be a result of granular and P-cell loss as early as the 3rd to 5th months prenatally (Courchesne *et al.*, 1988).

There is some evidence that there are two subphenotypes of people with autism—one group with hypo- and one hyperplasia of the cerebellar vermal region (Courchesne *et al.*, 1994a,b). This may account for earlier data that seemed to contravene the hypothesis that the cerebellum is affected in ASD subjects. However, a strong link between cerebellar volumes and ASD is still an open question. Multiple different cerebellar subphenotypes may also be responsible in part for the recent analysis of the ABIDE cohort that identified no relationship between cerebellar volume and ASD (Traut *et al.*, 2017).

Altered cerebellar activity in autism

As indicated above, the structure of the cerebellum, and particularly the midline posterior cerebellum (vermis lobes VI–VIII) that is known to be involved in eye-movement control, is altered in at least a subpopulation of people with autism. In addition, the neural activity of the cerebellum has been shown to be different in people with autism compared to neurotypical subjects. For example, Mostofsky and colleagues (Mostofsky *et al.*, 2009) report a reduced activation of the ipsilateral cerebellum in children with ASD during an appositional finger-tapping task. In addition, they report a diffuse reduction in connectivity across the cerebral-cerebellar motor network consistent with difficulty in shifting motor control from cortex to regions associated with learned performance. Using a different type of task (button press in a go-nogo paradigm) Allen and colleagues (Allen *et al.*, 2004) report an increase in ipsilateral anterior cerebellar activity in eight ASD subjects compared to age-matched TDs. They also report atypical activation in other cerebellar regions in this group of subjects. In their study, increased activation of the anterior cerebellum was correlated with the degree of structural abnormality (Allen *et al.*, 2004).

Saccades in autism

There is considerable variability in the data with respect to saccades in ASD. But some experiments, with relatively large sample sizes, do seem to show some consistent deficits. One of the most recent studies to address this issue reported reduced accuracy, increased trial-to-trial variability, prolonged acceleration phase and duration, and reduced peak velocity (Schmitt *et al.*, 2014), but no effects on latency were reported. Stanley-Cary *et al.* (2011) also reported increased variability in saccade end points and increased kinematic variability in ASD. In the Stanley-Cary study, saccades were slower overall and peak velocities varied so the main sequence relationship was not nearly as systematic in ASD subjects compared to TDs. Stanley-Cary and colleagues also compared their ASD subjects with Asperger's syndrome subjects and saw no change in saccade kinematics in Asperger's subjects compared to TDs, but clear differences in their ASD subject pool. They concluded that the deficits they saw in ASD subjects were consistent with deficits in cerebellar function. Johnson and colleagues (Johnson *et al.*, 2012) also demonstrated inaccurate saccades and hypometricity in saccade end points.

Adaptation in autism

Given the hypoplasia of the cerebellar vermis (Courchesne, 1991; Courchesne *et al.*, 1994a) and fastigial nuclei (Bauman, 1991) in ASD, it is reasonable to look for deficits in behaviors strongly associated with normal functioning of these regions. Rapid alteration of saccade amplitude in response to persistent (experimentally induced) visual errors is dependent on intact function of the vermis and fastigial nuclei and so this type of sensorimotor adaptation is a good candidate as a metric of cerebellar dysfunction in ASD or in other developmental disorders. Two relatively recent reports address this directly. Using the McLaughlin task (McLaughlin, 1967), Johnson and colleagues (Johnson *et al.*, 2013) show a difference in rate of adaptation in subjects with high-functioning autism, compared to those with Asperger's disorder and typically developing subjects. They also highlight a small change in velocity during adaptation in the TDs but not in the HFA or AD groups. In a second study (Mosconi *et al.*, 2013), 56 ASD subjects were compared to 53 age-matched controls in a similar saccade adaptation paradigm. These authors also suggest that the rates of adaptation in ASD subjects were slower than in TDs and importantly point out that ~30% of participants with ASD failed to adapt the amplitude of saccades (Mosconi *et al.*, 2013). We have some preliminary data on saccade adaptation in children with ASD and age-matched typically developing subjects. Below is an example of the differences we have seen (Fig. 1). On the left is an example of saccade amplitude adaptation in a TD subject. After making a series of saccades to the T1 target location (left of the vertical line), adaptation trials are started. Over the course of ~30 adaptation trials, saccade amplitude systematically declines, reducing the imposed visual error. On the right are the results of a similar session with an ASD subject. Here, the control movements are significantly hypometric and the end point variability is higher than in the TD subject. After adaptation trials begin, there is little or no change in saccade amplitude over the 70 adaption trials presented. End point variability during adaptation in this subject is also high. Although preliminary, these results are consistent with those mentioned above and also consistent with the general hypothesis that altered cerebellar activity in ASD might lead to a failure of normal sensorimotor adaptation.

While previous studies and our preliminary data suggest deficits in saccade adaptation in at least a subset of people with ASD, more

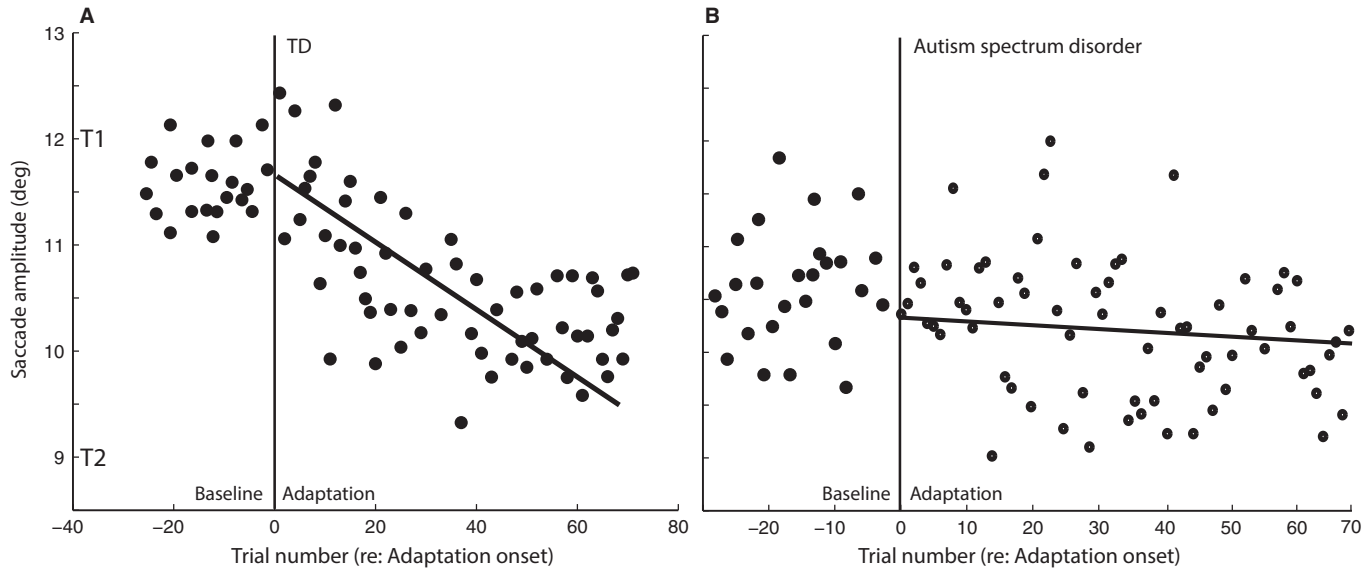

FIG. 1. Gain-down adaptation. A: Primary saccade amplitude is plotted as a function of trial number relative to the onset of adaptation (vertical line). Baseline trials to the T1 target location using the 'Step' task were carried out first. Data from a typically developed (TD) subject (A) and (B) from a subject with Autism (ASD) are illustrated. Lines of best fit for the adaptation trials are also shown.

study is clearly needed. For example, two of the commonly reported deficits in saccadic eye movements made by people with an ASD are that saccades tend to be hypometric (i.e., they fall short of the target) and that saccade end points are highly variable (Takarae *et al.*, 2004; Nowinski *et al.*, 2005; Mosconi *et al.*, 2010; Schmitt *et al.*, 2014). As mentioned above, this finding is consistent with non-human primate studies that disturb the normal function of the cerebellar vermis (Takagi *et al.*, 1998; Quinet & Goffart, 2005; Jenkinson & Miall, 2010). Both of these differences in saccades will reduce the likelihood of observing gain-down saccadic adaptation. It remains possible that people with ASD can in fact adapt saccade amplitudes in response to persistent visual errors but that this ability has been masked by the hypometry and variability of their saccades. Particularly in light of the study by Golla and colleagues (Golla *et al.*, 2008) that suggests cerebellar degeneration (and in particular lesions affecting the cerebellar vermis) can lead to a loss of the ability to increase saccade amplitude during adaptation, with less impact on gain decreases in amplitude. To our knowledge, there have been no systematic studies of adaptation to increase saccade size in a population with ASD. It will also be important to evaluate the ability to adapt saccades and correlate this behavioral assay with measures of cerebellar hypoplasia and link these with the symptom type and severity in ASD. Recent reports of saccade adaptation in infants as young as 10 months old (Alahyane *et al.*, 2016; Lemoine-Lardennois *et al.*, 2016) are intriguing as they might prove useful in predicting a future diagnosis of ASD. If this were the case, early remedial efforts could be targeted at this subgroup of young children and perhaps improve outcomes.

Potential implications of saccadic imprecision for the development of visual functioning

An intriguing developmental question arises when one considers that a subset of individuals with an ASD might suffer from persistently inaccurate saccades and poorer adaptation processes. The retinotopic maps of the visual cortex clearly develop over the course of infancy and early childhood, and it seems a reasonable proposition that the titration of these spatial maps would be affected by the fidelity and precision of the eye-movement system. Indeed, this would necessarily be an iterative process, with tuning of the cortical spatial maps being dependent on ever-more accurate eye movements, and the resultant increase in finer-grained maps leading to ever-more precise saccades, until presumably the system reaches optimal spatial tuning. The obvious question then is what would be the impact of greater intrinsic error or variability in the saccadic system. One prediction would be that cortical magnification factors, a hallmark of early visual cortical retinotopic maps, might be expected to be less well calibrated and that spatial receptive fields might be somewhat enlarged. In a recent study, our group used high-density visual evoked potentials (VEPs) to show that there was increased representation of more peripheral extrafoveal space in a cohort of ASD children (Frey *et al.*, 2013). We interpreted this as preliminary evidence for a reduction/shift in the cortical magnification factor and speculated that this was due to the effects of less accurate saccades during development. However, it must be pointed out that we did not measure saccade accuracy or adaptation in those children, so this could not be directly addressed. Functional neuroimaging work has also pointed to enlarged population receptive fields in extrastriate visual cortex, a finding that accords well with the saccadic imprecision thesis above (Schwarzkopf *et al.*, 2014), although it should be pointed out that increased receptive field sizes were not detected in area V1. A clear next step will be to assess whether children who show the greatest deficits in saccade accuracy and adaptation are those who show the greatest anomalies in the titration of the early retinotopic maps in cortex. Of course, in turn, it will be of considerable interest to understand whether these deficits relate to any of the key phenotypes observed in ASD.

If saccade adaptation deficits do turn out to be a consistent finding in a subgroup of children with an ASD, this raises the possibility that saccade adaptation measures may have utility as an early-detection endophenotype. In this regard, the fact that very recent work has shown that saccadic adaptation can be successfully measured in children as young as 10–41 months of age (Alahyane *et al.*, 2016; Lemoine-Lardennois *et al.*, 2016) is a most encouraging development indeed.

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Conflict of interest

None

Author contributions

Dr Freedman and Dr Foxe worked equally on all aspects of this article.

Data accessibility

This is a review article and the only data presented are preliminary results in Fig. 1. Upon request, and in accordance with University policies we are willing to share these data.

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