phosphorylation of Akt, through which PTEN exerts its main growth-promoting effects. There was also no effect on PTEN phosphatase activity or Forkhead transcription factor FoxO1 localization, although FoxO1 immunoreactivity was detected in nuclei, where it is presumed to be active. Further evidence is thus required for effects via PTEN-dependent downstream pathways.

Singh *et al*. (2014) extol the virtues of their non-viral method of delivering short interfering RNA by direct application to the nerve injury site (supplemented with injections into the sciatic notch and the plantaris muscle). Whether this method is as effective as delivery through recombinant viruses remains to be tested, especially given the chronic nature of diabetic neuropathy.

However, the big question remaining is whether PTEN activity plays a role in human diabetic neuropathy. The present study shows that thorough investigation into mechanisms of diabetic neuropathy can yield important new lines of research. Such studies should be encouraged, as should the study of diabetic neuropathy in general. To put matters into perspective, between 2010 and 2013, ~7500 papers per annum were listed in PubMed under the topic 'Alzheimer's disease' whereas only ~1100 papers per annum appeared with the subject 'Diabetic neuropathy', most being clinical reports. However, according to estimates from the World Health Organization, diabetes affects 347 million people worldwide, of whom 50% are predicted to develop some form of diabetic neuropathy, whereas 35.6 million people were estimated to be living with dementia in 2010. The case for conducting more research into diabetic neuropathy is overwhelming.

Funding

Our group has worked on responses of DRG neurons and Schwann cells to hyperglycaemia funded by an MRC Industrial PhD Studentship and by the Diabetes Research & Wellness Foundation. Current research is funded by the National Centre for the Replacement, Refinement & Reduction of Animals in Research (NC3Rs).

Aviva M. Tolkovsky
John Van Geest Centre for Brain Repair,
Cambridge CB2 0PY, UK

Correspondence to: Aviva M. Tolkovsky
E-mail: amt@mole.bio.cam.ac.uk

doi:10.1093/brain/awu048

References

Apfel SC. Nerve growth factor for the treatment of diabetic neuropathy: what went wrong, what went right, and what does the future hold? Int Rev Neurobiol 2002; 50: 393–413.

Calcutt NA, Jolivalt CG, Fernyhough P. Growth factors as therapeutics for diabetic neuropathy. Curr Drug Targets 2008; 9: 47–59.

Chadborn NH, Ahmed AI, Holt MR, Prinjha R, Dunn GA, Jones GE, et al. PTEN couples Sema3A signalling to growth cone collapse. J Cell Sci 2006; 119: 951–7.

Christie KJ, Webber CA, Martinez JA, Singh B, Zochodne DW. PTEN inhibition to facilitate intrinsic regenerative outgrowth of adult peripheral axons. J Neurosci 2010; 30: 9306–15.

Park KK, Liu K, Hu Y, Kanter JL, He Z. PTEN/mTOR and axon regeneration. Exp Neurol 2010; 223: 45–50.

Ropper AH, Gorson KC, Gooch CL, Weinberg DH, Pieczek A, Ware JH, et al. Vascular endothelial growth factor gene transfer for diabetic polyneuropathy: a randomized, double-blinded trial. Ann Neurol 2009; 65: 386–93.

Singh B, Singh V, Krishnan A, Koshy K, Martinez J, Cheng C, et al. Regeneration of diabetic axons is enhanced by selective knockdown of phosphatase and tensin homolog deleted on chromosome ten. Brain 2014; 137: 1051–67.

Tomlinson DR, Gardiner NJ. Diabetic neuropathies: components of etiology. J Peripher Nerv Syst 2008; 13: 112–21.

van Diepen MT, Eickholt BJ. Function of PTEN during the formation and maintenance of neuronal circuits in the brain. Dev Neurosci 2008; 30: 59–64.

Consulting the vestibular system is simply a must if you want to optimize gaze shifts

Even simple activities like reaching for our morning cup of coffee require precisely coordinated movements of multiple parts of the body. Successive attempts at these movements are characterized by 'repetition without repetition' (Bernstein, 1967). For this reason, it is thought that the brain does not enforce the details of a specific movement trajectory, but rather uses on-line feedback to optimize acquisition of the movement goal. However, a study in this issue of *Brain* demonstrates that when we make coordinated movements of the eyes and head to redirect our gaze, we use an optimal strategy that depends on vestibular sensory input: a strategy unavailable to patients with total vestibular loss. These results provide the first evidence that the vestibular system is critical for optimizing voluntary movements (Saglam *et al*., 2014).

When we make coordinated eye and head movements to redirect our axis of gaze relative to space (gaze = eye-in-head + head-

in-space), movement accuracy is preserved even when the head's trajectory is experimentally altered (Cullen, 2004). This happens because within milliseconds vestibular feedback rapidly alters the motor commands to the eye and head musculature to ensure gaze accuracy (Sylvestre and Cullen, 2006). For example, when a load is transiently applied to the head during a gaze shift, both the response duration and dynamics of neurons commanding the eye movement are updated—midflight—to preserve global movement accuracy. Thus, variability across movement trajectories is not problematic because the end goal of the movement is achieved as a result of on-line vestibular feedback. However, a remaining challenge has been to develop theoretical approaches to explicitly assess whether the gaze (as well as limb; Scott, 2004) control systems use such feedback signals to control movement dynamics in an optimal manner.

Saglam *et al*. (2014) tested the hypothesis that vestibular signals that are used on-line for gaze control, are also used to ensure that the motor control of eye-head gaze shifts is optimal across repetitions. The presence of this sensory input, rather than an intact cerebellum, is shown to be mandatory not only for the optimality of gaze movements from trial to trial, but also for ensuring that gaze shifts remain optimal after motor learning by setting movement kinetics to a new optimum.

Consider Canada's national winter sport ice hockey, for which each team member is required to wear an impressive collection of protective gear. Typically, a hockey helmet and face shield are put on just before starting to play, and these standard pieces of equipment change the centre of mass and moment of inertia of a player's head. Yet, players generally have no knowledge of the new biomechanical constraints placed on their gaze control systems as they play a game that requires phenomenal gaze accuracy while skating at incredible speeds. This is because their motor systems have rapidly adapted to the changes caused by the helmet from previous experience as a result of motor learning. In an earlier study, Saglam *et al*. (2011) demonstrated that in healthy subjects the coordination of eye and head movement is quickly set to a new optimum after such learning. In their current paper, Saglam *et al*. (2014) hypothesize that an intact vestibular input, rather than cerebellar function, is required to ensure movement optimality.

To test their hypothesis, Saglam and colleagues asked subjects (healthy subjects, patients with total vestibular loss, and patients with cerebellar lesions) to make gaze shifts to look at eccentric visual targets. Each target was only transiently presented so that no visual feedback was available at the end of the gaze movement. Thus subjects could not see whether their eye and head movements successfully aligned their gaze with the target, and so simply did their best to look at the location of each target. As previously shown, the eye and head movements of normal subjects are optimized to minimize gaze variability (Saglam *et al*., 2011). If vestibular feedback contributes to gaze optimality, then gaze shifts in patients with total vestibular loss should be characterized by non-optimal combinations of eye and head movements and indeed, data from these patients supported this hypothesis.

Once data were collected in this baseline control condition, Saglam and colleagues increased the inertia of the head by attaching an eccentric mass to the lightweight helmet that was worn by each subject. This led to characteristic head oscillations that were significantly more pronounced in patients with vestibular loss than in healthy subjects. Moreover, these patients also failed to update the kinematics of their eye and head movements to account for the new biomechanical requirements.

Motor learning, including the ability to adapt to the motor perturbations applied in this experiment, is commonly thought to rely on computations that are performed by the cerebellum. Theoretical studies suggest that the brain ensures the accuracy of movements by means of internal 'forward' models that predict the sensory consequences of motor commands such that the difference between this estimate and the actual consequences of the movements can be used to guide learning. This difference—termed sensory prediction error—is largely thought to be dependent on cerebellar-based mechanisms that ensure movement accuracy (Tseng *et al*., 2007). If the mechanism that updates gaze kinematics during motor learning is also based on a forward model within the cerebellum, then subjects with cerebellar lesions should be less adept at optimizing gaze movements when the head is weighted. Inconsistent with this prediction, in a parallel series of experiments, Saglam *et al*. (2014) found that patients with cerebellar ataxia not only made gaze shifts with optimal movement parameters in the initial unweighted condition, but were also able to optimize gaze kinematics to account for the new biomechanical requirements imposed by a change in the head's inertia. Importantly, however, these same patients were unable to make accurate gaze shifts; their gaze movements consistently undershot the target.

If cerebellar-based mechanisms mediate the optimization of gaze kinematics, as well as the minimization of endpoint errors, then cerebellar patients should have decreased gaze movement optimality as well as accuracy. However, the data from Saglam *et al*. (2014) instead indicate that gaze kinematics can be optimized by a computation performed outside the cerebellum. Moreover, this computation requires vestibular feedback to ensure optimal updating of movement kinematics during motor learning. Such updating of gaze motor commands can be accounted for by known neural mechanisms. Brainstem gaze circuits show nearly instantaneous updating as a result of vestibular feedback when head movement-related perturbations are applied during coordinated eye-head gaze shifts (Sylvestre and Cullen, 2006). A specific subclass of neurons in the vestibular nuclei—neurons that preferentially encode unexpected head motion—likely provide this essential feedback (Roy and Cullen, 2004). Saglam and colleagues' findings further imply that non-cerebellar based learning is performed by an 'inverse' model (which learns by

associating sensory goals with updated motor commands) rather than by a forward model (which learns by updating the sensory expectation of motor commands). There is also recent evidence that during reach adaptation, cerebellar patients similarly update their motor commands using inverse models (Izawa *et al*., 2012). Saglam *et al*. (2014) show that vestibular information is necessary to update the inverse model required for optimal gaze behaviour.

Before the present study, the control of gaze shifts had been considered in relation to the neural mechanisms that ensure gaze accuracy. Here, the authors have shown that cerebellar-based and cerebellar-independent mechanisms work together to guide motor learning. As noted above, the former is thought to rely on a forward model, which is used to compute sensory prediction errors. Indeed, a recent report showing that cerebellar output neurons encode the detailed time course of sensory prediction errors during voluntary gaze shifts (Brooks and Cullen, 2013) is consistent with the idea that gaze accuracy is maintained by updating a forward model in the cerebellum. This explains why patients with cerebellar ataxia make gaze shifts that remain hypometric after learning, even though movement kinematics are optimal. Conversely, vestibular sensory feedback, traditionally considered to ensure on-line corrections for head perturbations, is actually used to update the brain's inverse model during learning to guarantee the optimality of voluntary gaze shifts.

Funding

This research was supported by CIHR (K.E.C.) and FRQNT (Fonds de Recherche du Québec Nature et Technologies) (K.E.C. and J.X.B).

Kathleen E. Cullen and Jessica X. Brooks
Department of Physiology, McGill University, Montreal, PQ, Canada, H3G 1Y6

Correspondence to: Kathleen E. Cullen
E-mail: kathleen.cullen@mcgill.ca

doi:10.1093/brain/awu052

References

Bernstein NI. The coordination and regulation of movements. Pergamon: Oxford; 1967.

Brooks JX, Cullen KE. The primate cerebellum selectively encodes unexpected self-motion. Curr Biol 2013; 23: 947–55.

Cullen KE. Sensory signals during active versus passive movement. Curr Opin Neurobiol 2004; 14: 698–706.

Izawa J, Criscimagna-Hemminger SE, Shadmehr R. Cerebellar contributions to reach adaptation and learning sensory consequences of action. J Neurosci 2012; 32: 4230–9.

Roy JE, Cullen KE. Dissociating self-generated from passively applied head motion: neural mechanisms in the vestibular nuclei. J Neurosci 2004; 24: 2102–11.

Saglam M, Glasauer S, Lehnen N. Vestibular and cerebellar contribution to gaze optimality. Brain 2014; 137: 1080–94.

Saglam M, Lehnen N, Glasauer S. Optimal control of natural eye-head movements minimizes the impact of noise. J Neurosci 2011; 31: 16185–93.

Scott SH. Optimal feedback control and the neural basis of volitional motor control. Nat Rev Neurosci 2004; 5: 532–46.

Sylvestre PA, Cullen KE. Premotor correlates of integrated feedback control for eye-head gaze shifts. J Neurosci 2006; 26: 4922–9.

Tseng YW, Diedrichsen J, Krakauer JW, Shadmehr R, Bastian AJ. Sensory prediction errors drive cerebellum-dependent adaptation of reaching. J Neurophysiol 2007; 98: 54–62.