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A study of motor performance and motor learning in episodic ataxia

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EPISODIC ataxias are rare disorders in which periodic episodes of ataxia are separated by normal or near normal motor behaviour. They probably arise from dysfunctional membrane ion channels in the cerebellum. A patient with episodic ataxia EA-2 performed three motor tasks, before, during and after an ataxic episode. In all three tasks there were significant performance deficits during the ataxic episode. Two of the tasks also assessed motor adaptation (prism adaptation) or motor learning (ideogram drawing). In neither task was there significant disruption of motor adaptation or learning. These results suggest that the cerebellum may have separate roles in learning and in performance of visually guided movements, and that the dysfunction in this patient affected only his motor performance.

Key words: Cerebellum; Episodic ataxia; Human; Motor learning; Movement trajectories; Visuomotor control

Introduction

The cerebellum remains an enigma, with active debate about whether its role is restricted to motor control, or whether it has functions in sensory perception, language or cognition.[1] There is argument about its role in motor learning, about the site of synaptic plasticity underlying learning, and about the signals that might drive such learning.[2] In part, these uncertainties may arise because the many functions of the human cerebellum may be as unique as the functions of the expanded neocortex. Furthermore, lesion studies of the cerebellum show that the system is remarkably resilient, and functions impaired by small permanent lesions are rapidly and completely recovered. In contrast, in animals, temporary inactivation of the cerebellar cortex or nuclei by local cooling, anaesthetic infusions, or by pharmacological agents is effective and repeatable, and impairs motor performance,[3,4] motor learning[5] and conditioning[6]. These reversible cerebellar perturbations probably do not induce significant adaptive changes within the cerebellum or elsewhere, and they therefore allow a better understanding of the normal function of the cerebellum. Thus there would be great scope for studying the effects of brief, reversible, inactivation of the cerebellum in man.

Episodic ataxias are rare disorders in which periods of ataxia are separated by normal or near normal motor behaviour; they are thought to arise from dysfunctional membrane ion channels within the cerebellum.[7] Their episodic nature offers the possibility of studying cerebellar function in subjects who can act as their own controls. We recently had the opportunity to study a man with episodic ataxia during an attack. To test the consequences of cerebellar dysfunction on the subject's motor abilities, we measured his performance in three movement tasks before and during an ataxic episode. Two of these tasks also required either motor adaptation or motor learning, to allow us to test for a specific learning deficit.

Subject and Methods

Case report: The patient was a 50-year-old left-handed man with autosomal dominant episodic ataxia without myokymia, EA-2 (Ref. 8). He has suffered repeated attacks of ataxia, vertigo, nausea and vomiting since the age of 5. These episodes are triggered by stress, excitement, emotion, exercise, heat or minimal alcohol intake. The attacks usually last hours to days and are relieved by sleep and prophylactic use of a carbonic anhydrase inhibitor, acetozolamide. Other affected members of his family included his grandfather, mother, brother and son.

On neurological examination between attacks he had mild bilateral horizontal first degree nystagmus and mild impairment of tandem gait. An attack, which the subject reported to be typical of his previous attacks, was induced by attendance at a local football match in the presence of his neurologist. The subject sensed the onset of an attack during the match, and within 5 min he experienced the sudden onset of nausea, vertigo, dysarthria and incoordination, and was unable to walk unaided. Examination

revealed titubation, cerebellar dysarthria, increased magnitude of his horizontal nystagmus, severe truncal and gait ataxia with appendicular involvement most marked in the lower limbs.

Motor testing: The subject performed three motor tasks over three separate testing sessions, following Central Oxford Research Ethics Committee approval and with the subject's informed written consent. In Session 1, the subject was tested in his normal motor state on a 10 hole peg board, on prism adaptation, and on ideogram drawing (details below). Session 2 was held 4 h later, started 40 min after the onset of the ataxic episode, and lasted about 45 min. His ataxia was apparently stable throughout the test, and continued until the subject slept after its completion. Session 3 was held 1 month later, again when the subject was in his normal state.

For the 10-hole peg board test, the subject sat at a table, and was instructed to move 10 dowel pegs as rapidly as possible from one side of a peg-board to the other. This test measures visuo-motor coordination,[9] manual dexterity and handedness,[10] and is sensitive to cerebellar ataxia.[11] Left- and right-hand performance time was recorded twice each at the start of Sessions 1 and 2, using a stop watch.

Adaptation to prism goggles that deviate a subject's gaze laterally has been shown to involve the cerebellum by functional imaging[12] and by studies of patients[13,14] and of lesioned monkeys.[15] The subject sat at a table supporting a digitizing tablet and stylus (30 × 30 cm recording area, 0.25 mm resolution, 200 Hz sampling rate) with a black cross drawn at the centre of the board. He held the stylus in a power grip with his preferred left hand, but could see the stylus tip. He was instructed to make rapid, repeated, movements of the stylus from the tabletop adjacent to the nearest side of the digitising tablet to the target cross and back again. The stylus made no visible mark on the digitizing table; its position was recorded by computer as it hit the board, and the horizontal errors subsequently measured. Clear, planar safety glasses were worn, to which 14°-deviating perspex prisms could be attached by Velcro tape. Twenty practice movements were allowed without prisms, with instruction to maintain a high movement speed and not to attempt to correct for errors in final stylus position. The subject then made 20 targeted movements in rapid succession (~20 s). The prisms were then attached to the safety glasses in front of each eye. Another 40 movements were recorded; the prisms were then removed and a further 20 movements measured. Prism adaptation was assessed immediately after the peg-board test in Session 1 with the prisms deviating gaze to the left, and again in Session 2 with the prisms deviating gaze to the right.

Learning to draw novel ideograms has been shown to activate the dentate nucleus,[16] and practice at the task results in a significant increase in drawing speed.[16] Three plastic laminated sheets on which templates of ideograms were printed were in turn taped over the surface of the digitizing board. The subject held the stylus in his preferred hand using his normal writing posture, and was instructed to copy the ideograms repeatedly within guiding horizontal tramlines. As before, the stylus did not leave a visible trace on the digitizing surface but its position was recorded continuously by computer for subsequent analysis. Three pairs of ideogram patterns were used, in four sizes. One pair consisted of the capital letters R and G. Two novel ideogram pairs (called patterns A and B; Fig. 1) were selected which were similar in complexity and curvature, and which bore a resemblance to real characters. The subject was instructed to copy each pair as fast and as accurately as possible, moving immediately from one row to the next. Each sheet of four ideogram pairs was repeated three times. In Session 1, the subject was tested on patterns A, RG and B, in order. He was then given 10 min continuous practice in drawing pattern B, with encouragement to maintain speed and accuracy. After this learning session, he was tested again

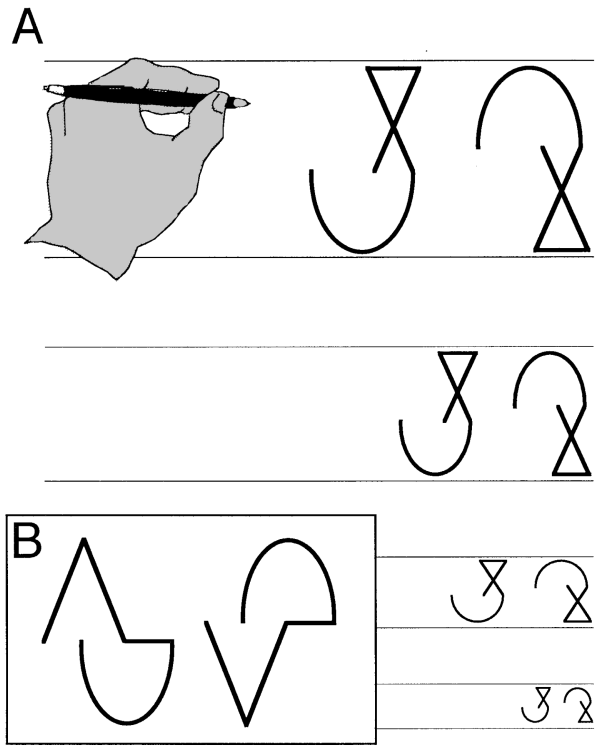

FIG. 1. Ideogram drawing. The main panel shows the four pairs of ideogram A and the guiding tramlines. The inset shows the ideogram B; the third set of ideograms was the capital letters RG. All three ideogram patterns were presented at four sizes: the distance between tramlines was 68, 46, 24 and 15 mm.

drawing, in order, pattern B and RG. A cross-over study was intended, in which the subject would be tested on both novel ideograms, and then practise one in the normal state, and the other in the ataxic state. This design had to be dropped when the subject was shown to have significantly different performance levels for the two ideograms. Thus a third testing session was held, and comparisons were only made between his performance before and after practice at drawing one ideogram (pattern A) in normal and ataxic states. In Session 2 (during the ataxic episode), he was tested on patterns B, RG and A; then trained for 10 min on pattern A; and then tested again on patterns A, RG and B. In Session 3, one month later and again in the normal state, the subject repeated the ideogram task with exactly the same order of trials as used in Session 2. Each ideogram pair was identified in the computer records, and the mean duration, mean length of the pen's motion ('pathlength') and mean velocity of the drawing of each pair calculated for the three repetitions recorded at each target size. The vertical size of each drawing pair (the vertical distance between the top and bottom positions of the stylus, Fig. 4A) was also measured, as an indication of accuracy compared to the target tramlines. The training data were not analysed.

Results

10 hole pegboard: The subject was able to complete the task without great difficulty, although on several occasions in the ataxic session, he required a second or third attempt to locate a peg in its hole. The time to complete the task did not differ between left and right hands in either session (Fig. 2); however, the times were significantly longer in the ataxic session (ANOVA, $F(1,4) = 132.5$, $p < 0.001$). This experiment showed a clear deficit in a visually guided task.

Prism adaptation: The subject accurately struck the target in both the normal and ataxic states prior to experiencing the prisms. On first wearing the prisms there were large horizontal errors in stylus position, which were corrected within about five trials (Fig. 3). To assess performance in the ataxic and normal states, we compared errors and variability within trials 1–20 in each state, before the prisms were in place, and within trials 41–60, after adaptation to the prisms. Mean absolute errors were about 60% larger during the ataxic episode than in the normal state (from 0.83 cm to 1.62 cm for trials 1–20, $p = 0.001$, Student's *t*-test; from 0.81 to 1.0 cm for trials 41–60, $p = 0.008$). The trial-to-trial variation of final pen position was also significantly greater in the ataxic state in comparison to corresponding trials in the normal state (F-tests: $F(19) = 3.072$, $p = 0.009$ for

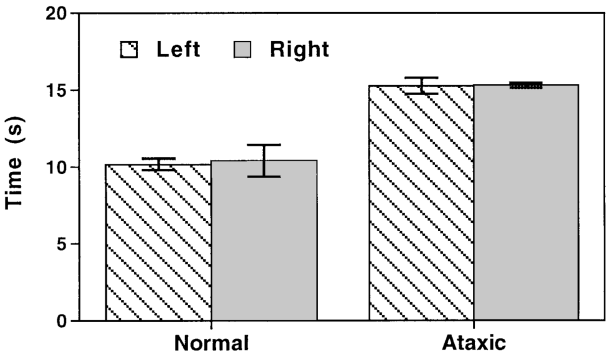

FIG. 2. Mean times to complete the 10-hole peg test. Left and right hands were tested twice each in the normal and ataxic state. The error bars indicate ± 1 s.d. of the mean ($n = 2$).

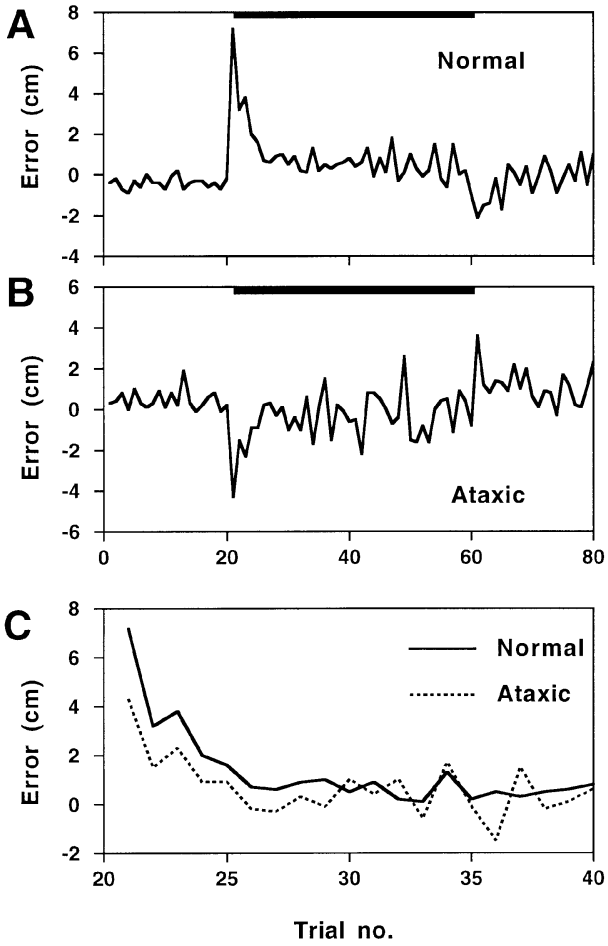

FIG. 3. Prism adaptation. The upper panels indicate the horizontal error in stylus position over 80 trials in the normal state (**A**) and the ataxic state (**B**). The prisms were in place for trials 21–60, indicated by the heavy black bars in (A) and (B). Prism orientation was reversed between the two sessions, hence the initial errors are in opposite directions. (**C**) Initial adaptation trials 21–40 on an expanded axis; the ataxic data has been inverted to allow easier comparison of the two sets.

trials 1–20; F(19) = 2.324, $p = 0.037$, trials 41–60). However, there was no evidence for a difference in adaptation rate or extent between the two states (Fig. 3C). Power curves gave a better fit to the adaptation data shown in Fig. 3C than decaying exponential curves, both in the normal state and in the ataxic state (normal: err = $6.8277t^{-1.0191}$, $r^2 = 0.628$; ataxic: err = $4.9692t^{-0.3445}$, $r^2 = 0.293$; err = horizontal error, t = trial number). On removing the prisms there was a small overshoot, seen most clearly in the normal state data, again rapidly corrected for. Thus, this experiment showed a deficit in performance, but gave no evidence for a deficit in sensorymotor adaptation.

Ideogram drawing: The subject was able to draw ideograms with the stylus held in a normal writing grip and with reasonable accuracy in both the normal state and in the ataxic episode. There were, as expected, strong relationships between the mean values of movement duration, velocity, pathlength and vertical range for the drawings produced across the four sizes of the ideogram pairs ($n = 3$; 4 sizes). These drawing size dependent scaling aspects of the task are not reported further.

In Session 1, there was a clear difference in speed in producing the well-practised pair (RG) compared to the two novel pairs (pattern A *vs* B; Fig. 4). After 10 min continuous practice at the pattern B, the subject was then tested again on patterns B and the RG letter pair. This produced a pronounced increase in speed of drawing the novel pattern (mean movement duration fell from 490 ms to 323 ms, $n = 12$); there was a smaller but still significant increase in the speed of the RG pair (267 to 201 ms). Unfortunately, we also found a significant difference in baseline speeds between the patterns A and B in this task (435 ms *vs* 490 ms, Fig. 4). Thus the planned statistical comparison between the effect of practising pattern B in the normal state with the effect of practising pattern A in the ataxic state was not possible. We therefore only report the changes in performance between the ataxic state (Session 2) and the normal state (Session 3, 1 month later) with practice of pattern A in both sessions.

Comparing Sessions 2 and 3, there was a highly significant reduction in performance in the ataxic state. Averaged across all three ideogram patterns and sizes, mean movement durations rose from 291 ms to 324 ms in the ataxic state; the mean path length was elevated from 48.5 cm to 54.8 cm; and the mean y-range was increased from 4.45 cm to 5.54 cm (ANOVA tests: $F(1,96) \geq 41.8$, $p < 0.0001$ in each case). The mean velocity was less affected, falling from 24.62 cm s^{-1} to 23.81 cm s^{-1} ($F(1,96) = 3.939$, $p = 0.050$).

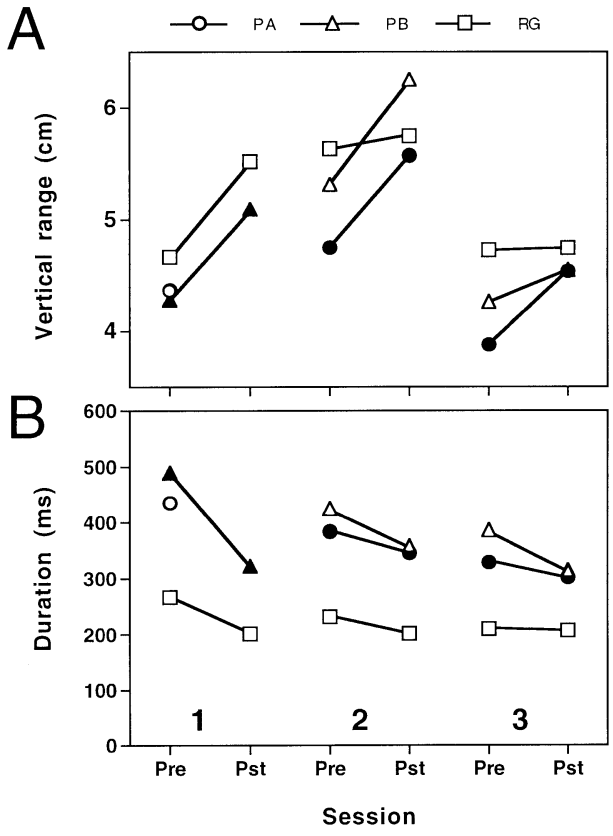

FIG. 4. Mean vertical range (**A**) and duration (**B**) of drawing each ideogram before (Pre) and after practice (Pst). The subject was in his normal state in Session 1, ataxic in Session 2 (4 h later), and normal again in Session 3 (1 month later). In Session 1, he practised ideogram pattern B (filled triangles); in Sessions 2 and 3 he practised pattern A (filled circles). Each data point is the mean value calculated across three repetitions of each ideogram at four target sizes ($n = 12$).

Practice significantly affected every measure of the subject's performance. Comparing pre- and post-practice measures in Sessions 2 and 3 showed that mean duration of drawing time (averaged across all three patterns and sizes) fell from 328 ms to 288 ms; mean pathlength rose from 49.6 to 53.7 cm; mean movement velocity rose from 22.0 to 26.4 cm s^{-1}; and the mean vertical size of the ideograms increased (ANOVA: $F(1,96) \geq 44.3$, $p < 0.0001$ for each comparison). If the ataxic episode impaired motor learning, we would expect a significant interaction between the effects of practice and ataxic state. There was no significant interaction effect on movement duration ($F(1,96) = 1.34$, $p = 0.25$), nor on the vertical size of the drawings ($F(1,96) = 2.6$, $p = 0.11$). For path length and mean velocity, there were significant interactions between practice and ataxia ($F(1,96) = 11.9$, $p = 0.0008$; and $F = 11.4$, $p = 0.001$, respectively). However, both path length and mean velocity increased even more following practice in the ataxic state than in the normal state. Therefore, although practice significantly altered performance, the two

statistically significant interactions found were not consistent with impaired learning during the ataxic episode.

To test for a specific effect of practising ideogram pattern A on drawing performance of that pattern, we looked for an interaction between the effects of practice and the ideogram pattern being tested. These interactions were highly significant, but mainly because there were small changes in performance of the over-learned pattern RG. *Post-hoc* comparison of the two novel ideogram patterns, ignoring the over-learned RG letter-pair, revealed the learning/pattern interaction terms were significant for duration and mean velocity ($F(1,64) \geq 5.285$, $p \leq 0.025$), but not for y-range or path length ($F(1,64) \leq 1.0$, $p \geq 0.32$). Thus the subject was selectively faster at drawing the pattern on which he had practised. If this selective learning was affected by ataxia, there should also be a further statistical interaction between practice, ataxic state, and the ideogram tested. Testing the effects of learning and ataxic state on patterns A and B revealed no significant interactions between these effects and the ataxic state ($F(1,64) \leq 1.9$, $p \geq 0.17$); the one exception was a just significant effect on path length ($p = 0.049$).

Thus the ideogram drawing tests demonstrated significant performance changes in the ataxic condition, but gave no evidence for a deficit in motor learning.

Discussion

The subject we have tested principally demonstrated midline cerebellar symptoms, which are likely to be restricted to the cerebellar cortical sheet. Thus his gait, balance and leg movements were more severely affected than his arm and hand. However, he was shown to have significant motor performance deficits in all three of the visually guided movement tasks with which we challenged him. We found no evidence for impaired motor learning or adaptation. Prism adaptation has been studied for many years and in many different conditions and it is clear that the cerebellum plays an important role in this process: a dentate nucleus lesion blocked adaptation in a monkey;[15] and patients with olivocerebellar damage have reduced or absent motor adaptation.[14] These patients had a common lesion site within the territory of the posterior inferior cerebellar artery, implicating the olivocerebellar tracts. Other cerebellar patients in the same study with cerebellar cortical lesions had intact learning but impaired performance, similar to that seen in this study. Surprisingly, a recent prism adaptation PET study[17] showed activation only in the posterior parietal cortex, and no specific activation within the cerebellum. However, in that study, the orientation of the prisms was alternated every four trials, and so the subjects were unable to successfully adapt to the task.

It is also clear from another PET study[16] that the dentate nucleus is highly activated in the ideogram drawing task that we have used, and blood flow levels in the dentate correlated best with increase in motor performance as the subjects practised the task. We have seen performance deficits in our patient during his ataxic episode, but no impairment of motor learning in this task, suggesting that dentate activity was still intact. Finally, we saw significant impairment in the 10-hole peg test during his ataxia, consistent with a visuo-motor deficit, although this task does not have a learning or motor adaptation component.

There remain exciting challenges to test more patients with inherited episodic ataxias. In particular, the two major disorders may show very marked differences in motor learning. Synaptic plasticity is intimately tied to post-synaptic Ca^{2+} influx, and there is compelling evidence for LTD at the parallel fibre to Purkinje cell synapse.[18] The underlying defect of EA-2 is unknown, but all families thus far examined show linkage to chromosome 19p13, and a voltage-gated calcium channel subunit is located in this region.[19] It is likely that the channel disorder in the patient reported here is restricted to the post-synaptic neurones, the Purkinje cells. The potassium channel defect in EA-1 is thought to be on granule cells, and therefore targets the presynaptic partner.

Conclusions

We have tested a patient with episodic ataxia in three movement tasks before, during, and after an attack. The subject was significantly impaired in all three visuo-motor tasks during the ataxic episode, but his motor learning and adaptation were unaffected. These results should not be considered to rule out a role for the cerebellum in motor learning, as it seems likely that the channel disorder causing his ataxia may affect only a region of the cerebellum. Instead, they demonstrate that episodic ataxic patients can prove useful subjects on which to test further questions of the cerebellar involvement in motor control. We hope also be able to gain greater insight into the vexed question of whether the cerebellum has a role in higher cognitive functions.

References

1. Leiner HC, Leiner AL and Dow RS. *Trends Neurosci* **16**, 444–447 (1993).
2. See Controversies in Neuroscience 4: Motor Learning and Synaptic Plasticity in the Cerebellum. *Behav Brain Sci* **19**, 339–502 (1996).
3. Flament D and Hore J. *J Neurophysiol* **55**, 1221–1233 (1986).
4. Miall RC, Weir DJ and Stein JF. *Exp Brain Res* **65**, 455–464 (1987).
5. Kerr GK, Miall RC and Stein JF. *Hum Movement Sci* **12**, 71–83 (1993).
6. Hardiman MJ, Ramnani N and Yeo CH. *Exp Brain Res* **110**, 235–247 (1996).

7. Griggs RC and Nutt JG. *Ann Neurol* **37**, 285–287 (1995).
8. Teh BT, Silburn P, Lindblad K *et al. Am J Hum Genet* **56**, 1443–1449 (1995).
9. Goodkin DE, Hertsgaard D and Seminary J. *Arch Phys Med Rehabil* 50–4 (1988).
10. Annett M. *Left, Right, Hand and Brain: The Right Shift Theory*. London: Lawrence Erlbaum Assoc., 1985.
11. Haggard PN, Miall RC, Wade DT *et al. J Neurol Neurosurg Psychol* **58**, 433–438 (1995).
12. Zeffiro T. *Hum Brain Mapping Suppl* **1**, 333 (1995).
13. Weiner MJ, Hallett M and Funkenstein HH. *Neurology* **33**, 766–772 (1983).
14. Martin TA, Keating JG, Goodkin HP *et al. Brain* **119**, 1183–1198 (1996).
15. Baizer JS and Glickstein M. *J Physiol (Lond)* **236**, 34P (1974).
16. Seitz RJ, Canavan AGM, Yaguez L *et al. NeuroReport* **5**, 2541–2544 (1994).
17. Clower DM, Hoffman JM, Votaw JR *et al. Nature* **383**, 618–621 (1996).
18. Ito M. *Annu Rev Neurosci* **12**, 85–102 (1989).
19. Diriong S, Lory P, Williams ME *et al. Genomics* **30**, 605–609 (1995).

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