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Non-commutativity in the brain

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In non-commutative algebra, order makes a difference to multiplication, so that $a \times b \neq b \times a$ (refs 1, 2). This feature is necessary for computing rotary motion, because order makes a difference to the combined effect of two rotations^{3–6}. It has therefore been proposed that there are non-commutative operators in the brain circuits that deal with rotations, including motor circuits that steer the eyes, head and limbs^{4,5,7–15}, and sensory circuits that handle spatial information^{12,15}. This idea is controversial^{12,13,16–21}: studies of eye and head control have revealed behaviours that are consistent with non-commutativity in the brain^{7–9,12–15}, but none that clearly rules out all commutative models^{17–20}. Here we demonstrate non-commutative computation in the vestibulo-ocular reflex. We show that subjects rotated in darkness can hold their gaze points stable in space, correctly computing different final eye-position commands when put through the same two rotations in different orders, in a way that is unattainable by any commutative system.

The vestibulo-ocular reflex (VOR) is perhaps the simplest of the many neural responses to rotary motion: sensors in the inner ear

measure head velocity and send commands to the eye muscles, moving the eyes in the opposite direction when the head turns, so as to keep the eyeballs from rotating relative to space⁶. By stabilizing our retinal images, the VOR allows us to see while moving.

An ideal VOR must be capable of non-commutative operations. This point has been argued before^{5,13}, but it is perhaps more clearly illustrated by the thought experiment in Fig. 1, which shows that the VOR, if it is to keep the gaze on target, must compute different final eye-position commands when a person undergoes the same two rotations in different orders. Starting by looking at a space-fixed target 30° to the left, a subject who turns first 10° counterclockwise (CCW) and then 60° left must end up looking 30° right and 5° up to stay on target (Fig. 1a). A subject who turns first 60° left and then 10° CCW must end up looking to the right and down (Fig. 1b).

Surprisingly, this ideal behaviour is not predicted by most models of the neural circuitry underlying the VOR. For example, Fig. 2 shows a computer simulation of an influential theory¹⁹. This model elegantly explains many features of the VOR, but as the simulation shows, it fails to keep the eye on target when put through the rotations from Fig. 1. Regardless of the order of rotations, it leaves the eye in the same final position relative to the head. Relative to

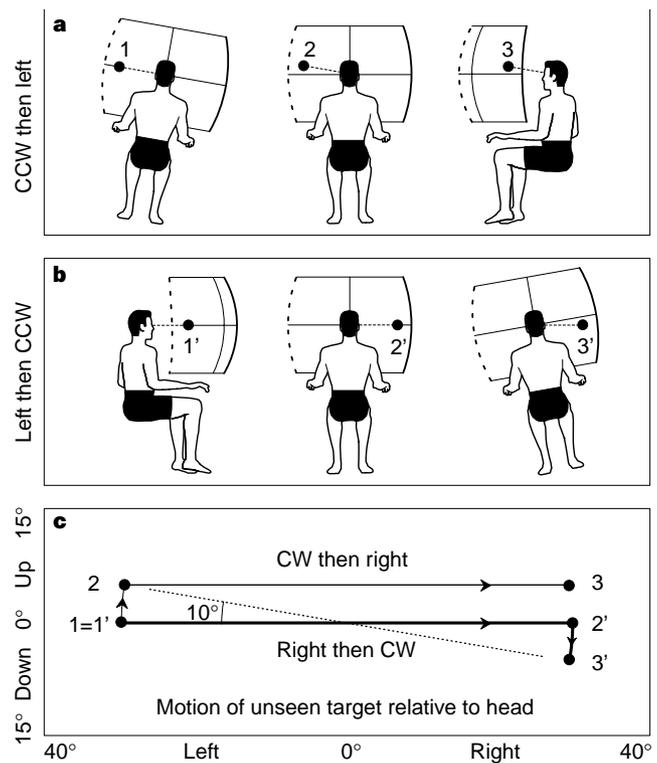


Figure 1 Why an ideal VOR must be non-commutative. **a**, Imagine yourself in a rotary capsule, tilted 10°, right ear down, as in position 1. Through a window you view a space-fixed target (black disc) 30° to the left relative to your head. The lights go out, but you are to maintain fixation on the unseen target as you rotate, first 10° counterclockwise (CCW) into position 2, then 60° left into position 3. **b**, The same rotations in the opposite sequence: starting upright, again looking 30° left relative to your head, you turn 60° left then 10° CCW. **c**, In both sequences, the space-fixed target starts at location 1 = 1' relative to your head. If you first rotate 10° CCW, the world turns 10° CW relative to you, so the target, 30° left, swings up $10^\circ \times \sin(30^\circ) = 5^\circ$, to location 2. Your subsequent rotation 60° left moves the target 60° right to location 3. But if you rotate first 60° left and then 10° CCW, the target moves via 2' to 3'. Owing to the non-commutativity of rotations, the final locations of the target, 3 and 3', differ by $2 \times 10^\circ \times \sin(30^\circ) = 10^\circ$. Hence your VOR, if it is to keep your eyes on the target, must be non-commutative: it must compute different final eye-position commands, depending on the sequence of body rotations. In all figures, heavy lines depict motion when the subject turns first left then CCW; light lines show the opposite order.

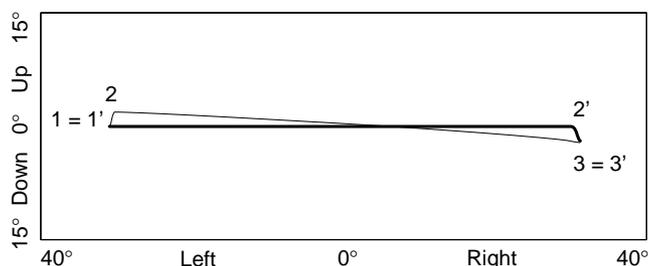


Figure 2 Computer simulation of a VOR model¹⁹ in which all neural processing is commutative. The plot shows the eye's predicted motion relative to the head when a simulated subject is put through the two sequences of rotations from Fig. 1. By the time the motions are over, the heavy and light lines coincide: the final eye position does not depend on the sequence of body rotations, and hence the eye does not stay on target.

space, then, the eye is incorrectly positioned, pointing above or below the target.

Figure 3a shows that, contrary to most theories, the actual VOR closely matches the ideal, non-commutative behaviour depicted in Fig. 1c, yielding different final eye positions depending on the sequence of rotations. In this subject, the difference (δ) between the average final eye positions, 3 and 3', was 9.0° vertical, as compared to the theoretical ideal of 10° shown in Fig. 1c. (This ideal of course depends on the rotations used: had they been larger, the ideal δ would have been larger.) Across all five of our subjects, δ averaged 10.3° (range 7.4–12.6°), and was significant (*t*-test, $P < 0.001$) for each individual. The time plots in Fig. 3b confirm that the distinct final eye positions were maintained: 3 s after the head rotations were over, δ was still 8.5° in this subject, and the average over all participants was 9.4° (range 6.5–13.9°). When the leftward and CCW head rotations in these experiments were replaced by rightward and clockwise (CW), the results were similar, with δ averaging 10.1° (range 7.6–14.3°), significant ($P < 0.001$) in each subject.

Why does the model in Fig. 2 fail to produce the necessary non-commutativity? Is it not a trivial matter to spin the eye at the same speed as the head and in the opposite direction, thereby holding it on target? Not quite. The eye-velocity command in the model is sound: it is computed in the brainstem, by taking head-velocity signals from the inner ear and multiplying them by approximately -1 , so it opposes the head motion as required. The problem is in the neural signals that code eye position. To hold the eye stable after the head rotation is finished, the model generates an eye-position command by integrating (in the calculus sense) the head-velocity signal multiplied by -1 . Unfortunately, an integrator stores no memory of the order of its inputs, so it is bound to behave commutatively: whether the head rotates first left and then CCW or first CCW and then left, it is all the same to an integrator, and so the final eye position in the model is also the same. Any model that uses solely commutative operators to transform vestibular input into eye-position commands will make the same error.

It has been proposed that non-commutative effects in ocular control need not imply non-commutative computations in the brain, because some of these effects can be explained by the geometry of the eye muscles, in particular the fact that the muscles run through pulleys in the orbital wall^{22,23}. Pulleys do have major implications for eye control^{12,19–23}, but neither they nor any other muscle geometry can explain the non-commutativity in Fig. 3. In fact, the model in Fig. 2 incorporates pulleys, but it remains commutative. Whatever the muscle geometry, there is always a correspondence between final, steady-state eye position and motor-neuron firing: to hold different eye positions, you need different firing rates^{6,24}. Even if the pulleys themselves are adjusted by a separate set of motor neurons, final eye position will still be determined by the total motor-neuron pool. The distinct final eye positions in Fig. 3 therefore imply that the final activities of the

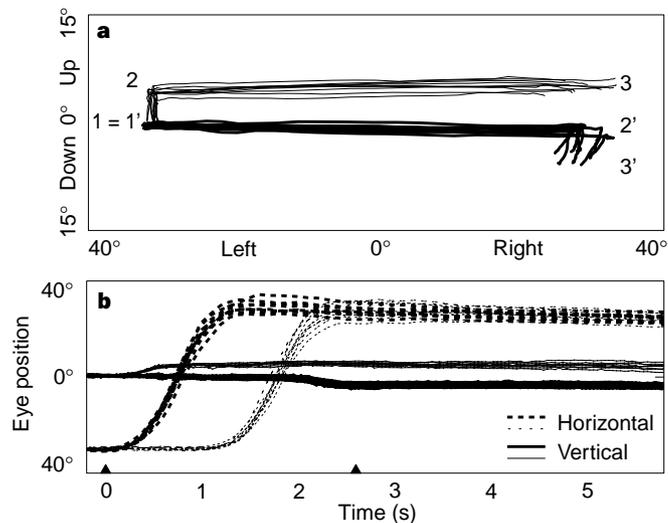


Figure 3 The actual VOR is non-commutative. A typical subject is put through the two sequences of rotations from Fig. 1. **a**, Plots of eye position in the head show near-ideal non-commutativity: final eye positions 3 and 3' differ by about 10° vertically. **b**, The same data plotted versus time. Triangles on the abscissa mark where the sequences of body rotations start and end. The heavy and light solid lines are separated by about 10° when the motions are over, showing that the final, vertical eye positions differed depending on the order of body rotations.

motor neurons differ, depending on the order of head rotations. There must be non-commutative processing between the inner ear and the motor endplate.

Various plausible mechanisms can be devised for the non-commutativity in the VOR, but all require non-commutative operators in the brain. One simple model, compatible with known physiology, differs from the model in Fig. 2 in just one essential way: it generates eye-position commands by integrating, not head velocity multiplied by -1 , but head velocity multiplied by eye-position information. This multiplicative interaction, described in the Methods, is non-commutative, and it suffices to give the eye-position command an appropriate memory of the order of head rotations. Simulations of this model are indistinguishable from the ideal trajectories plotted in Fig. 1c.

Further experiments are needed to test this model and to locate the non-commutative operators anatomically. One fundamental question is the role of gravity sensors and the associated otolith pathways. Our model implies that gravity sensors are not essential (though they may contribute) to the non-commutativity of the VOR, a claim that can be tested by performing the experiment from Fig. 1 in weightlessness. Another question is whether the non-commutative operators are wired into the brainstem circuits of the VOR or are located elsewhere. If the brainstem contains the necessary operators, then lesions elsewhere, for instance in the cerebellum, should not affect the non-commutativity of the VOR.

The VOR was chosen for this study because it is a relatively simple system where non-commutative computation is necessary for optimal function, as the thought experiment in Fig. 1 shows. However, by similar reasoning, one should also expect non-commutative operators in many other brain systems where they are needed, for example in systems dealing with rotary geometry, such as the circuits for head and limb control, auditory and visual localization, space constancy and mental rotation of objects^{11,14,15}. □

Methods

Subjects and stimuli. Our five subjects were healthy, aged 29 to 37, and gave informed consent; three were naive as to the purpose of the experiment, though this did not affect the results. Subjects were strapped into a rotary chair, with the head fixed to the chair by a helmet and bitebar. They were asked to maintain fixation on the centre of a target disc 5 cm across, 2 m away. Then, in the dark,

they were put through one of four sequences of rotations—left then CCW, CCW then left, right then CW, or CW then right—each repeated a total of 10 times in randomly ordered blocks of 5. All rotations were about the centre of the subject's head. Horizontal rotations were 60° and lasted 1.5 s, torsional rotations were 10° and lasted 0.75 s. With a 0.35-s pause between turns, each sequence of two rotations lasted 2.6 s, and was followed by 4 s stationary in darkness. Starting positions were chosen so that all horizontal rotations had earth-vertical axes, and so did not change the subject's orientation relative to gravity. This arrangement shows that gravity sensors cannot remove the need for non-commutative computations in the VOR: to keep the eyes on target, any gravity-based estimates of the subject's torsional rotation must be combined with other estimates of the horizontal rotation^{25,26}, and this combination must be non-commutative, if the eyes are to end up in distinct positions as in Fig. 3.

Eye movements. We recorded the position of the left eye 100 times per second using search coils²⁷. For analysis, we omitted all trials where saccades (sudden gaze shifts) occurred during the head rotations. All data figures and simulations express eye positions as gaze vectors, showing the horizontal and vertical components of a vector of length one that points forward along the gaze line.

Simulations. Figure 2 shows the predictions of Raphan's vector-pulley model of the VOR¹⁹, with $k_{\phi} = 0.25$. Vertical excursions in the figure are small owing to the model's low torsional gain and errors in its vertical eye-position commands. These errors show up even in the rotation between positions 1 and 2 because the eye starts at 30° left and the model does not correctly handle the non-commutative interaction with the preceding rotation(s) that brought the eye there. The non-commutative model described in the text is simplified from the one in ref. 5: both models match Figs 1c and 3, but the former used a four-component neural representation of eye position and no pulleys, whereas the present one uses three components and the linear-plant model¹² of the eye muscles, which is a simple way to model pulleys^{12–14,21}. The full equations for this non-commutative VOR model are: $e = -h - h \times x$, $dx/dt = e$, $m = kx + re$, $dq/dt = (m - kq)/r$. Here k and r are related to the stiffness and viscosity of the orbital tissues^{6,24}. All other variables are three-component vectors: q is eye position, m is motor-neuron activity, x is the eye-position command in the brainstem, h is the head-velocity signal from the inner ear, e is a command from vestibular nuclei to motor neurons, and \times is the vector cross product. The model is simple and biologically plausible, requiring only scalar integration, addition, subtraction and multiplication, all of which are believed to be in the repertoire of neurons²⁸. The formula for e implies that VOR circuits are cross-coupled, with vertical head-velocity signals influencing horizontal eye-position commands, and so on. Such cross-connections are also indicated by experiments in which the VOR was trained to produce eye movements about one axis in response to head motion about an orthogonal axis^{29,30}.

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Inhibition of caspase-1 slows disease progression in a mouse model of Huntington's disease

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Huntington's disease is an autosomal-dominant progressive neurodegenerative disorder resulting in specific neuronal loss and dysfunction in the striatum and cortex¹. The disease is universally fatal, with a mean survival following onset of 15–20 years and, at present, there is no effective treatment. The mutation in patients with Huntington's disease is an expanded CAG/polyglutamine repeat in huntingtin, a protein of unknown function with a relative molecular mass of 350,000 (M_r , 350K)². The length of the CAG/polyglutamine repeat is inversely correlated with the age of disease onset. The molecular pathways mediating the neuropathology of Huntington's disease are poorly understood. Transgenic mice expressing exon 1 of the human *huntingtin* gene with an expanded CAG/polyglutamine repeat develop a progressive syndrome with many of the characteristics of human Huntington's disease³. Here we demonstrate evidence of caspase-1 activation in the brains of mice and humans with the disease. In this transgenic mouse model of Huntington's disease, expression of a dominant-negative caspase-1 mutant extends survival and delays the appearance of neuronal inclusions, neurotransmitter receptor alterations and onset of symptoms, indicating that