Plasticity and tuning by visual feedback of the stability of a neural integrator

Guy Major*, Robert Baker†, Emre Aksay*, Brett Mensh§, H. Sebastian Seung‡, and David W. Tank*†

*Departments of Molecular Biology and Physics, Princeton University, Washington Road, Princeton, NJ 08544; †Department of Physiology and Neuroscience, New York University Medical Center, 550 1st Avenue, New York, NY 10016; ‡Howard Hughes Medical Institute and Brain and Cognitive Sciences Department, Massachusetts Institute of Technology, Cambridge, MA 02139; and §Department of Physical Medicine and Rehabilitation, Harvard Medical School, Boston, MA 02114

Contributed by David W. Tank, March 22, 2004

Persistent neural firing is of fundamental importance to working memory and other brain functions because it allows information to be held “online” following an input and to be integrated over time. Many models of persistent activity rely on some kind of positive feedback internal to the neural circuit concerned; however, too much feedback causes runaway firing (instability), and too little results in loss of persistence (leak). This parameter sensitivity leads to the hypothesis that the brain uses an error signal (external feedback) to turn the stability of persistent firing by adjusting the amount of internal feedback. We test this hypothesis by manipulating external visual feedback, a putative sensory error signal, in a model system for persistent firing, the goldfish oculomotor neural integrator. Over tens of minutes to hours, electronically controlled visual feedback consistent with a leaky or unstable integrator can drive the integrator progressively more unstable or leaky, respectively. Eye fixation time constants can be reduced >100-fold to <1 s. Normal visual feedback gradually retunes the integrator back to stability. Changes in the phase of the sinusoidal vestibulo-ocular response are consistent with integrator detuning, as are changes in ocular drift following eye position shifts compensating for brief passive head movements during fixations. Corresponding changes in persistent firing of integrator neurons are presented in the accompanying article. The presence, strength, and reversibility of the plasticity demonstrate that, in this system, external visual feedback plays a vital role in gradually tuning the stability of the neural integrator.

The ability to turn transient inputs into persistent changes in activity is a basic requirement for neural systems to be able to combine information from multiple inputs arriving at different times: temporal integration in the broad sense. In awake animals, many areas of the central nervous system have this capability, most notably prefrontal cortex, where items being held in working memory appear to be represented by persistent neural firing during the delay period of temporal association tasks, in the absence of on-going sensory inputs. Single neurons can show persistent firing at multiple different levels, depending on the stimulus and response (1, 2). In many cases, the persistent firing is graded or analog, the rate varying smoothly and continuously with some stimulus or response parameter (3), with stable firing being possible at any rate over a given range. Despite long persistence times of tens of seconds or more, inputs can cause rapid transitions in firing rates within hundreds of milliseconds (4). We still do not know the biophysical mechanisms underlying this nontrivial combination of long persistence times, rapid transitions, and stable firing at multiple or continuously graded rates.

The simplest in vivo system that has so far been found to demonstrate robust graded persistent neural firing with both rapid transitions and long persistence times is the horizontal oculomotor neural integrator in the goldfish (5, 6), composed of only 30–60 neurons (“area I”) on either side of the caudal brainstem. Area I is vital for maintaining stable eye position (fixation) between saccades, and for an effective vestibulo-ocular response (VOR) (5). In this system and other neural integrators (7), changes in persistent firing are proportional to the input, so the firing rate represents the time integral of past inputs, temporal integration in the strict mathematical sense.

In the dark, in the absence of rapid, online visual feedback, restrained normal goldfish move both eyes horizontally from left to right and then back again in a series of steps or saccades lasting about 100 ms (Fig. 1a) (5). Saccades are separated by fixations, which can last from <1 s to >10 s, during which the eyes are held almost stationary. This behavior depends on the activity of area I neurons (Fig. 1b and c) (5), which are excited by transient inputs during a saccade toward the ipsilateral side, resulting in a brief burst of action potentials and increased tonic firing in the next fixation (6, 8). The neurons also receive transient inhibitory inputs during saccades toward the contralateral side, causing a transient dip in their discharge, followed by tonic firing at a lower rate during the next fixation. To a first approximation, the tonic firing rate is proportional to eye position (6) and represents the time integral of velocity-encoding saccadic and vestibular inputs. Online proprioceptive feedback plays a minor role, if any, in generating persistent firing in this system (9–11).

There are many models of persistent firing and neural integration. The basic problem all of the models have to contend with is the seemingly contradictory requirements of achieving rapid changes in firing in response to transient inputs while maintaining firing at a constant level for extremely long times between inputs. The classical way of achieving this is through recurrent synaptic feedback, tuned extremely precisely to just maintain overall self-excitation (12, 13), although some models make use of other forms of positive feedback within a single cell (14) and/or dendritic bistability (15–18). All of these models can be regarded as involving some form of net positive feedback and therefore require careful choice of parameters, especially if they are to carry out accurate temporal integration. The parameter sensitivity of positive feedback led to the hypothesis that, in real animals, external visual feedback could be used to tune up the oculomotor neural integrator (19).

VOR phase or gain adaptation has been reported to cause leak or instability of the integrator (20, 21). Recently it has been observed that the ability of goldfish to hold their eyes at a constant position between saccades degrades roughly 2-fold when they are left in the dark for an hour (22). After this, fixation performance in the light is improved after an hour in the light. However, it is not clear whether these changes are caused by nonspecific effects, such as altered alertness or optokinetic response gain (23, 24), or whether they reflect tuning of the integrator by visual feedback. Reports of visual deprivation leading to integrator detuning in mammals are summarized in ref. 22.

External visual feedback could be used to tune the oculomotor neural integrator as follows. A perfectly stable integrator should...

Abbreviations: PV, position–velocity; VOR, vestibulo-ocular response.
*To whom correspondence should be addressed. E-mail: dwtank@princeton.edu.
© 2004 by The National Academy of Sciences of the USA
null position, as seen in many models when internal positive unstable, with eye position deviating exponentially away from
increase positive feedback within the integrator, which would impose a retinal slip vs. eye-position relationship consistent with instability by using an electronically controlled visual stimulus to tunes integrator stability, it should be possible to detune it to the integrator. We reasoned that if visual feedback normally would again tune it back toward stability.

Signal to decrease positive feedback within the integrator, which
Lower neural integrator. This is a clear demonstration of a progressive
Judging by independent tests of responses to vestibular inputs, control. Conversely, visual feedback from a stationary surround or 2 s, respectively, a two-orders-of-magnitude change from equal to 1 too weak, the visual surround will appear to move with a velocity proportional to eye position (Fig. 2a)

Conversely, rotating the surround with a velocity proportional to eye position, imposing unstable slip, should drive the integrator leaky (Fig. 2a Lower). This pattern of slip (“unstable slip”) could generate a signal to decrease positive feedback within the integrator, which would again tune it back toward stability.

Here we test the hypothesis that external visual feedback tunes the integrator. We reasoned that if visual feedback normally tunes integrator stability, it should be possible to detune it to instability by using an electronically controlled visual stimulus to impose a retinal slip vs. eye-position relationship consistent with the integrator being leaky. This effect could be achieved by rotating the visual surround horizontally with a velocity proportional to eye position (Fig. 2b, “training to instability”; see Supporting Methods, which is published on the PNAS web site). Conversely, rotating the surround with a velocity proportional to minus eye position, imposing unstable slip, should drive the integrator leaky (“training to leak”). Both manipulations simulate the normal pattern of visual feedback, but with an altered gain between retinal slip and eye position.

We report that the goldfish oculomotor neural integrator demonstrates remarkable plasticity when visual feedback is manipulated in this manner and is capable of being trained to instability or leak with an effective time constant reduced to ~1 or 2 s, respectively, a two-orders-of-magnitude change from control. Conversely, visual feedback from a stationary surround can gradually tune the neural integrator back toward stability. Judging by independent tests of responses to vestibular inputs, fixation instability and leak represent genuine detuning of the neural integrator. This is a clear demonstration of a progressive tuning mechanism for the dynamics of a model biological system for persistent neural activity. Corresponding changes in area 1 neural responses are described in a companion paper (25).

Methods
Preparation. All experiments (n = 100 fish) were Institutional Animal Care and Use Committee approved and performed in compliance with the National Research Council Guide for the Care and Use of Laboratory Animals. Goldfish [Carassius auratus, 3–5 inches (8–13 cm) tip to peduncle, from a commercial supplier] were acclimated to 20–23°C in a 50-gallon aquarium with daily light exposure. Awake fish were mounted head-fixed horizontally under water in the experimental tank (6, 22) at a temperature of 20–22°C. Eye movements were measured with scleral search coils (26) and were digitized along with planetarium velocity and head position (Digidata and CLAMPEX, Axon Instruments, Foster City, CA).

Visual Training. A planetarium above the head was rotated by a velocity-controlled servo motor and projected a random pattern of white dots moving horizontally on a plastic white screen, 15-cm radius, surrounding the animal (Fig. 2b). During training, the voltage output of one eye coil was filtered (50-Hz low pass), offset, amplified, and used as the planetarium velocity drive signal. This amplification or training gain (g) is presented in units of (degree/s of planetarium velocity per degree of eye position) or s⁻¹. The offset E₀ (eye position at which spots stationary) was adjusted to achieve roughly symmetrical leftward and rightward movements. Generally the eye providing the command was alternated every 10 or 20 min. Effective training was achieved by starting with a low g, then gradually increasing it (range, ±0.5 to ±5 s⁻¹). If too high a g was imposed when training to leak, the eyes would become trapped in a rapid sawtooth motion on one side, impairing training. A light shield surrounded the apparatus so that the planetarium provided the only source of light. Training was continued for up to 22 h, during which fixation performance was monitored every 20 min or longer by recording for 3–10 min in the dark.

Saccade Detection. When analyzing data, the beginning and end of a saccade were identified as the first and last time points at which the absolute value of acceleration exceeded a threshold (100–500 degrees/s²) after filtering with a 25-ms Gaussian.
Eye Position–Velocity (PV) Plots. Ocular drift during fixations was measured after excluding saccade-related transients in eye position (22). A period $t_d$ after every saccade was excluded, to avoid “postsaccadic slide” in eye position and firing rate (6), as was a period $t_s = 0.1$ s before the next saccade; $t_d$ ranged from 0.5 to 1.5 s (constant for a given animal, but varied between animals to allow for different slide durations). A straight line was fit by regression through the first $t_i = 1$ s segment of the remainder of the fixation (if at least $t_i$ long), to minimize effects of saturation and null-point shifts (see below) which were more pronounced at the ends of fixations. Eye position was the mean position of the fitted segment, and eye velocity was the slope of the regression line. Each fitted segment yielded a single (position, velocity) data point for the PV plot. Finally, standard least-squares linear regression was performed to obtain the slope $k$ of the best-fit line through all points in the PV plot.

Training Time Course Experiments. Twelve animals were trained to instability by using training gain $0.5$ s$^{-1}$ for 80 min, then $1$ s$^{-1}$ for 80 min. Every 20 min, fixations were assessed in the dark for 3 min, except immediately after training finished, when the assessment period was 10 min ($5 \times 2$-min measurement periods). After this, the fish were split into two groups. One group was left in the light (spots still) and tested in the dark for 3 min every 20 min. The other group was left in the dark. After a total of 380 min, fish kept in the dark were switched to the light recovery protocol. A similar experiment was performed on 10 fish trained to leak, following the same protocol but with negative training gains.

VOR. For vestibular stimulation, the tank, planetarium, field coils, and light shield were mounted on a rate table with a computer-controlled servo motor. Eye position was measured relative to head position. The fish’s head was at the center of rotation about a vertical axis, and the angular position of the head was measured with an axial potentiometer. Horizontal sinusoidal vestibular stimulation was carried out at $1/32$, $1/16$, or $1/8$ Hz with $8–32$ degrees/s peak head velocity. Peaks or troughs of eye position more than $4$ into the opposite half of the oculomotor range to the head were selected for phase-shift analysis (see Supporting Methods). Apparent phase shifts were determined from times of peaks and troughs of the eye position relative to the nearest trough or peak of the head position, respectively.

All data presented are from animals in the dark, unless otherwise stated.

Results

Artificially Imposed Visual Feedback Can Detune fixations to extreme instability or leak. (Left) Eye movements in dark, control animal. Red, fitted 1-s segments of data; each contributes one point to the PV plot. (Right) Quantification by PV plot least-squares fit line, slope $k$, effective time constant $\tau_{E}$, (5 min of data). (b) Same animal as in a, in dark, after training to instability for $6$ h, with gain $2.5$ s$^{-1}$. (Right) PV plot of 3 min of data. (c) Another animal, in dark, after training to leak for $16.5$ h, with gain $-2$ s$^{-1}$. (Right) PV plot of $14$ min of data. Drift depends primarily on eye position, as opposed to previous saccade direction (b and c). Green arrows highlight fixations following saccades toward but not crossing midposition; direction of drift is the same as in the previous fixation. When saccades cross midposition, the direction of drift reverses.

Fixations Can Be Detuned to Extreme Instability or Leak. Integrator performance was assessed from fixations in the dark, by means of PV plots (22), illustrated in Fig. 3 (see Methods), obtained by fitting straight lines to segments of fixations (Left, red). The slope $k$ of the regression line through all of the PV data points, and $\tau_{E}$, the effective time constant, defined as $1/|k|$, were used as measures of fixation performance. This procedure could be applied across the range of fixation behaviors explored, unlike exponential fitting, which could not be used on control data because the time constant was generally much longer than the fixations.

Control animals had roughly stable fixations in the dark, in the absence of visual feedback, yielding PV plots with nearly horizontal best-fit lines (Fig. 3a Right), with median $k = -0.004$ s$^{-1}$ (range $-0.068$ to $0.032$ s$^{-1}$, $n = 85$ fish), equivalent to median $\tau_{E} = 250$ s (range $15$ s leaky to $31$ s unstable). Following sufficient training to instability, generally 20 min or longer, PV plots developed positive slopes (Figs. 3b and 4a). Similarly, training control animals to leak for 20 min or more resulted in PV plots with negative slopes (Figs. 3c and 4b). In general, the longer an animal was trained (Fig. 4 a and b), and the more extreme the training gain $g$, the steeper the slope $k$ of the PV plot would become (when the animal was tested in the dark). Over the entire data set, the most positive $k$ value achieved was $0.92$ s$^{-1}$ ($\tau_{E} = 1.1$ s). Three animals were trained to $k > 0.8$ s$^{-1}$ or $\tau_{E} < 2.5$ s, and $30$ to $k > 0.2$ s$^{-1}$ or $\tau_{E} < 5$ s. The median $k$ for animals trained to instability for at least an hour with $g \geq 0.5$ was $0.23$ s$^{-1}$, equivalent to a $\tau_{E}$ of $4.3$ s ($n =$...
Feedback can retune fixation performance. The difference was less pronounced for animals trained to instability, reflecting the tendency for fixations to become progressively more leaky during long periods in the dark (Fig. 4 c and d) (22).

After instability training, the median half-life of the PV slope \( k \) was 43 min in the dark (\( n = 14 \) fish; see Supporting Methods), decreasing to 17 min with a stationary surround (\( n = 12, P < 0.001, \) Kolmogorov–Smirnov test). After leak training, the median half-life of \( k \) was 180 min in the dark (\( n = 5 \)), which was reduced to 30 min by a stationary surround (\( n = 14, P < 0.001 \)).

To confirm that visual feedback tunes up fixation stability under normal conditions, we examined dark fixations in animals that had been left in the dark for 80 min and were then placed back in a stationary visual surround, testing for 3 min in the dark every 20 min. In all cases, fixations became gradually leakier in the dark (Fig. 4 c and d), and the stationary surround progressively improved fixation performance, assessed in the dark. These experiments were repeated at two different temperatures, 21°C and 28°C. Detuning in the dark was more pronounced at the higher temperature, but the stationary surround retuned fixations to comparable stability at both temperatures.

**Fixation Detuning Is Due to Integrator Detuning.** During training, the planetariness velocity was proportional to eye position and, because of the optokinetic response, the eyes generally followed the stimulus. This means that during training to instability the eyes followed unstable trajectories, and during training to leak they followed leaky trajectories (see Fig. 7). Therefore, a key question is whether the detuning and retuning of fixations in the dark reflect changes in the oculomotor neural integrator itself or in some other process, such as training of an independent general-purpose trajectory mimicking or play-back circuit, which learns to anticipate the imposed pattern of drift of the visual surround or to imitate the pattern of eye movements during training. We tested these competing hypotheses by measuring responses to vestibular inputs that were never experienced during training and by attempting to train eye movements to mimic other kinds of surround motion.

In addition to saccadic burst inputs, the oculomotor neural integrator receives vestibular inputs encoding both head velocity and acceleration (29, 30). These are integrated with respect to time into position and velocity signals (5, 31) that are fed forward into the motoneurons to maintain a constant direction of gaze while the head moves. When control goldfish are sinusoidally rotated about a vertical axis in the dark at frequencies between 1/8 and 1/32 Hz, the VOR counterrotates the eyes almost perfectly with a gain close to unity (32). The turning points of the slow phases of the eye position (relative to the head) are in phase with the turning points of minus angular head position (dashed lines, Fig. 5a). A simple model of the integrator is governed by the first-order differential equation

\[
dE/dt = kE + \text{[inputs]},
\]

where \( E \) is eye position. The solution has two components: sinusoidal and exponential. The first is the response to continuous sinusoidal inputs; the second is the response to brief saccadic and other transient inputs (see Supporting Mathematical Appendix, which is published as supporting information on the PNAS web site) (33). If the integrator is unstable, the sinusoidal component of \( E \) will have a phase lag with respect to head position, whereas with a leaky integrator the sinusoidal component will lead head position. The phase shift \( \phi \) of the sinusoidal component, in degrees (derived in Supporting Mathematical Appendix) is

\[
\phi = (360/2\pi)\tan^{-1}(-k/2\pi)
\]
where $f$ is the frequency of rotation. This equation is most accurate at predicting the phase shift of the overall response when the exponential components are small, which occurs when the peaks of eye position are well into the opposite half of the oculomotor range to the head (see Supporting Mathematical Appendix). When such cases were analyzed, animals with pronounced fixation instability showed clear phase lags, as predicted (Fig. 5b, arrows). Animals with very leaky fixations showed clear phase leads, also as predicted (Fig. 5c, arrows). In Fig. 5d, phase shifts are plotted against $k$ for nine animals at various stages of training and retuning, at three test frequencies. The shifts are generally more pronounced at lower frequencies, as expected from Eq. 2. Phase lags grow with increasing instability, and phase leads grow with increasing leak, consistent with integrator detuning.

Brief vestibular stimuli were also used to verify that detuning of dark fixations reflected detuning of the neural integrator. The eyes were counterrotated across the null position by means of a transient head movement part-way through a fixation ($n = 4$ animals). In animals with unstable fixations, forcing the eyes across the midposition caused them to carry on diverging from this position, but from the opposite direction (Fig. 6a). Likewise, in animals with leaky fixations, forcing the eyes across the midposition caused them to carry on converging exponentially toward this position, but from the opposite direction (Fig. 6b). Across fish, a median of 92% of midfixation null crossings led to the expected direction change (range 89–100%; unstable $n = 111$, leaky $n = 184$ crossings). In all cases, PV plots of pre- and postmovement data were qualitatively consistent, having slopes of the same sign (data not shown). Because there were no head movements during training, a general-purpose trajectory mimicker would have no means of learning this midfixation direction switch in response to vestibular stimulation.

If the brain contained a general-purpose visual surround trajectory-mimicking circuit responsible for the all results above, it ought to be able to learn simple patterns of movement, such as saccade-triggered delayed ramps. Saccades were detected online during the experiment, and after a delay of 1 s the planetarium was rotated with a constant velocity of between 5 and 30 degrees/s until the next saccade (see Supporting Methods). During training, the eyes moved qualitatively in the same manner as the planetarium position (Fig. 6c). In the dark, however, even after many hours of training, there was no obvious “playback” or imitation of this pattern of movement (Fig. 6d, $n = 3$ fish). The general-purpose trajectory-mimicking capabilities of

![Fig. 5. VOR phase shifts are consistent with integrator detuning.](image-url)
goldfish are therefore limited and are unlikely to contribute much to fixation instability and leak.

Discussion

We have shown that, over tens of minutes to hours, the goldfish oculomotor system makes use of visual feedback to tune the stability of its neural integrator. The mechanism and locus of plasticity are yet to be established, although area I, area II (the velocity storage neural integrator), and cerebellum are prime candidates (5, 34). We have not established whether a direct error signal is used or whether the system adjusts itself indirectly by some kind of associative or Hebbian mechanism operating during the training-imposed trajectories, gated by light or the optokinetic response (OKR). The system appears to tune its own position relationship by using the retinal slip vs. eye position relationship that it itself generates; steeper slopes generally lead to faster training rates (Fig. 4, retuning data). The OKR gain and eye PV relationship may also be involved; animals whose eyes follow the rates (Fig. 4, retuning data). The OKR gain and eye PV relationship may also be involved; animals whose eyes follow the training stimulus better train better (data not shown). The system gradually changes itself so as to progressively reduce the slip vs. position slope (gain) toward zero. A simple alteration to normal visual feedback, such as artificially changing this slip/position gain, can drive the neural integrator to extremes of instability or leak, depending on the sign and magnitude of the imposed gain. This plasticity is bidirectional and is reversed by normal visual feedback from a stationary surround, or by changing the sign of the gain, i.e., training to the opposite direction or magnitude of drift after instability or leak training depended primarily on eye position, not the direction of the preceding saccade. When a saccade returned the eyes toward but not across the midposition, the direction of drift was unchanged (Fig. 3, green arrows), but when the eyes crossed the midposition, the direction of drift reversed. Second, drift occurred throughout fixations lasting many seconds, whereas postspasmodic slide is generally limited to a few hundred milliseconds (6). Third, postspasmodic slide plasticity would not lead to the observed phase shifts in sinusoidal VOR responses, or the reversal of drift direction after counterrotation of the eyes across the null position. Unlike the plasticity demonstrated here, postspasmodic slide plasticity does not appear to be caused by internal changes in the integrator itself.

In conclusion, we have demonstrated that the goldfish oculomotor neural integrator is strongly tuned by its visual environment. The integrator time constant can be reduced 100-fold to <1 s in either direction (instability or leak), consistently high with excellent sensitivity, strong sensitive to the direction and magnitude of the slip signal.

We thank Georgi Gamkrelidze, Owen Debowy, Jim Beck, Tom Adelman, Carlos Brody, John Hopfield, and Samuel Wang for comments and help. This work was supported by Lucent Technologies, Princeton University, the National Institutes of Health, the National Science Foundation, and the Wellcome Trust.