

RESEARCH ARTICLE

Multiple behavior-specific cancellation signals contribute to suppressing predictable sensory reafference in a cerebellum-like structure

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ABSTRACT

Movement induces sensory stimulation of an animal's own sensory receptors, termed reafference. With a few exceptions, notably vestibular and proprioception, this reafference is unwanted sensory noise and must be selectively filtered in order to detect relevant external sensory signals. In the cerebellum-like electrosensory nucleus of elasmobranch fish, an adaptive filter preserves novel signals by generating cancellation signals that suppress predictable reafference. A parallel fiber network supplies the principal Purkinje-like neurons (called ascending efferent neurons, AENs) with behavior-associated internal reference signals, including motor corollary discharge and sensory feedback, from which predictive cancellation signals are formed. How distinct behavior-specific cancellation signals interact within AENs when multiple behaviors co-occur and produce complex, changing patterns of reafference is unknown. Here, we show that when multiple streams of internal reference signals are available, cancellation signals form that are specific to parallel fiber inputs temporally correlated with, and therefore predictive of, sensory reafference. A single AEN has the capacity to form more than one cancellation signal, and AENs form multiple cancellation signals simultaneously and modify them independently during co-occurring behaviors. Cancellation signals update incrementally during continuous behaviors, as well as episodic bouts of behavior that last minutes to hours. Finally, individual AENs, independently of their neighbors, form unique AEN-specific cancellation signals that depend on the particular sensory reafferent input it receives. Together, these results demonstrate the capacity of the adaptive filter to utilize multiple cancellation signals to suppress dynamic patterns of reafference arising from complex co-occurring and intermittently performed behaviors.

KEY WORDS: Sensory feedback, Purkinje neuron, Ascending efferent neuron, Forward model, Elasmobranch, Sensory noise

INTRODUCTION

A parallel fiber network in the cerebellum-like sensory nuclei of fish generates predictions of sensory reafference as inputs to Purkinje-like neurons. Parallel fiber circuitry is a hallmark feature that is phylogenetically conserved among cerebellums of all vertebrates, and generates predictions, termed forward models, that are central to vertebrate cerebellar function (Bell, 2002; Montgomery et al.,

2012). The capabilities of this parallel fiber circuitry provide the power and versatility of both adaptive filter sensory predictions and cerebellar forward models. Here, in the cerebellum-like electrosensory nucleus of elasmobranch fish, we take advantage of the relative ease with which inputs can be controlled and functional outputs recorded during behaviors to better understand the full capabilities of parallel fiber circuitry.

In an aquatic environment, elasmobranch electroreceptors are exquisitely sensitive to weak electric fields originating from biologically relevant sources, including prey, predators and conspecifics (Kalmijn, 1971). These electroreceptors are also self-stimulated by behaviors, such as breathing and swimming, which create sensory reafference that their brains must selectively filter (Montgomery and Bodznick, 1994). Evidence demonstrates that Purkinje-like neurons in cerebellum-like electrosensory nuclei utilize corollary motor commands and sensory feedback from ongoing behaviors to develop cancellation signals, which are negative images of reafference, to suppress predictable self-generated noise (Bodznick et al., 1999; Montgomery and Bodznick, 1994).

Suppression of electrosensory reafference occurs in the cerebellum-like dorsal octavolateralis nucleus (DON) in hindbrains of little skates (*Leucoraja erinacea*) (Montgomery and Bodznick, 1994). Ascending efferent neurons (AENs), which are the principal Purkinje-like cells of the DON, receive peripheral electrosensory inputs on their basal dendrites, whereas internal reference signals from granule cells via their parallel fibers arrive on AEN apical dendrites. The receptive fields of AENs are organized into focal excitatory centers (generated by direct electrosensory afferent inputs) with diffuse inhibitory surrounds (from indirect inhibitory interneuron inputs). This organizational arrangement of the receptive field enables a 'common-mode suppression' mechanism to cancel a portion of self-generated sensory noise (Montgomery, 1993). To cancel remaining self-generated reafference, AENs additionally make use of an adaptive filter mechanism in the cerebellum-like hindbrain in order to faithfully transmit signals from unpredictable external stimuli. Evidence for the adaptive filter is provided by coupling experiments. AENs learn to filter out repetitive electrosensory stimuli that are coupled to sensory feedback from the fish's own movements, such as ventilation-associated and swimming-associated movements. Experiments in paralysed animals demonstrate that in the absence of sensory feedback, AENs can also use corollary motor commands as reference signals to cancel coupled electrosensory inputs (Bodznick et al., 1999). Furthermore, non-continuous, sporadic coupling sessions have demonstrated that cancellation signals develop incrementally despite intermittent pauses in behavior (Zhang and Bodznick, 2008).

The basis of the adaptive filter mechanism lies in associative synaptic plasticity at the parallel fiber–AEN synapses (Montgomery and Bodznick, 1994). In the adaptive filter model, thousands of

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parallel fibers of granule cells deliver information about the animal's ongoing behaviors to the apical dendrites of AENs. Information carried by parallel fibers include corollary discharges of motor commands, proprioceptive information related to ongoing movements, and descending electrosensory feedback (Hjelmstad et al., 1996). The underlying assumption of the adaptive filter model is that among the internal reference signals available, each AEN selects, through coincident activity and synaptic plasticity at parallel fiber–AEN synapses, the relevant parallel fiber inputs necessary to remove ongoing reafference. However, it is unknown how cancellation signals interact under situations where multiple behaviors are co-occurring. In this study, we demonstrate the capacity of the adaptive filter to utilize multiple cancellation signals to suppress dynamic patterns of reafference arising from continuously, intermittently and concurrently performed behaviors. Specifically, we demonstrate that when two unsynchronized reference signals are available, individual AENs form cancellation signals for the temporally coincident signal, and not the unpaired signal. Furthermore, we provide evidence that individual AENs can generate multiple behavior-specific cancellation signals simultaneously for co-occurring behaviors and modify distinct cancellation signals independently. These cancellation signals could be updated incrementally and are maintained during periods of inactivity. Finally, we demonstrate that each AEN generates its own unique cancellation signal to specifically negate its ongoing reafference independently of neighboring AENs. Consequently, these findings reveal the computational power of cerebellum-like structures in processing signals in a behaviorally relevant context, and further shed light on the generation and subtraction of sensory expectations in cerebellum forward models.

MATERIALS AND METHODS

Animals and surgery

Wild-caught adult little skates, *Leucoraja erinacea* (Mitchill 1825), of both sexes were obtained from the Long Island Sound and housed in local facilities at Wesleyan University (Middletown, CT, USA) or Marine Biological Laboratory (Woods Hole, MA, USA). Hindbrains of skates were surgically exposed under anesthesia (immersion in 0.04% benzocaine in artificial seawater). Animals were decerebrated and immobilized by intravenous tail injections of pancuronium bromide (2.0 mg ml^{-1}). After surgery, animals were transferred to an experimental tank with circulating seawater (10°C) and artificially respired by a flow of oxygenated artificial seawater ($0.4 \text{ liters min}^{-1}$) through the mouth. The skates were held with a plexiglass head restraint so that exposed hindbrains were positioned above seawater to facilitate electrode recordings. All procedures complied with animal care and use guidelines from Wesleyan University and Marine Biological Laboratory.

Experimental methods

The AENs in the electrosensory DON were recorded extracellularly using platinum-tipped indium microelectrodes ($2\text{--}5 \text{ }\mu\text{m}$ tip, $2\text{--}8 \text{ M}\Omega$). Units were identified by their characteristic low spontaneous activities ($2\text{--}5 \text{ Hz}$) and antidromic responses to contralateral electrosensory mesencephalic nucleus stimulation. All neural responses were filtered $0.1\text{--}5 \text{ kHz}$, amplified and acquired using Spike2 software (Cambridge Electronic Design, UK). Electrosensory stimuli were local dipole fields of $2\text{--}5 \text{ }\mu\text{V}$ steps, $200\text{--}450 \text{ ms}$ duration presented in the water to a subset of electroreceptors via insulated silver wires with exposed tips separated by 0.5 cm .

The apical dendrites of AENs receive multiple internal reference signals that carry information about ongoing behaviors (or fictive

behaviors in experimental animals that were pharmacologically paralysed) (Bodznick et al., 1999; Hjelmstad et al., 1996). Our experimental protocol used three of these reference signals: (1) ventilatory motor commands (VMC); (2) swimming motor commands (SMC); and (3) proprioceptive signals induced by passive fin movements (FM). These internal reference signals were monitored or induced as follows. (1) VMC, which were spontaneous and continuous, were recorded from the efferent hyomandibular seventh cranial nerve using a whole nerve suction electrode. (2) SMC were recorded from the ventral root of a spinal nerve using a second suction electrode. Fictive swimming was in many cases spontaneous, but in others elicited by direct electrical stimulation of the midbrain locomotory region (MLR), an area located anterior to the cerebellar overhang at a depth of $3000\text{--}4000 \text{ }\mu\text{m}$. Stimulation of the MLR with brief ($2\text{--}5 \text{ s}$) stimulus trains ($2\text{--}5 \text{ V}$, 50 Hz) elicited bouts of 'fictive swimming' that continued for varying periods of time after the stimulation period. (3) Proprioceptive signals from FM were induced by mechanical deflections of the ipsilateral pectoral fin. A motorized fin clamp and sinusoidal function generator were used to direct continuous fin motions (0.6 Hz , $0.5\text{--}1.0 \text{ cm}$).

A previously described three-phase coupling paradigm was replicated in this study (Bodznick et al., 1999). In the pre-coupling phase, the AEN baseline spiking activity was recorded. During the coupling phase, AENs were stimulated by a local dipole presented in their receptive fields. The onset of local dipole stimulations was synchronously timed with cycles of a specified internal reference signal. Finally, in the post-coupling phase, the local dipole was terminated and the AEN responses were measured in the absence of peripheral electrosensory stimulation. In some experiments, AEN responses were recorded during electrosensory coupling to sequential or overlapping internal reference signals.

Data analysis

To assess AEN responses, as in previous studies (Zhang and Bodznick, 2008), a subtracted spike count (SSC) was calculated: $\text{SSC} = S_I - (S_O \times T_I/T_O)$. For each cycle of an internal reference signal (e.g. VMC, SMC, FM), the number of spikes that occurred inside the stimulus interval (S_I) is subtracted from the number of spikes that occurred outside the stimulus interval (S_O), and scaled to account for the difference in interval durations (T_I/T_O). The stimulus interval (S_I) is the period during which the local dipole is presented during the coupling phase, or absent during the pre- and post-coupling phases. Positive SSC values indicate more firing during the stimulus interval than outside of the stimulus interval. Negative SSC values indicate more firing outside the stimulus intervals than within the stimulus interval.

AENs form 'cancellation signals' using their internal reference signals delivered by parallel fibers to suppress their responses to predictable electrosensory reafference. The formation of a cancellation signal can be observed during the coupling phase as an AEN's responses to electrosensory stimuli (paired with an internal reference signal) gradually decline over repeated cycles. During the post-coupling phase, the local dipole is removed and the cancellation signal is immediately observable as a 'negative image'. After coupling with an excitatory electrosensory stimulus, the negative image appears as significantly decreased AEN firing specifically during the stimulus interval where the local dipole is now absent and increased firing outside of the stimulus interval. The inverse is true when coupling with an inhibitory dipole stimulus, meaning the negative image appears as increased firing within the stimulus interval at stimulus offset. Over time, negative images fade

as cancellation signals are updated to reflect the absence of persistent electrosensory stimulation. Negative images were frequently more robust indicators of a cancellation signal than a decline in electrosensory response during the coupling phase. The magnitude of negative images was quantified by comparing the mean SSC of the 40 or 100 cycles during the pre-coupling phase to the mean SSC of the 40 or 100 cycles immediately at stimulus offset during the post-coupling phase. Unpaired non-parametric Mann–Whitney two-tailed tests were used to test whether the difference in mean SSC during the pre-coupling phase was significantly different from mean SSC during the post-coupling phase. All values are reported as means±s.e.m. and $P<0.05$ was considered statistically significant.

RESULTS

Cancellation signals form during continuous and intermittent non-ventilatory behaviors

Efference copies of ventilatory motor commands have been shown to serve as a reference input to suppress ventilation-associated reafference (Bodznick et al., 1999). Motor commands for other behaviors presumably serve as additional reference inputs to suppress reafference under those behavioral contexts. To test in skates whether efference copies of SMCs serve as reference inputs for suppressing swimming-associated reafference, electrosensory coupling experiments were performed with SMCs.

Fictive swimming was elicited by delivering short stimulus trains to the MLR (Fig. 1A). Electrosensory stimuli were coupled to spontaneous fictive swimming when available (Fig. 1B; top trace). For most experiments, short stimulus trains were applied to the MLR to elicit fictive swimming that lasted well beyond the duration of the applied stimulus (Fig. 1B; bottom trace). As swimming, unlike ventilation, is a non-continuous behavior, some coupling periods were continuous (Fig. 1C), while other coupling periods were intermittent with bouts of swimming separated by variable rest periods (Fig. 1D). After coupling electrosensory stimuli continuously to SMC, a significant negative image (i.e. reduced firing during the stimulus interval) was observed at stimulus offset, which is indicative of a cancellation signal (pre-coupling $SSC=0.095\pm 0.91$, post-coupling $SSC=-0.22\pm 0.69$; $P=0.003$; Fig. 1C). Cancellation signals, as observed by negative images, also developed during an episodic coupling experiment to SMC (pre-coupling $SSC=0.095\pm 1.05$, post-coupling $SSC=-0.37\pm 0.68$; $P=0.005$). Of the AENs tested, 67% ($N=8/12$) developed significant cancellation signals as measured by the difference in SSC between pre- and post-coupling phase. This is a percentage similar to what we have observed in our earlier studies with coupling to ventilation (Bodznick et al., 1999). Half of the AENs that developed significant cancellation signals with SMC were tested with continuous coupling phases ($N=4$), while half were tested with episodic coupling phases ($N=4$). These results indicate that AENs can use swimming motor commands as reference inputs to suppress swimming-associated reafference. Furthermore, the incremental formation and dynamic updating of cancellation signals occurs not only for repetitive behaviors, such as ventilation, but also for intermittent behaviors, including swimming.

AENs use multiple reference inputs to form cancellation signals associated with distinct behaviors

According to the adaptive filter model, each AEN has access to a multitude of reference signals via parallel fiber inputs, and AENs use temporal coincidence between apical reference inputs and sensory reafference arriving on basal dendrites to generate

reafference-suppressing cancellation signals. External signals escape this suppression because they are unpredictable and thus not consistently coincident with any of the reference signals. In order to test whether multiple cancellation signals associated with distinct behaviors can be formed in a single AEN, two reference signals were utilized in a coupling experiment: passive fin movements to mimic swimming behaviors (FM) and ventilatory motor commands associated with ventilation (VMC). These two reference signals occurred at temporally independent rates, while electrosensory stimuli were paired to only one reference signal at a time. In the first phase, electrosensory stimuli were paired to VMC, while the fin was moved passively to induce proprioceptive feedback (Fig. 2A). Raster plots triggered by VMC showed robust time-locked AEN responses to electrosensory stimuli, whereas FM-triggered raster plots showed dispersed spiking throughout FM cycles. Terminating the electrosensory stimuli showed a clear negative image in this AEN (i.e. reduced firing within the stimulus interval where electrosensory stimuli were previously presented and increased firing outside of the interval) in VMC-triggered histograms (pre-coupling $SSC=-0.13\pm 0.90$, post-coupling $SSC=-0.62\pm 0.76$; $P=0.01$). Each of the AENs that showed a distinct negative image after VMC coupling underwent subsequent coupling sessions where electrosensory stimuli were paired to FM, which were out-of-sync with VMC cycles. The recorded AEN exhibited robust electrosensory responses to paired FM signals and developed a significant negative image after FM coupling (pre-coupling $SSC=0.66\pm 1.82$, post-coupling $SSC=-0.48\pm 1.08$; $P=0.001$) (Fig. 2A). During FM coupling, VMC-triggered raster plots showed temporally non-specific spiking throughout VMC cycles. Of the AENs tested, 53% ($N=8/15$) developed a significant cancellation signal for VMC, and among these, 75% ($N=6/8$) subsequently developed a significant cancellation signal for FM.

It seemed possible that these behavior-associated cancellation signals formed due to the distinct nature of their reference inputs (i.e. sensory versus motor). Swimming-associated cancellation signals were formed from sensory feedback induced by passive fin movements, whereas ventilation-associated cancellation signals were formed from corollary motor commands originating from the brainstem. To further probe the capacity of AENs to form behavior-specific cancellation signals, sequential coupling experiments were performed using only efference motor copies of swimming and ventilatory motor commands as reference inputs (SMC or VMC, respectively). Electrosensory stimuli were first paired to VMC (while SMC occurred independently), then subsequently paired to SMC, while the VMC was uncoupled (Fig. 2B). The AEN developed negative images after each SMC and VMC coupling session ($P<0.001$, both). From the AENs tested, 67% ($N=4/6$) developed negative images for both reference inputs sequentially.

Thus, individual AENs can form multiple and distinct behavior-specific cancellation signals by utilizing coincident reference inputs to suppress reafference associated with that behavior. Furthermore, both efference copies of motor commands and sensory feedback may serve as internal reference signals.

AENs can form cancellation signals for concurrently occurring behaviors

Multiple, co-occurring behaviors can increase the complexity of behavioral reafference that an AEN receives from its peripheral electroreceptors. To test whether the adaptive filter can suppress electrosensory reafference associated with co-occurring fictive behaviors, AENs were tested with three sequential coupling

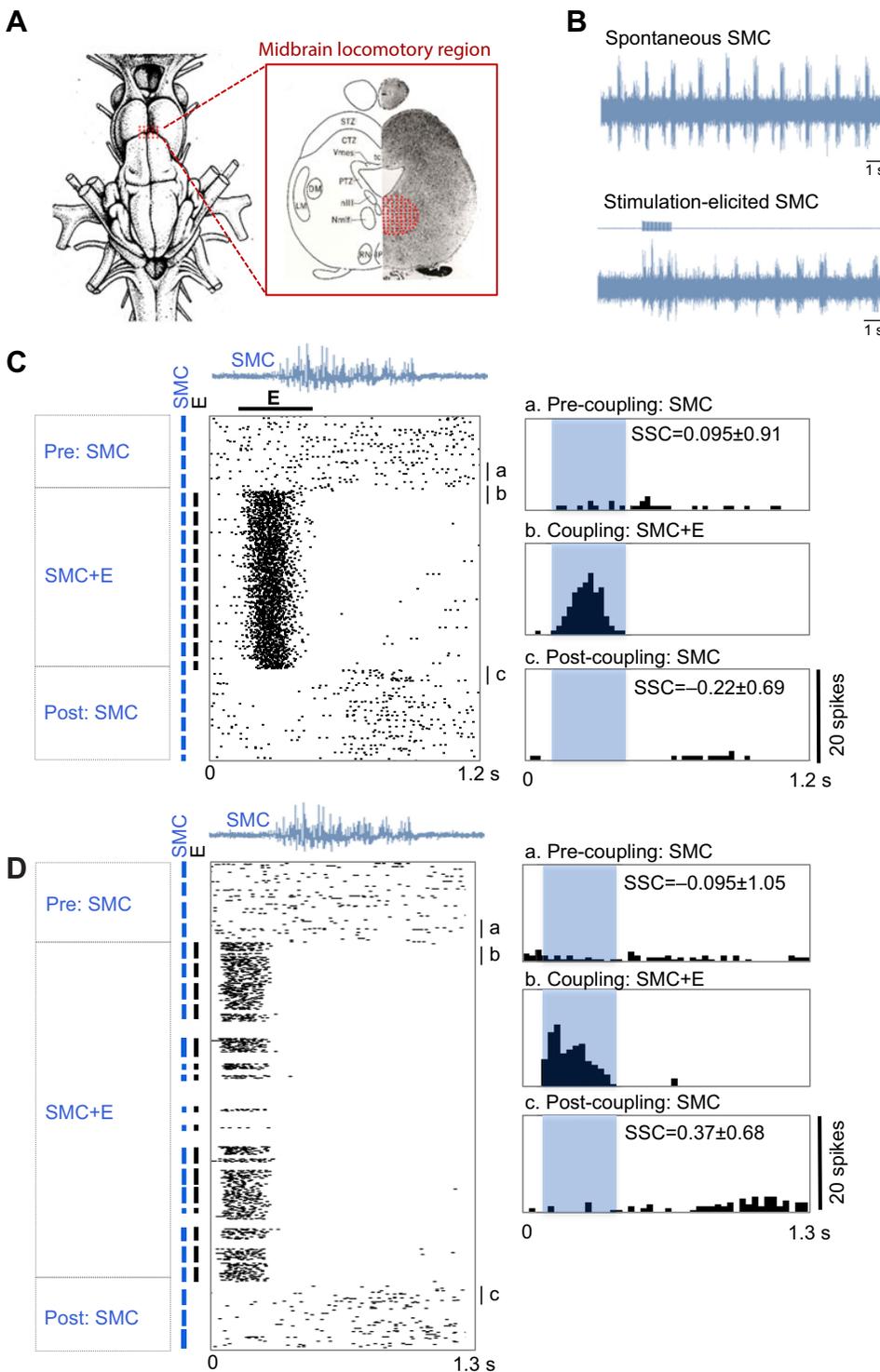


Fig. 1. Cancellation signals associated with fictive swimming form during both intermittent and continuous behaviors in *Leucoraja erinacea*. (A) Dorsal view of the brain and cross-section through the midbrain anterior to the cerebellar overhang (inset). Red stippling indicates location of midbrain locomotory region (MLR) where fictive swimming was evoked by electrical stimulation. (B) Multi-unit discharge from spinal root shows spontaneous swimming motor commands (SMC) associated with fictive swimming (top), and SMC elicited during and continuing after MLR stimulation (bottom). (C) Representative raster plot and histogram of an AEN firing during a continuous coupling experiment with SMC. Upon stimulus offset, a significant negative image was observed during the stimulus interval where electrosensory stimuli (E) were previously presented. (D) Representative raster plot and histogram of an AEN firing during a coupling experiment to intermittent fictive swimming. Gaps in the raster plot indicate pauses where the animal stopped fictive swimming. Stimulus trains (not shown) were delivered to the MLR during each gap to re-initiate fictive swimming. On the left, blue dashes indicate ongoing SMC cycles; black dashes indicate delivery of electrosensory stimulus coupled to SMC during the coupling phase. a–c indicate time periods from raster plots from which histograms are drawn. Blue shading over histograms indicates stimulus interval within the SMC cycle.

sessions: first, VMC coupling; second, FM coupling; and third, VMC+FM coupling. In the first two sessions, the VMC and FM cycles occurred simultaneously and asynchronously. In the third session, VMC was used to initiate FM such that they occurred in synchrony. FM cycles (1.7 s) ended slightly before VMC cycles (~2.0 s) and fin movements were paused until the start of the next VMC cycle to prevent overrun. During each coupling session, AENs showed robust temporal and input-specific responses to the electrosensory stimuli (Fig. 3A). Of the AENs tested, 53% ($N=8/15$) developed a cancellation signal for VMC, and 47% ($N=7/15$)

developed a cancellation signal for FM. Importantly, 69% ($N=9/13$) of AENs that exhibited a cancellation signal for either VMC or FM alone subsequently exhibited a cancellation signal for VMC+FM (Fig. 3B). Thus, AENs can form and degrade distinct cancellation signals using the relevant reference inputs, and furthermore re-form cancellation signals despite additional behaviors occurring simultaneously.

Moreover, this experimental paradigm allowed us to examine whether the combined cancellation signal of two co-occurring fictive behaviors was more effective in suppressing reafference than

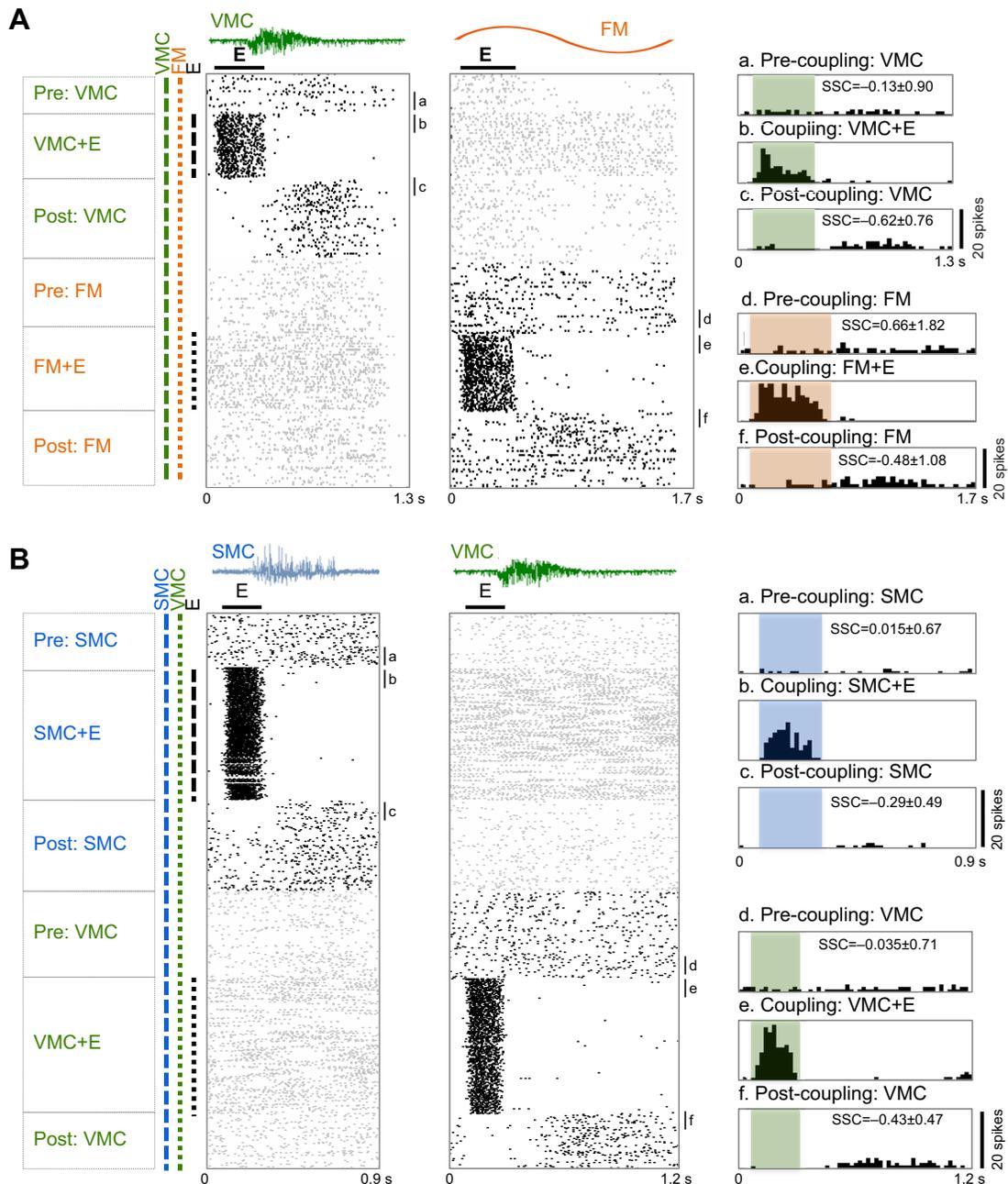


Fig. 2. AENs use multiple reference inputs to form cancellation signals associated with distinct behaviors. (A) Cancellation signals for ventilatory motor commands (VMC) and proprioceptive fin movements (FM) formed in a single AEN. During VMC coupling, electrosensory stimuli (E) were paired to VMC cycles, while FM cycles occurred at a temporally independent rate. Subsequently in the same AEN, E were paired to FM cycles with ongoing temporally unrelated VMC cycles. Note the robust, input-specific electrosensory responses during each coupling session, and input-specific negative images at stimulus offset during the post-coupling phase that exist only for paired inputs (black raster plots). The unpaired input exhibited sporadic firing throughout cycles (grey raster plots). (B) Cancellation signals for VMC and SMC formed in a single AEN. VMC and SMC cycles occurred asynchronously with E coupled to SMC during the first session, then E coupled to VMC during the second session. On the left, green dashes denote ongoing VMC cycles; orange dashes denote ongoing FM cycles; blue dashes denote ongoing SMC cycles; black dashes denote electrosensory stimuli coupled to a particular reference input during the coupling phase. Raster plots are shaded to emphasize the relevant input used for coupling sessions (black, paired input; grey, unpaired input). a–f indicate time periods from raster plots from which histograms are drawn. Green shading, stimulus interval during VMC cycles; orange shading, stimulus interval during FM cycles; blue shading, stimulus interval during SMC cycles.

their singular cancellation signals (Fig. 3C). Overall, we did not find the magnitude of combined cancellation signals associated with co-occurring behaviors (VMC+FM) (i.e. difference in SSC between pre- and post-coupling phase) to be additive when compared with their individual component cancellation signals (VMC or FM alone).

Behavior-associated cancellation signals are independently modified

Intermittent behaviors, such as swimming, create dynamic electrosensory reafference that disappears during behavioral pauses and reappears when behavior resumes. The adaptive filter model predicts that the strength of parallel fiber–AEN synaptic

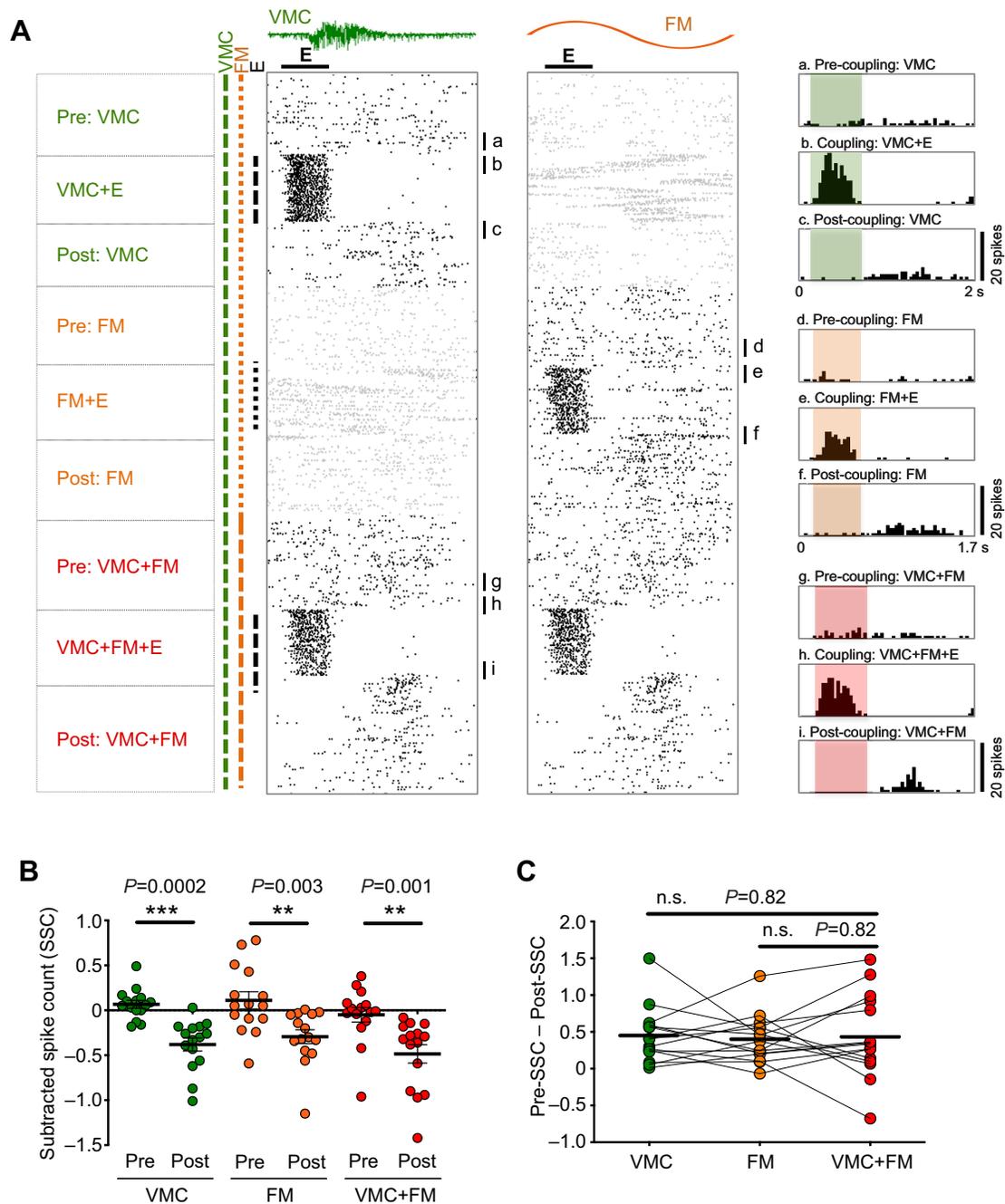


Fig. 3. Cancellation signals associated with different behaviors can form simultaneously within individual AENs. (A) Cancellation signals formed in a single AEN for VMC, FM, then jointly for VMC+FM. In three sequential coupling experiments within the same AEN, electrosensory stimuli (E) were first coupled to VMC, then E were coupled to FM during the second session, and finally, E were coupled to VMC+FM during the third session. During the first two sessions, VMC and FM cycles co-occurred at temporally independent rates. During the third coupling session, VMC cycles were used to trigger FM cycles, thus VMC+FM cycles occurred synchronously. Input-specific negative images were evident at stimulus offset for each coupling session. Raster plots, histograms and labels are as in previous figures. (B) For each AEN ($N=15$), the subtracted spike count (SSC) was calculated within the stimulus interval relative to spike counts outside the stimulus interval during pre-coupling and post-coupling phases. SSCs decreased significantly after each coupling session relative to before coupling. Each point is an individual AEN. Paired t -tests; ** $P<0.01$, *** $P<0.001$. (C) To quantify the magnitude of negative images, pre-coupling SSC was subtracted from post-coupling SSC for each AEN ($N=15$) during the three coupling sessions. There was no difference in the magnitude of Pre-SSC - Post-SSC across the different coupling sessions; one-way ANOVA.

inputs are modified and updated through coincident activity (Bodznick et al., 1999). Cessation of behaviors halts their associated activity in parallel fibers and is predicted to be stable and maintain synaptic weights during behavioral pauses. Given that AENs can develop multiple, behavior-specific cancellation signals, we tested whether distinct cancellation signals could be stored

during behavioral pauses and independently modified. In this paradigm, electrosensory stimuli were first paired with FM to form a swimming-associated cancellation signal. Continual fin movements with a brief pause in the electrosensory stimulus confirmed the formation of a swimming-associated cancellation signal (as observed by a FM-specific negative image), which was followed

by additional FM coupling for reinforcement. Fin movements were subsequently paused, and a ventilation-associated cancellation signal was formed by coupling electrosensory stimuli to VMC cycles. During the VMC post-coupling phase, we observed a VMC-specific negative image that gradually dissipated in the absence of electrosensory stimuli as the ventilation-associated cancellation signal was updated. Fin movements were resumed to test for the reappearance of a FM-specific negative image (Fig. 4A). We found that 73% (8/11) of AENs displayed a negative image during the post-coupling phases for FM, VMC, and notably, FM2 upon resumption of fin movements (Fig. 4B). The magnitude of the cancellation signal for FM2 did not differ from the initial FM cancellation signal (Fig. 4C). This indicated that the cancellation signal for FM persisted despite the intervening formation and degradation of a separate cancellation signal for VMC. These results show that multiple, behavior-specific cancellation signals can co-exist within an AEN and that they can be independently created, stored and modified.

Cancellation signals are strengthened by prolonged coupling and are stable during long behavioral pauses

The proposed function of the adaptive filter is to suppress predictable electrosensory consequences of behaviors. Variations in behaviors that animals perform in their natural environment necessitates that cancellation signals are continually updated throughout their lifetime. Some behaviors exhibit long pauses between bouts of activity, such as when the animal rests, and presumably the associated parallel fiber activity is also halted. We predicted that the adaptive filter stores cancellation signals during inactive periods by maintaining synaptic weights of specific parallel fiber–AEN synapses, then reactivates them when behaviors resume. Additionally, from our recordings, we observed that while AEN responses to behavior-coupled electrosensory stimuli declined over several minutes, AENs rarely completely suppressed their responses. To test whether longer coupling periods could suppress reafference further, we used fin movements as a reference signal and coupled electrosensory stimuli repeatedly for varying lengths of

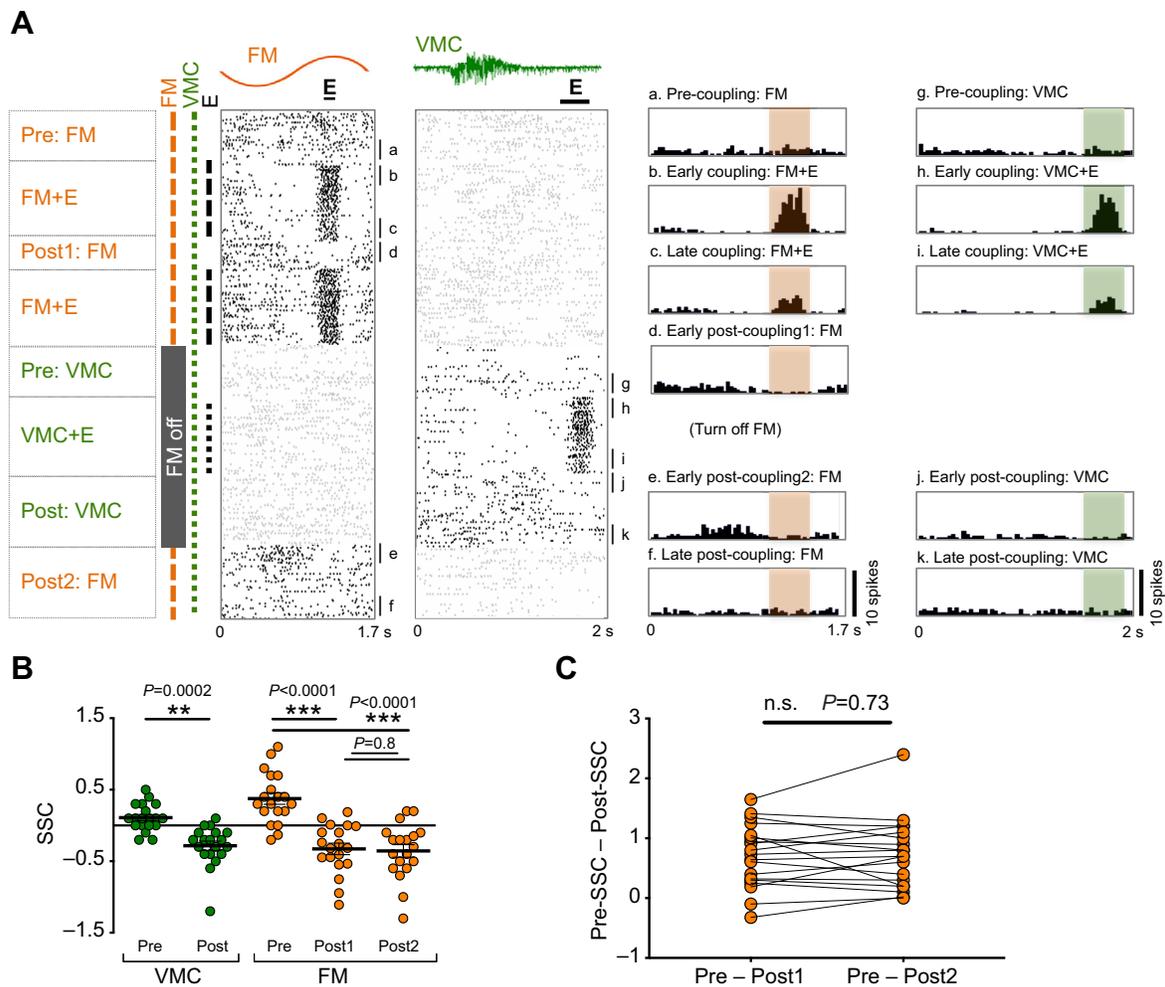


Fig. 4. Cancellation signals associated with different behaviors can be independently modified. (A) A cancellation signal for FM was maintained in an AEN during a pause in FM cycles where a separate cancellation signal was formed for VMC. Electrosensory stimuli were first paired to FM cycles (FM+E). Upon confirming an initial negative image (Post1: FM), FM+E pairings were reinforced, then fin movements were subsequently paused. A second cancellation signal for VMC was developed through VMC+E pairings, and a negative image specific for VMC was observed at stimulus offset. Resuming fin movements reactivated the latent FM-specific cancellation signal (Post2: FM). Raster plots, histograms and labels are as in previous figures. (B) Subtracted spike counts (SSC) calculated for pre- and post-coupling periods for AENs ($N=19$) during sequential FM and VMC coupling experiments. Notably, the SSC for the second FM post-coupling period was significantly decreased relative to FM pre-coupling, and no different from the first FM post-coupling period; one-way ANOVA; ** $P<0.01$, *** $P<0.001$. (C) To quantify FM-specific negative images, pre-coupling SSC was subtracted from post-coupling 1 SSC and from post-coupling 2 SSC for each AEN ($N=19$). There was no significant change (n.s.) in the magnitude of negative images when FM were resumed after VMC coupling; paired t -test.

time. We examined whether cancellation signals could be stored during behavioral pauses lasting minutes to hours. In the lengthiest case, we found that during a 2 h FM coupling session, there was a significant and steady decline in the electrosensory responses during the stimulus interval and gradual appearance of AEN firing outside of the stimulus interval. We observed significant decreases in responses to electrosensory stimuli during both the first hour (43% decline from 7.2 to 4.1 spikes, $P < 0.0001$) and second hour of coupling (44% decline from 4.1 to 2.3 spikes, $P < 0.0001$) (Fig. 5A). Presumably, even longer coupling sessions would result in further diminution of electrosensory responses. At this point, the electrosensory stimulus was turned off and a robust negative image was observed with a brief bout of fin movements. Fin movements were paused for an extended period of 10 h to test the long-term persistence of the cancellation signal. In the absence of fin movements, the AEN exhibited dispersed spontaneous firing similar to baseline levels. At 6 h into the pause, the fin was briefly moved, without electrosensory stimuli, to probe reactivation of the cancellation signal, and again, a robust FM-specific negative image was observed (mean SSC at 6 h probe = -1.0 ± 0.7 spikes, $P < 0.0001$ compared with baseline). After a 10 h pause, fin movements were continued without electrosensory stimulation, resulting in the cancellation signal slowly fading (post-coupling SSC at 0 h, -0.7 ± 0.5 spikes; at 1 h, -0.4 ± 0.5 spikes; at 2 h, -0.4 ± 0.7 spikes). Over 2 h of continuous fin movements, AEN activity had clearly begun recovery, but had yet to reach pre-coupling baseline levels (Fig. 5B). This is in agreement with previous findings that potentiation of postsynaptic potentials after coupling occurs more slowly than depression during coupling (Bertetto, 2007).

Each AEN forms cell-specific cancellation signals

During the performance of any given behavior, the spatial distribution of AEN receptive fields will expose each AEN to differing magnitudes and patterns of reafference. As the generation of cancellation signals occurs by adjusting the synaptic weights of parallel fiber inputs onto the AEN's apical dendrites, we hypothesized that different AENs, when simultaneously exposed to behavioral reafference, would each form their own unique cancellation signal by adjusting their relevant synaptic inputs to cancel the particular reafference it receives.

AENs are somatotopically organized within the DON. AENs in close proximity to each other within the DON have receptive fields that are positioned close together at the skin's surface. In rare instances where we could simultaneously record from two adjacent AENs, we found that a dipole positioned near the skin's surface could deliver electrosensory stimulation to the center of one AEN's receptive field and to the inhibitory surround of the other AEN's receptive field, thus exciting one AEN while simultaneously inhibiting the other. In two of these cases, the electrosensory stimuli were then coupled to the VMC. In both cases, each AEN developed a significant cancellation signal that was appropriate for its own response to the dipole and opposite to that of its neighbor AEN. The initial stimulus polarity inhibited one AEN (AEN1) and excited the second AEN (AEN2) (Fig. 6A). Cessation of the electrosensory stimuli produced corresponding negative images of opposite polarity in their respective AENs. The AENs were allowed to recover for 30 min before the experiment was repeated with the opposite stimulus polarity to excite AEN1 and inhibit AEN2 (Fig. 6B).

When the electrosensory stimulus was excitatory, AENs displayed significant decreases in their electrosensory responses

over the course of the coupling period. For AEN2 (Fig. 6A), the excitatory electrosensory responses decreased from 3.1 ± 1.5 during the early coupling phase to 1.9 ± 1.9 during the late coupling phase ($P < 0.0001$). Similarly, for AEN1 (Fig. 6B), excitatory electrosensory responses decreased from 3.36 ± 1.59 to 2.37 ± 1.79 ($P = 0.0002$) from early to late coupling phase. During the post-coupling phase, both AEN1 and AEN2 exhibited significant negative images in the absence of excitatory electrosensory stimuli (AEN1: -0.31 ± 0.44 , $P = 0.006$; AEN2: -0.31 ± 0.53 , $P = 0.0002$).

Conversely, when electrosensory stimuli were inhibitory, these AENs exhibited significantly reduced firing during the stimulus interval that significantly declined over the course of the coupling phases. Inhibitory electrosensory responses for AEN1 (Fig. 6A) weakened from -0.48 ± 0.39 during early coupling phase to -0.37 ± 0.39 during late coupling phase ($P = 0.043$). For AEN2 (Fig. 6B), inhibitory electrosensory responses significantly changed from -0.60 ± 0.58 to -0.42 ± 0.41 ($P = 0.017$) during the coupling phase. During the post-coupling phase, negative images for inhibitory stimuli (i.e. increased firing during the stimulus interval) were observed, but failed to reach statistical significance (AEN1: 0.45 ± 1.21 , $P = 0.14$; AEN2: 0.002 ± 0.81 , $P = 0.82$). These results show that individual AENs can simultaneously and independently generate their own cell-specific cancellation signals to match and suppress the unique reafference they each experience.

DISCUSSION

Self-induced reafference poses a noisy problem for most sensory systems as the system must be able to eliminate predictable sensory noise in order to faithfully transmit externally relevant novel signals from the environment. In elasmobranchs and other organisms, reafference patterns carried by peripheral sensory afferents can be dynamic and complex due to highly variable movements that an animal performs in its behavioral repertoire. Despite receiving noisy sensory input, AENs in elasmobranchs are capable of filtering reafference by using internal signals to generate cancellation signals that predict and subtract the sensory consequences of behavior. The same adaptive filter mechanism was found to exist in two independently evolved weakly electric fishes, gymnotids and mormyrids (Bastian, 1996; Bell et al., 1997) and in the lateral line mechanosensory system (Perks et al., 2020). The adaptive filter is now also considered to be a basic signal processing algorithm of vertebrate cerebellums (Bell et al., 2008; Montgomery et al., 2012; Porrill et al., 2013; Sawtell and Bell, 2008). The studies reported here have extended our understanding of the full capabilities of the adaptive filter in cerebellar-like systems. (1) We first expanded earlier findings (Bodznick et al., 1999) that internal signals of different modalities – both proprioceptive feedback and ventilatory motor commands – can be used to form cancellation signals within a single AEN. (2) We showed for the first time that motor commands associated with the skate's swimming can also be used to develop cancellation signals; and it seems likely that behavior-specific cancellation signals extend to virtually all behaviors within each animal's repertoire. (3) We showed that each AEN can individually form cancellation signals associated with multiple behaviors, some of which are stereotyped and continuous (e.g. ventilation), and others that are irregular and intermittent (e.g. swimming). (4) Cancellation signals could be generated in increments, stored during behavioral pauses that lasted minutes to at least 10 h, and reactivated when behaviors resumed. (5) Individual AENs were capable of generating multiple cancellation signals simultaneously during co-occurring behaviors, and furthermore, modify them independently.

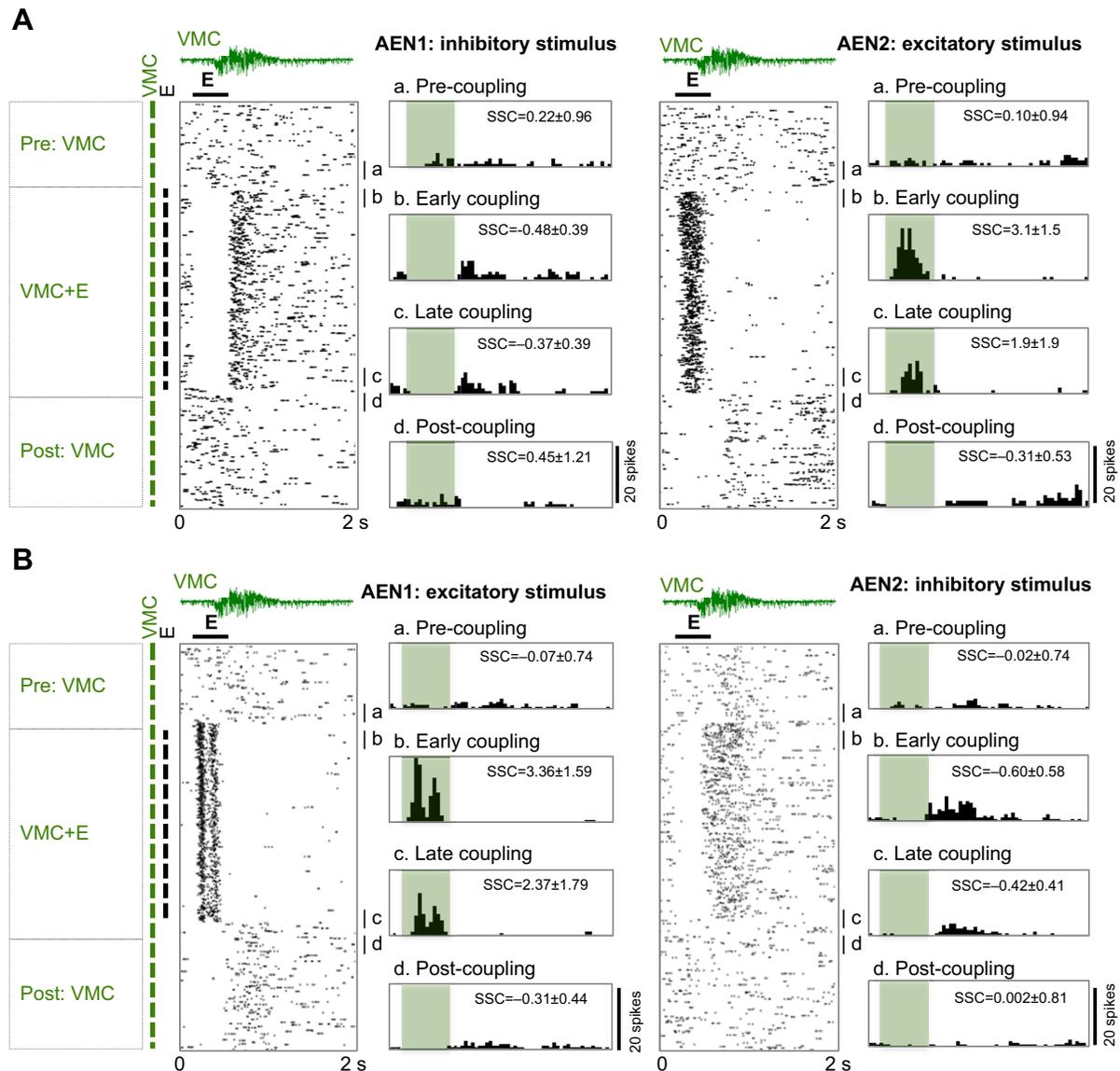


Fig. 6. Cancellation signals are cell specific as each AEN forms its own negative image based on the reafferent signals it receives. (A) Simultaneous recordings of two adjacent AENs with slightly offset receptive fields enabled concurrent coupling experiments delivering inhibitory electrosensory stimulation to AEN1 and excitatory stimulation of AEN2. Both AENs exhibited decreasing responses to electrosensory stimulation during the coupling phase. Negative images of opposite polarity were observed in AEN1 and AEN2 at stimulus offset during the post-coupling phase. (B) The polarity of the electrosensory stimulus was reversed to excite AEN1 and inhibit AEN2. A cancellation signal formed within AEN1 as observed by significantly decreased responses during the coupling phase ($P=0.0002$) and a significant negative image upon stimulus offset ($P=0.006$). In AEN2, electrosensory responses declined significantly during the coupling phase ($P=0.017$), but the negative image did not reach significance upon stimulus offset.

(6) Each AEN assembles its own distinct cancellation signal specifically to match the reafference it receives, thus cancellation signals are cell specific. These results support a model where AENs *en masse* utilize multiple reference inputs to form and dynamically update their cell-specific and context-specific cancellation signals to eliminate highly specific, yet changing patterns of predictable sensory reafference.

From a functional viewpoint of sensory systems, suppressing predictable reafference using a multitude of cancellation signals is useful due to the complex nature of behaviors. Utilizing several component reference signals may allow finer tuning of the reafference suppression associated with different aspects of behavior. These reference signals include both the corollary motor commands that elicit behavior and the sensory consequences of the behavior

feeding back through descending pathways to the DON. In the current study, we extended our previous work on ventilation-associated cancellation signals (Bodznick et al., 1999; Zhang and Bodznick, 2008) by showing that swimming-associated cancellation signals can be formed from motor commands recorded from the spinal nerve, as well as to proprioceptive signals induced by passive movement of the fin. These findings demonstrate an important concept that reafference from a single behavior can be suppressed by predictive inputs of multiple modalities. Similarly to others, we find that the minor temporal delay in sensory feedback signals arriving on AEN apical dendrites was not too long to allow cancelling of reafference (Bastian, 1995; Requarth et al., 2014; Wurtz, 2008).

For episodic behaviors, such as swimming, cancellation signals were updated over successive bouts of behavior and stored during

behavioral pauses. Brief electrosensory coupling sessions to experimentally manipulated fin movements demonstrated that swimming-associated cancellation signals developed incrementally and were maintained during intermittent rest intervals (Zhang and Bodznick, 2008). Here, we showed for the first time that incremental cancellation signals can also develop when coupled to the naturally occurring reference signals (i.e. spontaneous swimming motor commands). These data lend support to the idea that cancellation signals can be stored and continually updated over several sessions rather than developing *de novo* each time a behavior resumes. Indeed, a clear instance of long-term storage of cancellation signals was presented in this study where the negative image associated with passive fin movements was stored during a pause lasting up to 10 h and robustly reactivated upon resuming fin movements.

An important feature of the parallel fiber array is that AENs have access to many thousands of parallel fiber inputs. The adaptive filter model predicts that each AEN selects via anti-Hebbian plasticity those inputs useful for developing cancellation signals to suppress reafference associated with distinct behaviors. This synaptic plasticity has been directly demonstrated in each of the three independently evolved electrosensory systems (Bastian, 1999; Bell et al., 1997; Bertetto, 2007). However, it was unclear how cancellation signals interact under situations where multiple behaviors are co-occurring. Firstly, we showed that when two unsynchronized reference signals are available, AENs formed cancellation signals for the paired signal, but not the unpaired signal. This demonstrated that internal reference signals, through temporal correlation between apical synaptic input and peripheral electrosensory input, contribute independently to the formation of cancellation signals. Subsequent electrosensory pairing with the alternate signal verified that AENs have access to both internal reference inputs and can utilize either of them to form cancellation signals associated with distinct behaviors. Although we did not investigate the extent of the number of cancellation signals an individual AEN can store, we predict that many more can be stored given the number of parallel fiber inputs that AENs receive.

Secondly, cancellation signals associated with separate behaviors could form simultaneously in a single AEN. AENs that formed cancellation signals for two different behaviors on separate occasions could also form a cancellation signal for each behavior when the two behaviors occurred at the same time. These results provide evidence that AENs utilize temporal coincidence between active parallel fiber inputs and reafference to form cancellation signals, and that the simultaneous activation of parallel fiber inputs associated with different behaviors did not interfere with the formation of the cancellation signal for each. Given the highly specific nature of cancellation signals, we hypothesized that each parallel fiber input carries a distinct type of reference signal pertaining to a behavioral state that can independently contribute to a composite cancellation signal within an AEN; and that AENs utilize separate reference inputs for distinct behaviors. However, we did not observe an additive effect, or a stronger negative image, for the cancellation signal formed from two distinct reference signals. A possible explanation for this is that the intrinsically low spike rates of AENs prevented us from discerning stronger negative images for composite cancellation signals. Alternatively, parallel fibers may carry more than one type of internal reference signal. If internal reference signals related to separate behavioral states arrive via the same parallel fiber input, this may limit an AEN's ability to formulate behavior-specific cancellation signals and discern when single or multiple behaviors are performed. There is, however, evidence from morryrid fish that show a subset of granule cells

encodes multi-modal proprioceptive and motor corollary discharge signals (Requarth et al., 2014; Sawtell, 2010). By summing signals and firing only when proprioceptive feedback and motor corollary signals coincide, such granule cells may encode a higher order integrated behavioral state (e.g. when the body is in a certain position and coinciding within a narrow time range after a motor corollary command). In such cases, it is possible that a subset of granule cells may be multi-modal in nature, yet is only activated during a narrow and highly specific behavioral state. We believe parallel fibers in elasmobranch fish encode information pertaining to distinct, non-overlapping behavioral states, some of which are encoded by modality-specific signals. This hypothesis is supported by recordings from the elasmobranch dorsal granular ridge, where the granule cells of the electrosense are located. Granule cell recordings appeared to be either electrosensory or proprioceptive, and very few encoded both (Hjelmstad et al., 1996) (D.B., unpublished observation). Additional studies in mammalian cerebellums provide evidence for unimodal granule cells (Arenz et al., 2008; Bengtsson and Jorntell, 2009; Jorntell and Ekerot, 2006), while in contrast, other studies demonstrate the multi-modal capacity of granule cells (Huang et al., 2013; Ishikawa et al., 2015; Requarth et al., 2014; Sawtell, 2010). Clearly, further studies in both cerebellum-like structures and cerebellums of different species aimed at revealing where multi-modal sensory integration occurs, whether on granule cells or downstream on Purkinje neurons, will be important to advance our understanding of the computational encoding capacity of sensory processing in cerebellar networks.

To shed further light on this, a prominent finding of the current study was that a cancellation signal for passive fin movement persisted throughout the development and degradation of a separate cancellation signal for ventilatory motor commands. If two types of internal reference signals were delivered via one subset of parallel fiber input, then modification of one cancellation signal should be reflected in the modification of the other cancellation signal. In contrast, we found that these cancellation signals behaved independently where performance of another behavior did not inappropriately update or cause the degradation of a pre-existing cancellation signal. Furthermore, cancellation signals could be stored in the relative synaptic weightings during long pauses in behavior and reactivated when behaviors resumed. While this does not exclude the possibility of mixed granule cell inputs in elasmobranchs, these lines of evidence argue in favor of a role for distinct internal reference signals arriving through separate, non-overlapping sets of parallel fibers.

Finally, in simultaneous recordings of two AENs, one of which received excitatory stimuli and the other inhibitory stimuli, we found that each AEN independently of its neighbor developed its own cancellation signal to suppress the particular pattern of reafference it received. The finding that AENs developed cell-specific cancellation signals to suppress reafference makes sense given that the bodily location of each AEN's electroreceptive field is unique, and therefore most movements would have AEN-specific electrosensory consequences. The somatotopic organization of both the AENs within the dorsal octavolateralis nucleus and the proprioceptive units in the dorsal granular ridge probably aids reafference suppression. The proprioceptive parallel fibers project homotopically to the AENs of the dorsal nucleus (Conley and Bodznick, 1994), and we believe this facilitates synaptic contacts between relevant parallel fiber inputs and AENs for cancelling reafference. In contrast, it seems reference signals such as motor commands are likely to be useful to AENs with quite different receptive field locations, and indeed ventilatory motor commands

were found in recordings throughout the dorsal granular ridge (Hjelmstad et al., 1996).

In sum, all animals must contend with the extraction of meaningful information from noisy inputs. Inverse sensory predictions that are generated based on internally available information represent an efficient neural strategy to separate novel signals from predictable sensory noise. As noted above, similar sensory extractions have been described in other cerebellum-like structures, such as mormyrid and gymnotid electrosensory lateral lobe (Bastian, 1996; Bell et al., 1993; Bell et al., 1999; Sawtell and Williams, 2008), as well as in mammalian dorsal cochlear nucleus (Singla et al., 2017; Tzounopoulos et al., 2004). There are a number of different avenues that still need investigating including the specific cellular and molecular mechanisms that generate these inverse sensory predictions, and the relative contributions of long-term potentiation and depression of synapses from excitatory or inhibitory inputs. In the cerebellum, plasticity that enhanced overall inhibitory tone was found at excitatory synapses onto inhibitory interneurons that fed forward onto Purkinje cells (as opposed to direct enhancement of interneuron–Purkinje cell synapses) (Smith and Otis, 2005). Whether this is also true of cerebellum-like structures, or if plasticity occurs elsewhere (e.g. interneuron–AEN synapses) remains to be seen. Additionally, as alluded to above, further study is needed to examine whether predictive information converges or remains separate within granule cells and their associated parallel fibers. Convergence of distinct information streams may reduce the system's capacity to discern when and which inputs are individually active, especially if these inputs arrive separately in time. However, convergence to detect coincident multi-modal inputs may enhance the capacity to encode higher level behavioral states. Examining how overlapping or non-overlapping inputs influence the activity of principal Purkinje cells and subsequent outflow of information is a critical step in understanding how cerebellums and cerebellum-like structures process multiple streams of information. The parallel fiber circuitry of cerebellum-like structures is identical in most important respects to that of the vertebrate cerebellum itself. In each of these circuitries there is an underlying powerful adaptive filter function, the essential role of which is to create predictions. In the cerebellum, motor commands and available sensory feedback are used to learn and refine predictions of the sensory consequences of upcoming movements. These predictions are the so-called forward models needed for coordinating multi-joint movements (Thach et al., 1992); performing accurate eye movements (Dean et al., 1994; Lisberger, 1988; Shidara et al., 1993); and using sensory feedback to modify motor movements in real-time skill learning (Anderson et al., 1996; Tseng et al., 2007). Here, we show that the adaptive filters in the cerebellum-like sensory nuclei of skates provide cell-specific, context-dependent sensory predictions to suppress complex reafference that result from diverse behaviors. These same capabilities are likely to be central and common features of context-dependent motor learning in cerebellum by allowing individual Purkinje neurons to dynamically participate in modifying multiple behaviors, each with their own unique forward model.

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Competing interests

The authors declare no competing or financial interests.

Author contributions

Conceptualization: N.Y.L., J.M.B., D.B.; Methodology: N.Y.L., D.B.; Investigation: N.Y.L., J.M.B.; Resources: D.B.; Data curation: N.Y.L., J.M.B.; Writing - original draft: N.Y.L.; Writing - review & editing: N.Y.L., J.M.B., D.B.; Visualization: N.Y.L., J.M.B., D.B.; Supervision: D.B.; Funding acquisition: N.Y.L., D.B.

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