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Principles of multimodal integration in the startle escape system of goldfish

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Abstract

Perception typically involves information from different sense organs and processing of multimodal information is essential to an organism's capacity to respond to environmental events. However, compared to unimodal processing, little is known about the principles and mechanisms that underlie multimodal integration and how they translate to behavior. Thus, the aim of the present study was to reveal how biologically relevant visual and audio stimuli are integrated during goldfish escape startles. Inspired by the work of Meredith and Stein on the 'inverse effectiveness principle' of multimodal integration, we tested the hypothesis of an inverse relationship between the effectiveness of individual visual and audio stimuli and the magnitude of their integration. For that, we analyzed startle response rates and latencies evoked by individual and combined presentations of a short (5 ms) audio pips and a long lasting (900 ms) gradually increasing visual looms. Results show that presenting a weakly effective audio pulse (152 dB or 159 dB) early during the visual loom (i.e to a weakly effective visual stimulus) produced a supralinear increase in responsiveness when compared to hypothetical linear addition of the individual stimuli effectiveness whilst an audio pulse presented later during loom duration i.e., close to loom collision (highly effective period) did not produce supralinear addition. Since startle escape response frequency in goldfish is directly correlated to excitation in the cell triggering the behavior, the Mauthner cell, results imply supralinear integration of synaptic inputs may occur at the level of this integrating neuron. More broadly, these results underline the significance of single neurons in multimodal integration and decision-making for a vital behavior.

Principles of multimodal integration in the startle escape system of goldfish

Processing of sensory information from different modalities is an elementary part of decision-making for appropriately evoked and timed behavioral responses. In humans, inefficiencies in processing and integrating multiple modalities have been connected to several disorders such as autism (Collignon *et al*, 2013; Brandwein *et al*, 2015), schizophrenia (Stekelenburg *et al*, 2013; Tseng *et al*, 2015), and dyslexia (Harrar *et al*, 2013; Hahn *et al*, 2014). Accordingly, multimodal integration has been extensively studied in the past (Stein *et al*, 2014; Van Atteveldt *et al*, 2014). However, the underlying mechanisms of multimodal integration and how these mechanisms connect to the behavior observed are not well understood. The challenge in addressing the neural and behavioral aspects of multimodal integration is due to its wide, neural complexity, particularly in mammals where it is most often studied. Integration is thought to be controlled by multisensory neurons found in individual sensory centers (King & Walker, 2012) as well as intersensory areas of the superior colliculus (Meredith, Nemitz, & Stein, 1987; Wallace, Meredith, & Stein, 1998), making multimodal processing complex and difficult to narrow down. Most current work focus in solidifying and understanding multimodal aspects related to timing of stimuli, spatial location between stimuli and inverse effectiveness (Stein, Stanford & Rowland, 2014).

The *Inverse Effectiveness Principle* (IEP) states that the integration of two weakly effective stimuli of different modalities will produce comparatively larger responses than an integration of stimuli with greater effectiveness (Meredith & Stein, 1986). This phenomenon has been a focus of investigation because it may divulge a means of sensory-based decision-making. The interaction between different intensities in the IEP may demonstrate how to determine the significance of stimuli in a situation when information of different forms and salience are

available (Holmes & Spence, 2005). In addition, IEP may also be modulated by situational context, emotions, and developmental experiences (Van Atteveldt *et al*, 2014; Ten Oever *et al*, 2016). With the difficulties brought about by the various forms of circuitry involved and situational plasticity, it is not clear how individual multisensory neurons play in moderating multimodal integration and when IEP is more likely to be observed (Van Atteveldt *et al*, 2014).

In teleost fish, a pair of large neurons called the Mauthner cells (M-cell) located in the medulla of the hindbrain controls the startle escape behavior. Each M-cell has two major dendrites; the lateral and ventral dendrite, which receive auditory and visual inputs, respectively (Zottoli and Faber 1999; Sillar, 2009; Medan and Preuss, 2014). A single action potential in the M-cell will initiate the C-start startle behavior through activation of the contralateral muscles while the other M-cell is inhibited. This results in a short latency C-shaped body bend, or "C-start" in one direction, a startle escape response typically away from the stimulus (Eaton, Lee, & Foreman, 2001; Fetcho, 1991; Weiss *et al,* 2006).

There are several reasons why fish startle escape system is ideally suited for studying multimodal integration. Firstly, both neurons receive several types of stimuli simultaneously from multiple sensory systems including, visual, acoustic, lateral line, and somatosensory (Korn & Faber, 2005). Indeed, the processing of auditory and visual inputs has been studied to some detail. Auditory 8th afferences provide a direct (disynaptic) fast (1.8 ms) inputs via mixed electrical and chemical synapses (Zottoli, 1976; Szabo *et al*, 2006). In contrast, visual information is mediated through a polysynaptic pathway to the ventral dendrite with a minimum delay of about 20 ms (Zottoli, Hordes, & Faber, 1987; Preuss *et al,* 2006). Furthermore, recent work has revealed that excitatory inputs from sensory centers to the M-cells are increased and quicken by interneurons called spiral fiber neurons (Lacoste *et al*, 2015). Secondly, due to their

large size and large extracellular potential, the M-cells are identifiable for in vivo electrophysiological recordings wherein soma and dendrite can be reliably recorded from *in vivo* during stimulation (Preuss *et al*, 2006; Szabo *et al*, 2006). Importantly, M-cell mediated startle escapes are mediated by a single action potential (AP) thereby providing a one-to-one relationship between behavior and the neural activity in the M-cell. (Zottloi, 1979; Weiss *et al*, 2006). Therefore, the teleost startle escape system became a well-established system in neuroscience and decision-making (Korn & Faber 2005; Medan & Preuss, 2014).

Here we test the effects of audio-visual integration on the startle escape behavior in the common goldfish. The goal was to observe quantitative addition of multiple modalities using behavioral analysis to more clearly understand: (1) the inverse relationship of the salience of individual sensory inputs, (2) the terms of their integration and (3) how the startle escape response is modulated. Fish were exposed to visual looms (black discs that increase in size) and short auditory pulse stimulation. Both stimulus modalities have successfully proven to elicit M-cell driven startle escape responses as they simulate a threat by an avian predator diving from above (visual loom) and hitting the water surface (audio pulse) (Preuss *et al*, 2006; Szabo *et al*, 2006; Neumeister, Szabo, & Preuss, 2008).

Methods

Subjects

A total of 12 common goldfish (*Carassius auratus*) of similar standard body length (6.15 ± 0.39 cm) and weight (9.17 ± 1.53 g) purchased from Ozark fisheries were maintained in plexiglass holding tanks (23.2G; 30 x 30 x 60 cm) filled with recirculating conditioned filtered

water (pH 7.2- 7.6, temperature $18 \pm 1C°$, conductivity 200-300 µm/cm) and acclimated for at least one week prior to experimentation.

Apparatus

Camera and experimental setup (Fig.1) was similar as described in Preuss *et al* (2006). The circular experimental tank (77.5 cm diameter, 30.5 cm deep) tank was located on an anti-vibration table to minimize vibrations and covered with an opaque plastic lid. A high-speed camera (Olympus iSpeed2) received the image of the arena from below via a mirror situated at 45° underneath the anti-vibration table. A digital light processing (DLP) projector (Plus model # U4-131) installed 134 cm above the experimental tank was the only light source (196-197 lux at the screen; 128-130 lux at the water surface) and used to project the visual stimuli onto the lid. Audio stimulation was produced by two underwater loud speakers (Electro-Voice model # UW-30) on opposite sides of the tank.

Water conditions in the experimental tank matched those of the home tanks and a circulation system was connected to keep water temperature consistent at $18 \pm 1C°$ as well as provide oxygenation. Ceiling lights remained off during experiments and outside illumination and sound was limited. A circular mesh (27.6 cm height; 39 cm diameter) made of two layers of plastic netting (black outside, white inside) positioned in the center of the tank served as the swimming arena. The water column was maintained at a height of 17.5 cm in order to keep loud speakers submerged and water circulation system flowing.
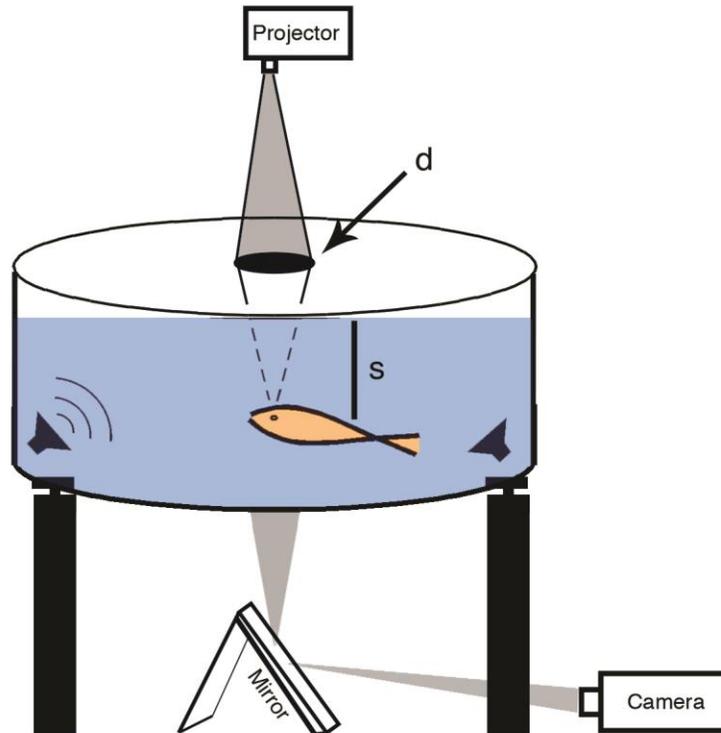
Figure 1. Diagram of experimental setup. To expose fish to multimodal stimulation, a visual loom is projected onto the translucent lid of the tank and an audio pulse is simultaneously delivered through underwater loud speakers. A camera records startle escape responses from below the tank.

Visual Stimulus

Visual loom projections were controlled through a custom made software (Visloom 1.01). For each experiment, the visual stimulation consisted of the same black looming disc projection (initial size 8mm, final size 360 mm, duration 900 ms; table 1). There was a contrast (L1/L2) of 1.8 between the luminosity of the background screen (55 lux) and luminosity of the stimulus (19 lux). This contrast was particularly chosen to reduce the loom to a subthreshold stimulus, which is defined as eliciting 20% startle probability (or lower) as previously described (Preuss *et al*, 2006). The loom was projected in the center of the arena in all trials containing visual stimulation. To avoid surface water movements during auditory stimuli, the water level in the tank was raised to clearly submerge the underwater speakers (22 cm). Consequently, the

positions of goldfish in the water column during stimulations and the view angle of the stimulus subtended on the retina, (calculated by $2 * Tan^{-1}$ of the diameter of loom (d) divided by twice the fish's distance from screen (s)), may have varied from trial to trial.

Table 1					
Stimulus intensities and duration for each experiment					
Experiment	**Loom Size [mm]**	**Loom Duration [ms]**	**Initial View Angle Range**	**Final View Angle Range**	**Audio Pulse [dB] re 1 μPa in water**
1	8 - 360	900	16 - 53	162 - 175	152
2	8 - 360	900	16 - 53	162 - 175	152, 159

Audio Stimulus

Auditory stimuli were produced, a square wave pulse, generated by a stimulator (Master 8 A.M.P. Instrumental) that was connected to a power amplifier (Samson Servo 120) that and activated underwater speakers (Electro-Voice Model # UW-30) either left or right one at a time (Table 1).

Stimulus Conditions & Audio Timing

Visual differs from auditory processing in that it is significantly slower. Information from retinal stimulations take about 20 ms to reach the M-cell ventral dendrite (Zottoli, Hordes, & Faber, 1987) while it only takes 1.8 ms for audio information to reach the lateral dendrite (Szabo *et al*, 2006). In terms of behavior, startle latencies (i.e., the first detectable head movement) in response to abrupt sound pips range from 10-15 ms (Preuss & Faber, 2003), while responses for

visual loom stimuli can be hundreds of milliseconds long depending on the duration of the loom (Preuss *et al*, 2006). The latter is due to the processing time required to detect motion and calculate critical stimulus parameter such a threshold view angle or rate of expansion (Fotowat & Gabbiani, 2011; McMillian & Gray, 2015). In goldfish threshold view angles are typically reached at about 21°, however, responses can be observed throughout the duration of the loom (Preuss *et al*, 2006). In other words, stimulus effectiveness increases slowly for early parts of the loom but exponentially during later part of the loom (Fig. 2). This notion provided the experimental rational to produce weak, medium and high effectiveness stimuli to which sound pips were added for audio-visual (AV) combination stimuli.

Experiment 1 consisted of 24 trials presenting four stimulus conditions (6 trials for each): audio only, visual only, audio-visual low (AV Low) and audio-visual medium (AV Medium). In the audio only and visual only conditions, stimulation was unimodal i.e., only one, either the visual or the auditory stimulus was presented to the goldfish. AV Low and AV Medium conditions were multimodal and differed in the timing when the audio stimulus was delivered within the duration of the visual loom. In the AV Low condition, the audio stimulus was triggered at 25% duration of the loom (225 ms) while in the AV Medium condition audio (was triggered at 75% duration of the loom (675 ms). Experiment 2 consisted of 30 trials and used the same stimulus conditions as Experiment 1 and one additional, the AV High condition that was triggered approximately at 95% duration of the loom (850 ms).
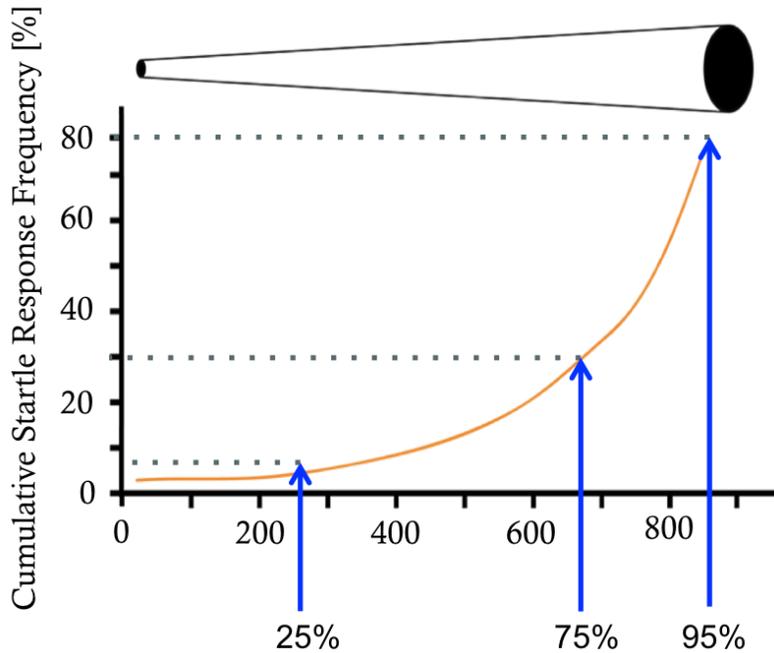
Figure 2. Example illustration showing how startle probability typically changes over loom duration. Arrows indicates targeted percentages of the loom duration in which audio was triggered for multimodal conditions. Note: All response typically occurs before stimulus offset (Preuss *et al*, 2006).

Procedure

In each experiment, an individual goldfish was transferred into the mesh arena using a small container and allowed to acclimate for 30 mins. Within 5 min after acclimation, stimulus trials were started with randomized time between trials that were either to 3, 4, or 5 mins. Stimulus conditions and speakers were randomized in a manner that each of the audio intensities was distributed equally to the speakers. For each trial, the startle escape response and its latency were recorded. The latter was determined by stimulus onset to the first appearance of the fish's head turn. For trials with visual loom conditions, startle responses with latencies longer than 920 ms (i.e. 20 ms after the duration of the loom) were considered invalid and these trials were repeated.

Statistical Analysis

Startle frequency and latency were analyzed for each fish in each condition. Differences in frequency between the estimated linear addition of unimodal stimuli, i.e. the sum of the startle probabilities of audio only and visual only conditions, and the observed startle probabilities for the multimodal conditions were analyzed using Fisher's exact test. Fisher's exact test was also used to analyze differences between multimodal conditions (Upton, 1992). In order to identify the magnitude of the difference between conditions in these comparisons, the odds ratio was reported (Glas *et al*, 2003; Upton & Cook, 2014). The odds ratio (OR) provides the relationship between conditions by stating that, for every amount of response in control condition, what are the "odds" of having a certain amount of the responses in the test condition. The odds ratio may be from zero to infinity, wherein the ratio > 1 indicates that the test condition (multimodal conditions) is larger than the control while a ratio< 1 indicates the opposite.

Results

Unimodal Startle Response Frequencies and Latencies

We observed 164 escapes out of a total of 324 trials for all four stimulus paradigms. The results showed both auditory pips we used produced comparable low response probability (152 dB re. 1μPa; M=0.11, SD =0.21 and 159 re. 1 um dB; M=0.08, SD=0.09). Two-tailed Fisher's exact test revealed there was no significant difference between the two audio intensity conditions, p= 0.749, therefore the results of these trials were collapsed for the analysis of multimodal effects. Mean latency for sound evoked responses was around 15 ms (M=15.4 SD=3.88), with most responses occurring at about that time (Fig. 4B).

In contrast, visual looms by themselves (i.e., unimodal condition) produced overall responses in about half the trials (Fig.3). However, further analysis showed that startle response probability increased throughout the loom with most startles occurring between 75-95 percent of loom duration (Fig. 4B).
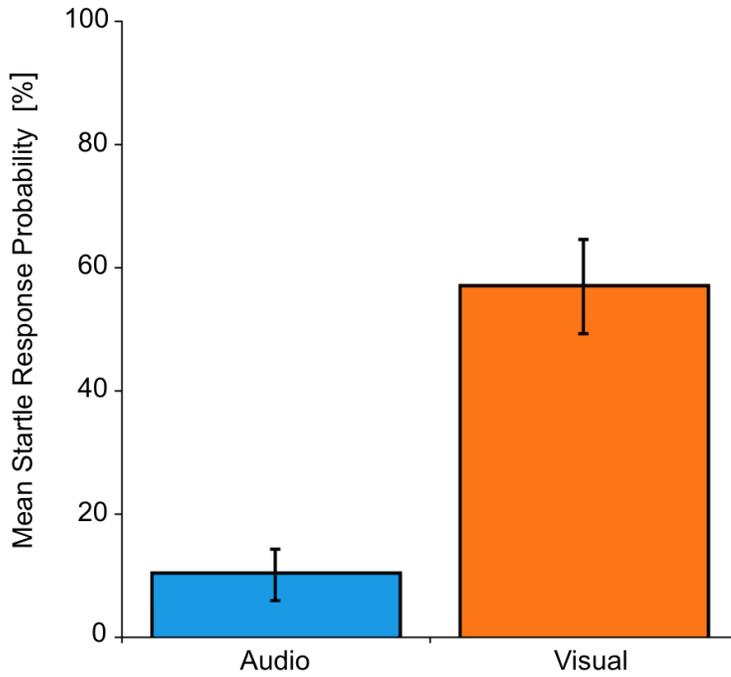

Figure 3. Mean startle response probability for unimodal audio (152 dB and 159 dB re. 1µPa) and unimodal visual conditions. N=12
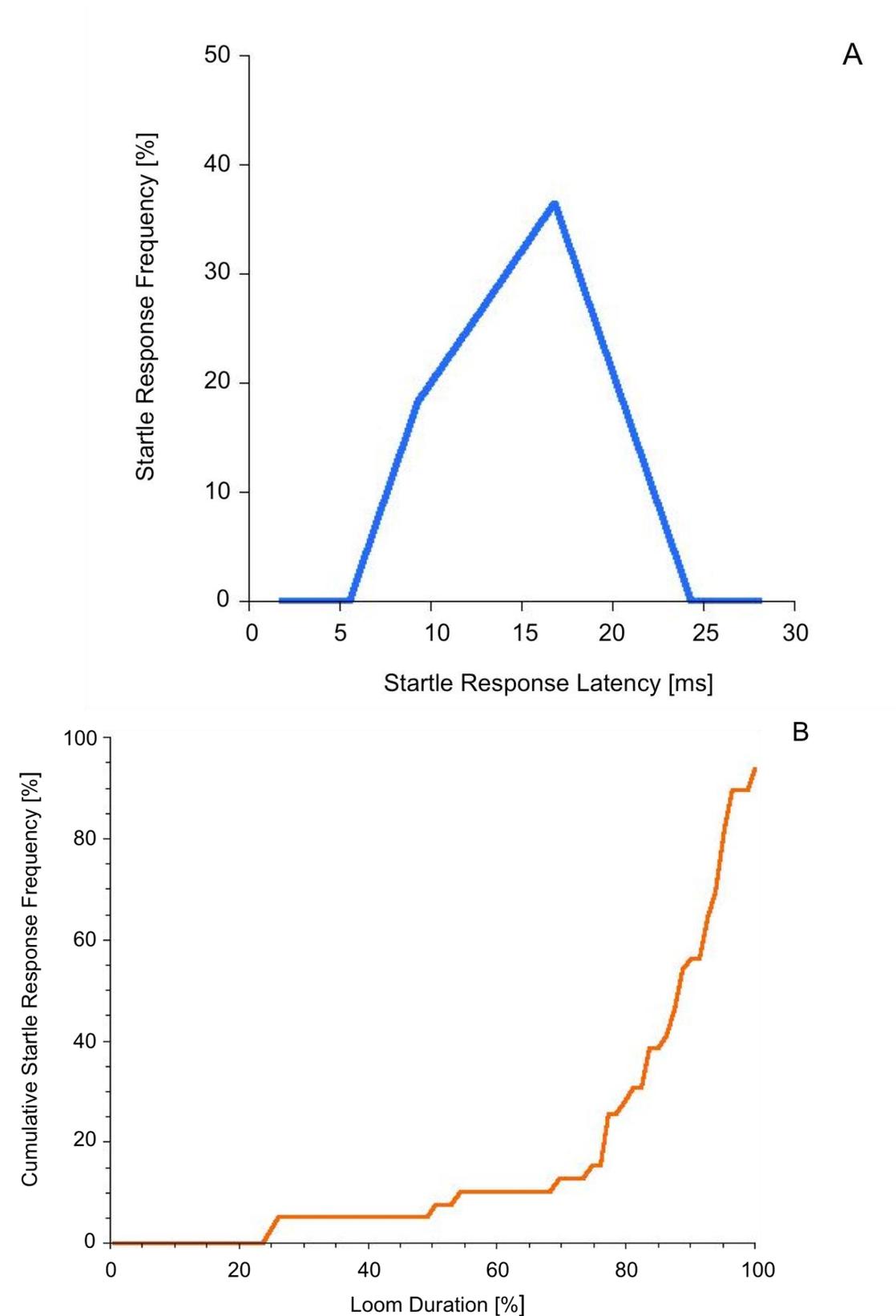
Figure 4. (A) Line graph displays distribution of unimodal audio (152 dB and 159 dB) startle response latencies. Most audio evoked startle response occurred at 15 ms. N=12 (B) Line graph displays cumulative startle frequency

distribution of unimodal visual startle response latencies. Most startle responses occur before the end of the loom's duration. N=12

Multimodal Startle Latencies

We next compared the startle latencies between the different multimodal conditions (i.e., AV low, medium and high) by graphing their startle frequency over the duration of the loom (Fig. 5). The results suggest that most of the startles in response to multimodal stimuli occurred shortly after the audio stimulus was triggered, (i.e., with latencies typical for auditory responses; Fig 4A) suggests that the distinct modes (M1, M2, & M3) in the latency graph (Fig.5) are the product of the auditory excitation superimposed onto the underlying visual excitation, i.e, they are a product of multimodal integration.

Accordingly, to determine the putative effectiveness of the visual loom during multimodal responses, we calculated the frequency of visual responses in unimodal (i.e. loom only) trials that occurred up to 30 ms after a prospective sound stimulus was applied in AV low, medium and high trials (see Fig 2 and below).
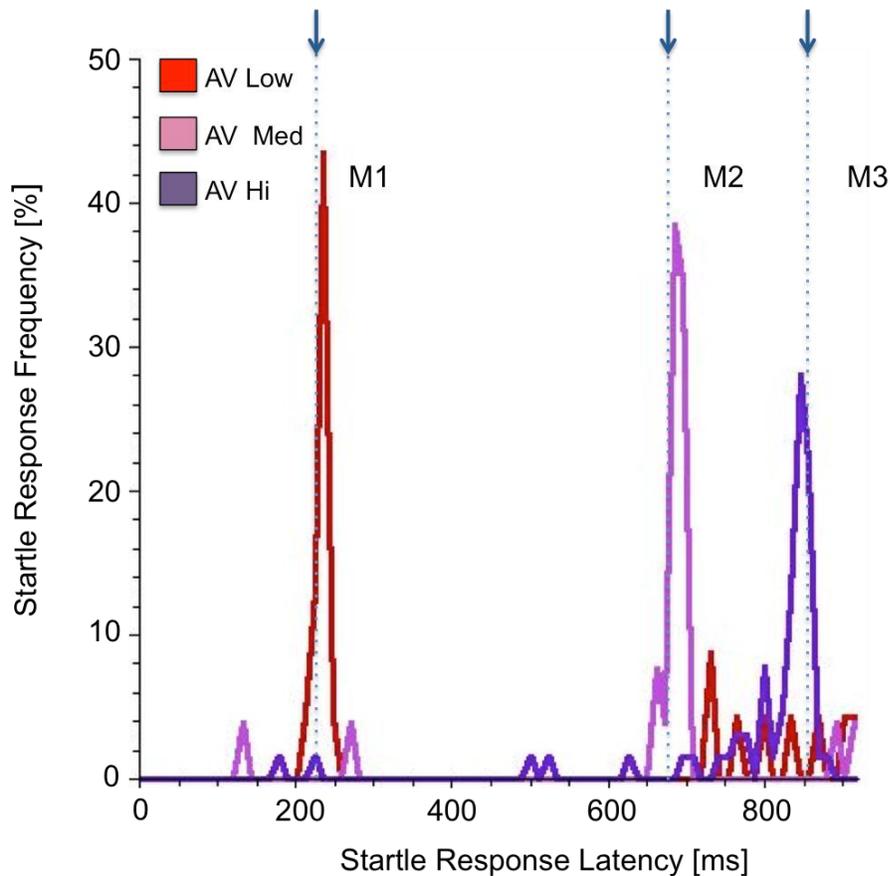
Figure 5. Line graph illustrates frequency distribution of escape latencies for audio-visual combination trials. Arrows indicate auditory stimulus onset for low, medium and high trials. N= 12

Multimodal Startle Frequencies

Figure 6 shows the unimodal audio, the calculated unimodal visual startle frequencies (low, medium, and high), as well as startle frequency during multimodal (AV Low, AV Med, AV High) trials. One-tailed Fisher's exact tests were used to compare startle frequency between multimodal conditions and the calculated linear addition of their respective unimodal conditions. Results show that AV Medium condition evoked a 53% (19/36) startle rate that was significantly larger than its linear addition at 19% (14/72); $p<.001$, OR=4.63, i.e. a supralinear response. AV Low conditions evoked a 31% (11/36) startle rate that was larger, but not significantly different from the linear addition of its two unimodal conditions at 19% (14/72), p=.15. AV High evoked

19% (14/72) startle rate that was smaller but was not significantly different from its linear addition at 31% (22/72); *p=.089*.

In order to compare the differences in effectiveness between multimodal responses, we used a two-tailed Fisher's exact test. The results showed AV Medium condition's startle rate was significantly larger than the startle rate evoked by AV High stimuli, p=.002, OR=3.91. However, the startle rate during AV low stimulus conditions and the startle rate during AV Medium were not significantly different from each other, p=.094. The startle rate during AV Low stimulus conditions was also not significantly different from the startle rate during AV High stimulus condition, p=.36.
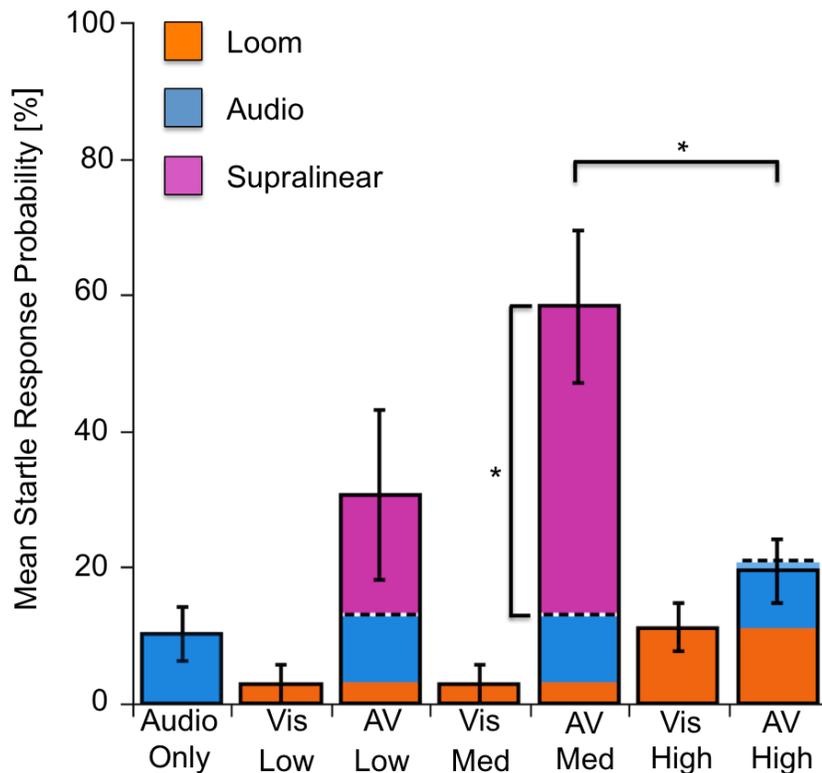

Figure 6. Mean startle response probability for a unisensory and multisensory stimulus conditions. Dashed line in combined conditions indicates the assumed linear summation of individual auditory and visual startle frequencies.

Note: unimodal visual frequencies are adjusted for each audio trigger time for each AV condition. *: $p<.01$ for one – sided Fisher's exact test between multimodal results and linear estimation as well as two-sided Fisher's exact test for comparisons between multimodal conditions. N= 6

Discussion

Multimodal Stimuli: Supralinear versus Sublinear Addition of Startle Response Frequency

The main results of the study were that multimodal integration of visual and auditory stimuli in the M-cell system occurs and this is consistent with the inverse effectiveness principle (IEP). Specifically, we found supralinear integration of two low effective stimuli. Given that the M-cells are the final common path for motor decisions in the startle network decision, these results suggest that single neurons indeed can provide a neural correlate for the IEP phenomenon. In mammals, there is some evidence for IEP in the level of individual cells. Electrophysiological recordings from singular granule cells in the cerebellar cortex of Lister-hooded rats show that simultaneous presentation of auditory and visual stimulation produce supralinear addition of spiking in those cells (Ishikawa, Shimuta, & Håusser, 2015). Work in single superior colliculus neurons has not only demonstrated IEP supralinear addition, but also suggest that the magnitude of this addition decreases as the difference between intensity of the unimodal stimuli increases (Miller *et al*, 2015).

In regards to how our results fit in with previous findings in fish, Page (1970) tested audio-visual (light) integration in the tegmentum of common goldfish and reported linear addition of the neural response, but not supralinear addition. Mu *et al* (2012*)* work in the startle responses larval zebrafish found that presenting visual stimulation briefly before a subthreshold audio stimulus produced supralinear addition in both behavioral and eletrophysical responses but did not report linear or sublinear addition. However, it is important to note that both of these studies used light flashes as their visual stimulation, which are significantly shorter stimuli and

have been shown to stimulate the M-cells differently from looming stimuli (Preuss *et al*, 2006, Dunn *et al*, 2006). In general, methods, stimulus conditions and context described largely vary in the literature of multimodal integration and thus might not allow for direct comparison in all cases (Stevenson *et al*, 2014,Van Atteveldt *et al*, 2014; ten Oever *et al*, 2016).

On the other hand, it has been proposed that multimodal integration is typically either linear or sublinear (Stanford & Stein, 2005; Stanford e*t al*, 2007). In contrast, examples of supralinear interaction of stimuli are rare. In Holmes and Spence 's review (2005), supralinearity of responsiveness to two weak stimuli occurring almost simultaneously is explained through the increase in signal-noise relationship wherein individual weak stimuli may be perceived as noise but perceived as a signal when together. These authors provide a functional example of this idea with the scenario of a cat breaking a vase: the peripheral view of a cat running or the sound of the vase breaking alone may not alert you, but both simultaneously most likely will. Extending this example to the goldfish's perspective, a weak sound could be a false alarm, but a weak sound paired with a shadow (such as the loom simulates) is more likely to be a predator and trigger a response. The context dependent selectivity of supralinear addition and the common occurrence of either sublinear or linear addition may provide another explanation for variation in results amongst multimodal studies and conditions.

Biological significance

Given, the scenario of a diving bird hiding the water surface during a predator attack on a fish gives our results a putative relevant biological context. Previous work using visual looms has demonstrated that startle responses occur within 80% of loom duration, i.e. before apparent collision with an object (Preuss *et al*, 2006; Dunn *et al*, 2016). Several studies have shown that,

because collision means confrontation with a predator, an animal's behavior in these instances is based on calculating this critical period and responses may differ according to context (Santer *et al*, 2012; Scarano & Tomsic, 2014; McMillan & Gray, 2015). For example, the speed and frequency of an animal's response may change according to a predator's movements (Scarano & Tomsic, 2014; McMillan & Gray, 2015), the presence of conspecifics (Bennaragama & Gray, 2014; Fischer *et al,* 2015) or information provided by a physical trait of the predator such as the slight movements of a bird's wing (Santer *et al*, 2012).

The AV High stimulus used here is defined by a very late occurrence of the audio stimulus during the visual loom (95%), later than most startle responses typically occur. In a biological explanation involving the specific context of the startle response and the projection of our chosen loom, the timing of the sound trigger for AV High could be considered later than a fish would respond if it hopes to escape from the predator. The decrease in startle frequency observed in the AV High condition compared to other multimodal conditions may be due to either most of that startle responses already occurring and/or the M-cell already reaching its peak of excitation. Response frequency is slightly reduced in our results, suggesting that inhibitory circuits at the level of the Mauthner cell may play a role as well in the restriction of "late" startle responses. Future investigation of using electrophysiological methods might shed light on this idea.

Furthermore, considering that inverse effectiveness principle may be context dependent (Stanford & Stein, 2005; Stanford e*t al*, 2007; Van Atteveldt *et al*, 2014; Ten Oever *et al*, 2016), looking into how social-related factors interaction with integration effects on startle behavior may provide a means to test this concept. Fischer *et al*'s (2015) work with guppies has shown changes in startle behavior when conspecifics are present. Moreover, our lab has done research

involving the startle hierarchy in the African cichlid *Astatotilapia burtoni* and how social stress can modulate startle behavior and physiology (Neumeister *et al*, 2010; Whitaker *et al*, 2011; Ryan *et al*, 2011). Since it has an important role in modulating the startle response and M-cell, it is possible that sociality may affect multimodal integration in fish as well.

Summary and Scientific Impact

Our results show that the inverse effectiveness principle can be behaviorally observed and quantified in goldfish. The startle escape frequency is directly correlated to excitation of the cell triggering the behavior, thus the significance of singular neurons in decision-making and multimodal integration for this vital behavior is evident. With the accessibility of these neurons to electrophysiological, pharmacological and genetic manipulation (Korn & Faber, 2005; Medan & Preuss, 2014) as well as the history of using e.g., zebrafish to simulate neural diseases (Parker *et al*, 2014), the teleost startle system has proven to be a flexible model for studying several neural processes.

Furthermore, the use of teleost fish in studying multimodal integration in particular is not a completely new concept. In fact, interest using teleost fish has increased over the years and expanded to explore the multisensory aspects of various behavioral endpoints. Such studies have focused on the convergence of modalities in, e.g. object location, schooling behavior and spatial learning in electric fish (Moller, 2002; Sawtell, 2010). Several studies have also investigated the role of stimulus integration and individual sensory organs on predatory behavior (New, 2002; Montgomery *et al*, 2002). Overall, the M-cell's long history and our results here provide merit in suggesting expansion of the use of the teleost startle system as a model in the field of multisensory integration for both behavioral and neural research.

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