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Review

Tactile, acoustic and vestibular systems sum to elicit the startle reflex

John S. Yeomans[a,*], Liang Li[b], Brian W. Scott[c], Paul W. Frankland[d]

[a]*Department of Psychology, University of Toronto, Toronto, Ont., Canada M5S 3G3*
[b]*Department of Psychology, Peking University, Beijing 100971, People's Republic of China*
[c]*Department of Pharmacology, Medical Science Building, University of Toronto, Toronto, Ont., Canada M5S 3G3*
[d]*Department of Neurobiology, Brain Research Institute, Gonda Building, 695 Young Dr S., University of California at Los Angeles, Los Angeles, CA 90095, USA*

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Abstract

The startle reflex is elicited by intense tactile, acoustic or vestibular stimuli. Fast mechanoreceptors in each modality can respond to skin or head displacement. In each modality, stimulation of cranial nerves or primary sensory nuclei evokes startle-like responses. The most sensitive sites in rats are found in the ventral spinal trigeminal pathway, corresponding to inputs from the dorsal face. Cross-modal summation is stronger than intramodal temporal summation, suggesting that the convergence of acoustic, vestibular and tactile information is important for eliciting startle. This summation declines sharply if the cross-modal stimuli are not synchronous. Head impact stimuli activate trigeminal, acoustic and vestibular systems together, suggesting that the startle response protects the body from impact stimuli. In each primary sensory nucleus, large, second-order neurons project to pontine reticular formation giant neurons critical for the acoustic startle reflex. In vestibular nucleus sites, startle-like responses appear to be mediated mainly via the vestibulospinal tract, not the reticulospinal tract. Summation between vestibulospinal and reticulospinal pathways mediating startle is proposed to occur in the ventral spinal cord.

Keywords: Pons; Medulla; Evolution; Trigeminal; Giant neurons

Contents

1. Introduction

The startle reflex is the most extensive of all reflexes, activating hundreds of competing muscles throughout the body in a stereotyped way [12,15,19,28,34,49,53,67,73].

* Corresponding author. Tel.: +1-416-978-7618; fax: +1-416-978-4811.
E-mail address: yeomans@psych.utoronto.ca (J.S. Yeomans).

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The startle reflex is easy to observe, and is easy to elicit with appropriate acoustic stimuli [12,16]. The short latency of the acoustic startle reflex has been useful in identifying neurons and circuits mediating the response [19,47,90].

The startle reflex can be modified in several ways [1,16,41] and so has provided a model system to study plasticity and learning. Startle is increased by threatening stimuli (e.g. pictures of attacking animals in humans, stimuli paired with shock or anxiogenic drugs in rats) [8–10,20,29,51,71]. Startle is reduced by rewarding or threat-reducing stimuli (e.g. erotic pictures in humans, stimuli associated with rewards or anxiolytic drugs in rats) [18,20,51,77,81]. Consequently, startle has proven to be a useful probe for studying the psychology, anatomy and pharmacology of emotions and emotional disorders [9,20,50].

The occurrence of acoustic startle in virtually all mammals studied, and at all postnatal ages in humans [5], suggests that the startle must have some important and lasting survival value. There is, however, no generally accepted view on the function of the acoustic startle response in the literature. The first suggestion was that the acoustic startle merely functions to interrupt ongoing behaviors [49, p. 317]. Graham [32] concluded that "…it is difficult to see in what way the wide-spread flexor contractions [in startle] offer protection". Recently, it was proposed that the acoustic startle "…probably represents a protective response, because its behavioral pattern consists of reactions that are likely to prevent serious injury from an attack…" [47, p. 35]. This idea, while almost certainly correct, does not explain what the possible relation might be between acoustic stimuli, attacks and injury.

Acoustic startle is often maladaptive in noisy urban life. If elicited during coordinated motor activity, the startle response interferes with that activity [49]. Background noise increases the sensitivity to startling stimuli [40,42]. Furthermore, startle disrupts sensory and cognitive processing [33] and is followed by heart rate increases and other sympathetic activation [32].

We review evidence here that the tactile and the vestibular systems can also activate startle, and that cross-modal summation of acoustic, tactile and vestibular stimulation is more effective than single-modality summation. The evidence for cross-modal summation further suggests a critical survival function for the startle reflex in protecting against blows, and may even suggest an evolutionary principle for brain stem organization. We then compare the putative startle-mediating circuits for each modality, and propose where summation occurs between modalities.

Previous reviews have emphasized the neural circuits mediating acoustic startle [16,47,52,90], and the inhibition and potentiation of startle [20,21,24,41,50]. Reviews of the eyeblink reflex have compared acoustic and trigeminal influences, and neural pathways [6,65]. In this review, we emphasize tactile and vestibular influences on the full startle reflex, the neural pathways for these, and their relation to the better-known acoustic pathways.

2. Stimuli that elicit startle

Startle-like responses (bilaterally symmetric responses of the whole body at very short latencies) are evoked by strong and sudden acoustic, tactile or vestibular stimuli in cats and rats [34,38,54,55,80,90]. Very bright light flashes can elicit full eyeblink responses or EMG responses in eye-closure muscles in humans [21,49]. Olfactory or visual stimuli alone, however, are not known to reliably evoke whole-body startle responses [17,49].

All three modalities that activate startle use fast (i.e. ionotropic) mechanoreceptors that detect mechanical forces applied to the body. In the somatosensory system, these stimuli involve displacement of the skin and muscles. In the vestibular system, head displacements result in movements of inner ear fluids and otoconia to activate hair cell mechanoreceptors. In the auditory system, acoustic stimuli conduct via air and bones to activate hair cells in the cochlea. This suggests that the mechanical actions to the body surface may be important for startle. By contrast, olfactory and visual systems respond via slow (i.e. G-protein-coupled) receptors [72].

2.1. Tactile stimuli

Electrical stimulation of the skin or trigeminal nerve is an effective stimulus for startle that activates somatosensory systems without activating other sensory systems [43,80]. In humans, cutaneous and acoustic stimuli evoke a similar pattern of muscle activation, suggesting that shared motor systems generate tactile and acoustic startle responses [12,49]. In rats, unilateral trigeminal nucleus stimulation activates a startle-like response at latencies of 6–7 ms [53,78]. Furthermore, trigeminal and acoustic stimuli sum powerfully in eliciting startle or eyeblink reflexes [53,69].

The lowest thresholds yet reported for activating startle-like responses in the brain are in the ventralmost quarter of the spinal trigeminal tract and the adjacent trigeminal nuclei (principal nucleus, Pr5, and spinal trigeminal nucleus, pars oralis, Sp5O) [54,78]. These thresholds (11–50 μA for a 0.1 ms duration pulse) are an order of magnitude lower than in the nearby cochlear nuclei, and one-quarter those in the most sensitive reticular formation sites. These ventral Pr5 and Sp5O regions receive input from the ophthalmic division of the trigeminal nerve, originating in receptors of the head dorsal to the nose (including axons carried by the supraorbital branch) [83]. These sites are much more sensitive than the more dorsal regions of Pr5 and Sp5O receiving inputs from the maxillary division of the trigeminal nerve, originating in receptors of the mouth, vibrissae and ventral face. In humans, cold-water jets elicited startle if delivered to the back between the shoulder blades [49].

A commonly used tactile stimulus for startle in animals is

a strong air-puff. Although air-puffs can evoke startle, the startle response is much weaker if the rats are deafened before testing [82]. This suggests that the acoustic component of the stimulus is as important as the tactile component to air-puff induced startle [25]. Therefore, an air-puff is not an optimal tactile stimulus, perhaps because it activates hair receptors better than other cutaneous receptors.

2.2. Acoustic stimuli

Startle response systems are relatively insensitive to air-conducted acoustic sources (>80 dB in most situations). Startle is evoked at all frequencies in the audible range in humans and rats, with a peak sensitivity similar to that for normal hearing [26,68]. There is strong binaural summation for startle, with a preference for acoustic stimuli delivered near the midline to activate both ears simultaneously [48,53]. If the acoustic stimulus increases gradually to 120 dB over a 50 ms period, there is no startle response. The rapid temporal summation for acoustic startle (within 20–50 ms in humans, and within 12 ms in rats) differs from the slower temporal summation for loudness perception (within about 200 ms in humans) [6,26,31]. Therefore, the acoustic stimulus for startle must have a sharp and sudden onset.

Startle responses can be evoked by stimulation of the cochlear nuclear complex in rats [19,54,78]. The lowest threshold sites near the cochlear nuclei were not in the cochlear nuclear complex itself (150–1000 μA for a 0.1 ms duration pulse), but in the medially adjacent caudal Pr5 and rostral Sp5O (below 50 μA) [11,78]. This suggests that the electrical stimulation applied to the medial half of the cochlear nucleus also involves activation of non-acoustic trigeminal and/or vestibular systems (a point that will be discussed later).

2.3. Vestibular stimuli

Intense free-fall stimuli evoke a motor response nearly identical to the acoustic startle in rats, cats and humans [2,34]. In cats, stimulation of the vestibular branch of the VIII nerve evokes a startle-like response [38]. In rats, stimulation of the vestibular nucleus evokes a startle-like response at very short latencies (5–6 ms in hindlimb muscles) that sums strongly with acoustic or trigeminal stimuli that produce startle [55]. The most sensitive sites were in the ventral part of the lateral vestibular nucleus, near the efferent fibers of the lateral vestibulospinal tract. More work is needed to define the precise head perturbations that are most effective in eliciting startle, and how these sum with natural acoustic or tactile stimuli.

In the Gruner [34] study, vestibular stimulation was induced by releasing animals into a free fall. Free-fall results in both the removal of antigravity body supports, detected by the somatosensory system (e.g. in extensor muscles), and the removal of gravity signals in the vestibular system (e.g. in otolith detectors). EMG responses evoked by free fall showed a pattern of muscle activation similar to that for acoustic startle. In avestibular humans, the startle-like response to free fall still occurred, suggesting that the somatosensory stimuli alone can elicit startle [2]. Therefore, free-fall is not an ideal vestibular stimulus.

2.4. Relation of startle to eyeblink

Electrical stimulation of the trigeminal nerve above the eye (the supraorbital branch of the ophthalmic root) evokes a short-latency eyeblink (e.g. Refs. [70,74]). However, eyeblink reflexes involve more than the eyeblink component of startle. First, the eyeblink reflex can be evoked by bright flashes [50,87], or by saccadic gaze shifts [23], but the whole-body startle reflex cannot [16,49]. Second, the shortest latency EMG correlate of the trigeminally evoked eyeblink reflex (called R1 in the orbicularis oculi muscle) is a unilateral response (latency 11 ms in humans), but the startle reflex is bilaterally symmetric [70]. Third, R1 is not evoked by acoustic stimulation, but the startle reflex is. The longer latency EMG component, called R2 (latency 35 ms in humans), is evoked by acoustic stimulation, is bilateral, and is associated with full eye closure [4]. These results suggest that the R2 is relevant to the eyeblink component of startle, but R1 is not (e.g. Ref. [41]).

2.5. Summation between tactile, acoustic and vestibular stimuli

When tactile and acoustic stimuli are matched to elicit equivalent startle responses, summation between equivalent stimuli can be measured at various interstimulus intervals (ISIs) [54]. The stimulus pairs were either two acoustic stimuli, or two trigeminal nucleus stimuli, or one trigeminal nucleus and one acoustic stimulus. Within a modality, either two acoustic or two trigeminal stimuli produced strong summation, with a rapid decline as the ISI increased from 3–15 ms (Fig. 1A and B) (see also Ref. [59]). The cross-modal summation between noise and trigeminal stimuli (Fig. 1D), however, was almost twice as strong as the intra-modal summation (Fig. 1A–C). For startle, stimulation of the trigeminal nucleus resulted in peak acoustic/trigeminal summation when the acoustic stimulus preceded the trigeminal stimulus by 3–5 ms, due to the 1 ms conduction time from the speaker to ear, plus 2–4 ms to activate the cochlear nucleus (Fig. 1D) [54].

Cross-modal summation between acoustic and vestibular nucleus stimulation, or between trigeminal nucleus and vestibular nucleus stimulation, was also very strong. That is, the startle response was 3–5 times larger than if vestibular nucleus or acoustic stimulation was presented alone (Fig. 2). The summation was the strongest if the vestibular stimulation preceded the acoustic stimulation by 5–7.5 ms (Fig. 2B), suggesting that the vestibular nucleus substrates for startle are even closer to the cross-modal integrator for startle than the trigeminal nucleus. Furthermore, the latencies to hindlimb EMG responses following vestibular

nucleus stimulation were about 1 ms shorter than the shortest latencies in the trigeminal or cochlear nuclei. Summation between all three modalities was slightly stronger than stimulation of two modalities [55].

These data indicate that the startle is most sensitive to combinations of trigeminal, acoustic and vestibular stimulation, especially when these stimuli arrive nearly simultaneously on the surface of the head. The auditory component is most effective if the onset is extraordinarily fast, and the frequency range is very broad. Location is not critical for auditory stimuli, but tactile stimuli are more effective if applied dorsally to the head or back.

2.6. Summation of stimuli for eliciting eyeblink

Cross-modal summation is similar for the R2 component of the eyeblink reflex in humans. That is, cross-modal summation of trigeminal and acoustic stimuli is about twice as strong as intramodal summation of trigeminal or acoustic stimuli [37,69,75,76] (Fig. 1E). The R2 response was strongest when the supraorbital stimulus was slightly after the acoustic stimulus and declined sharply when the two stimuli were separated by more than 20 ms [7,62,74,76]. The peak summation was at an ISI of 20 ms, due perhaps to use of an acoustic stimulus with a 20 ms rise time [76] (see the caption of Fig. 1). By contrast, the R1 response was strongest if the acoustic stimulus preceded the trigeminal stimulus by about 60 ms, again suggesting that the R1 response is less relevant to startle than the R2 response.

3. Startle as a protective response to head and body blows

What is the natural stimulus that evokes nearly simultaneous tactile, acoustic and vestibular stimulation? A blow to the head, neck or upper body (Fig. 3) induces a strong and sudden acoustic stimulus, and, simultaneously, strong and sudden tactile and vestibular stimuli. Impact stimuli have a rapid onset and induce a wide range of acoustic frequencies. Blows are more likely to come from the exposed dorsal surface of rodents rather than from below, which may explain why tactile stimulation of the dorsal head and body is more effective in eliciting startle.

The form of the startle reflex in each species protects them from such blows. In humans (Fig. 3, right), the eyes close, the neck flexes in the dorsal direction, while the mouth and ventral neck muscles tense [49]. The shoulders are elevated in the rostral direction, while the back is elevated in the dorsal direction. These actions deflect dorsal blows away from the neck, and stiffen the muscles against penetration. At the same time, thoracic and abdominal muscles stiffen, the elbows are pointed outward, but the forelimbs stay in with the hands clenched to protect abdominal areas. The bilateral symmetry of the response leaves sensitive areas minimally exposed in the brief period before the source of blow can be assessed, and directed evasive or defensive action can be initiated. The short-term loss in coordination of motor skills, cognitive attention and visual input is a small price to pay for this protection against strong blows.

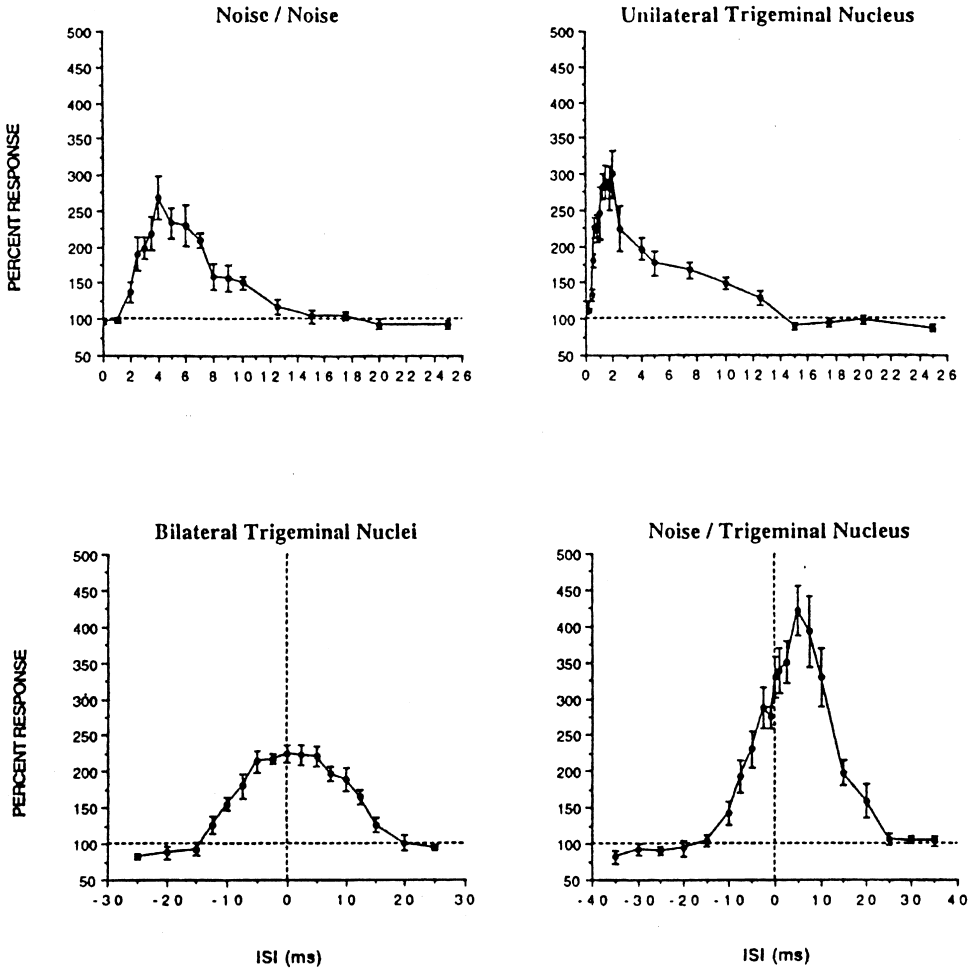
In rats, the acoustic startle response results in shortening of the body due to retracting the head into the body, and arching of the spine dorsally (Fig. 4). These movements reduce the exposure of the neck region and force more skin and hair into that smaller space. The dorsal arching of the back also can deflect an impacting force away from the head and neck.

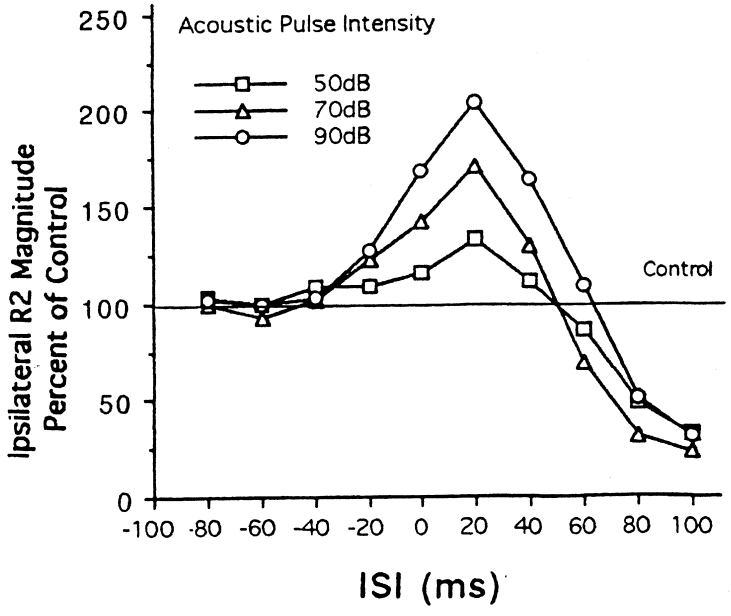
Although objects falling from above can be life-threatening, they are perhaps rare. By contrast, predatory attacks are more common and dangerous. Mammals have excellent vision in front of their heads, or to the sides in some species, but poor vision or no vision caudally and dorsally. Also, their best defensive attack systems (teeth and claws) are in front and below [3]. So, predators often attack from behind and above, and often target the neck region.

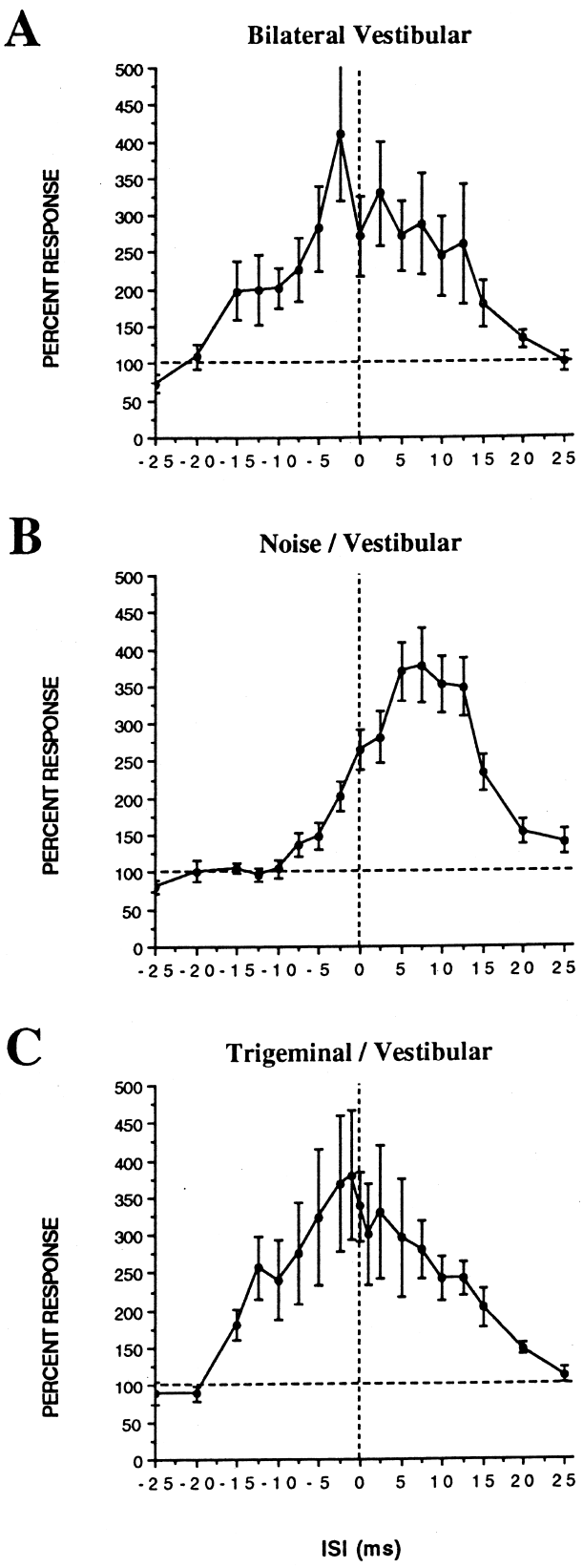
According to this view, the startle reflex is a necessary response to protect against life-threatening blows or predatory attacks. During a head impact, dorsal tactile systems are most sensitive, but acoustic and vestibular systems provide information about the mass and timing of mechanical stimuli that contact the head. Startle is sensitive to rapid-onset acoustic transients that provide information about the onset of head impact, but is insensitive to distal or delayed acoustic stimuli, conducted slowly by air at the speed of sound, that provide information about the larger acoustic environment. Vestibular stimulation provides information about the mass and force of the impacting stimulus, important in evaluating the threat of coordination loss and brain injury that can result from head acceleration. Therefore, cross-modal combinations of stimuli that best simulate life-threatening head and body impacts are most effective in eliciting startle.

Although startle is primarily a fast protective response in

Fig. 1. Cross-modal summation between tactile and acoustic stimuli is stronger than summation within each modality. (A) Startle reflex in rat. Two acoustic stimuli elicit a startle response that is twice as strong if the two noises are 4 ms apart. (B) Two electrical stimuli to the trigeminal nucleus increase startle by almost three times if the stimuli are 1.5 ms apart. (C) Two electrical stimuli to opposite sides of the trigeminal nucleus (avoiding the neural refractory period in one site) double the startle response. (D) One acoustic and one trigeminal stimulus increase startle by over four times. The 4 ms offset in the peak of cross-modal summation is due the time delay for acoustic information to enter the brain stem (from Ref. [54]). (E) In the human eyeblink reflex, trigeminal summation with acoustic stimulation depends on the intensity and timing of the acoustic stimulus. The optimal summation occurs with nearly simultaneous tactile and acoustic stimuli. The peak of cross-modal summation is delayed by 20 ms here, due to the 20 ms rise time of the acoustic stimulus used (from Ref. [76]).


Noise / Noise
Unilateral Trigeminal Nucleus
Bilateral Trigeminal Nuclei
Noise / Trigeminal Nucleus
PERCENT RESPONSE
ISI (ms)


Acoustic Pulse Intensity
50dB
70dB
90dB
Control
Ipsilateral R2 Magnitude
Percent of Control
ISI (ms)



our view, secondary benefits of startle may include behavioral arrest, preparation for action, arousal, sympathetic activation and visual display. These secondary effects can assist in the recovery from startle, and facilitate the subsequent behavioral responses needed to escape from predation and blows.

The stimulus intensities needed for cross-modal summation are far below the intensities required for startle when these stimuli are presented individually. As seen in Fig. 1E, acoustic stimuli 40 dB below threshold for startle reliably increased the R2 response evoked by subthreshold trigeminal stimuli [76]. Weak acoustic or tactile prepulses that the normally inhibit startle can excite eyeblink or startle responses when ISIs are 0–20 ms (e.g. Refs. [41,74]).

4. Neural circuits for startle

4.1. Integrators

Integration of the cross-modal information for startle must occur in a system shared by tactile, acoustic and vestibular modalities (e.g. Refs. [36,75]). These integrators must have rapid input from each modality, and rapid outputs to muscle groups throughout the body to evoke a whole-body startle reflex at short latencies.

Essential neurons for the acoustic startle response in rats and cats are found in the ventrocaudal pontine reticular formation (PnC) [19,48,52,86,90] (Fig. 5). Lesions of PnC block the startle response elicited by acoustic or air-puff stimuli [14,19,35,48,52]. In this PnC site, a small cluster of giant neurons, the largest neurons in the entire reticular formation, are activated by high-intensity acoustic stimulation at latencies of 3–8 ms [56,57,86,90]. PnC neurons can also be activated by tactile stimuli applied by electrical stimulation on the body surface [66,80], or by stimulation of the vestibular nerve [66].

Large neurons projecting directly to the PnC have been found in cochlear, vestibular and spinal trigeminal nuclei of rats [39,46,91]. Within each primary sensory nucleus, startle is electrically elicited by short refractory period substrates (i.e. 0.3–0.8 ms), suggesting that large-diameter, myelinated axons mediate startle [55,78,90,92]. These short refractory periods further show that the slower pain fibers (A-delta and C fibers) do not mediate the trigeminal startle response.

In rats, large cochlear root neurons project to PnC giant neurons and to ventrolateral tegmental nucleus (VLTg)

Fig. 2. Cross-modal summation between vestibular nucleus, trigeminal nucleus and acoustic stimulation for eliciting startle (from Ref. [55]). Panel A: Summation between stimulation of each side of the vestibular nucleus (with the solid line showing bilateral stimulation of principal trigeminal nucleus). Panel B: Summation between acoustic stimulation and vestibular nucleus stimulation (with the solid line showing acoustic/trigeminal nucleus summation). Panel C: Summation between trigeminal nucleus and vestibular nucleus stimulation.

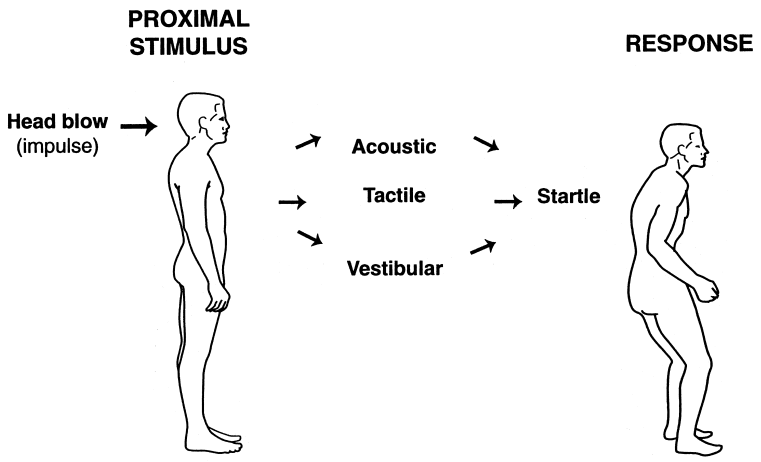


Fig. 3. The form of the human acoustic startle reflex at the peak of responding (right drawing and below) is taken from drawings of Landis and Hunt [49], based on high-speed film pictures. Above, lateral view of body; Below, frontal view of head and neck. A head or upper body blow elicits startle by activating auditory, tactile and vestibular systems at nearly the same time.

neurons most important for acoustic startle [58]. Lesions of cochlear root neurons block acoustic startle [52]. In addition, the anteroventral cochlear nucleus can mediate acoustic startle: The lateral half of this nucleus is activated by acoustic stimulation within 2 ms, and this acoustic-startle-mediating activation is relayed to the PnC and VLTg about 2 ms later [78,88]. Also, dorsal cochlear nucleus, superior olivary nucleus and VLTg neurons contribute less strongly to acoustic startle [60,84,88,90]. The trigeminal projections to PnC are from caudal Pr5 and rostral Sp5O, most heavily from large neurons of the ventralmost region [30]. Only sparse projections to PnC are found from more dorsal Sp5O regions. These large neurons in the ventral-most Sp5O are the largest neurons in the spinal or principal nuclei

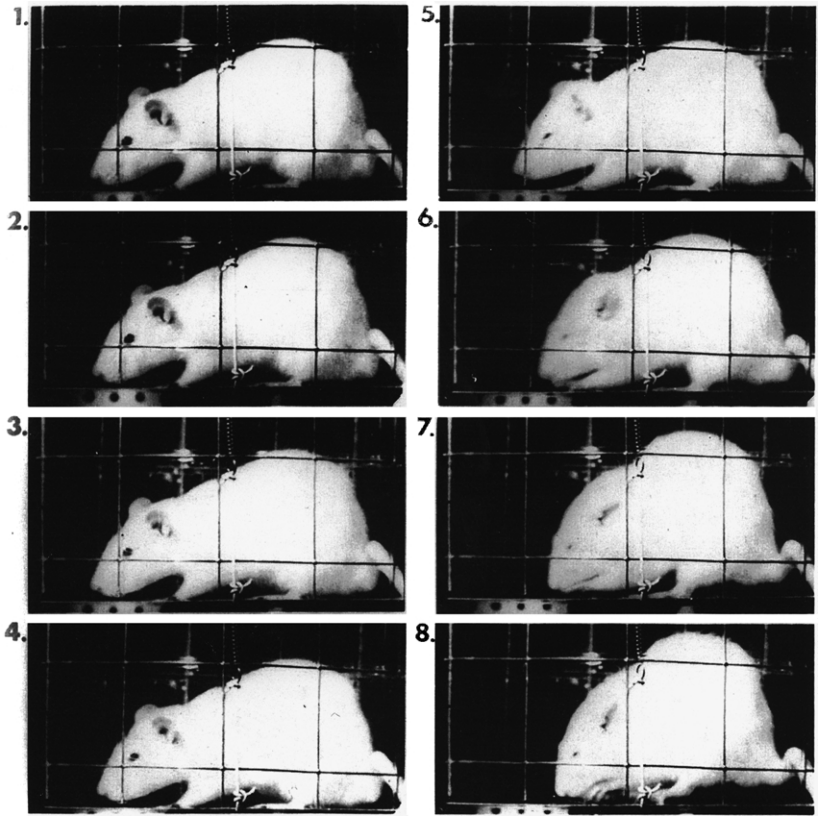


Fig. 4. The form of the rat startle reflex, shown immediately before (pictures 1 and 2), and from 5-38 ms (pictures 4–8), and after the onset of the acoustic stimulus. (From Horlington [44]).

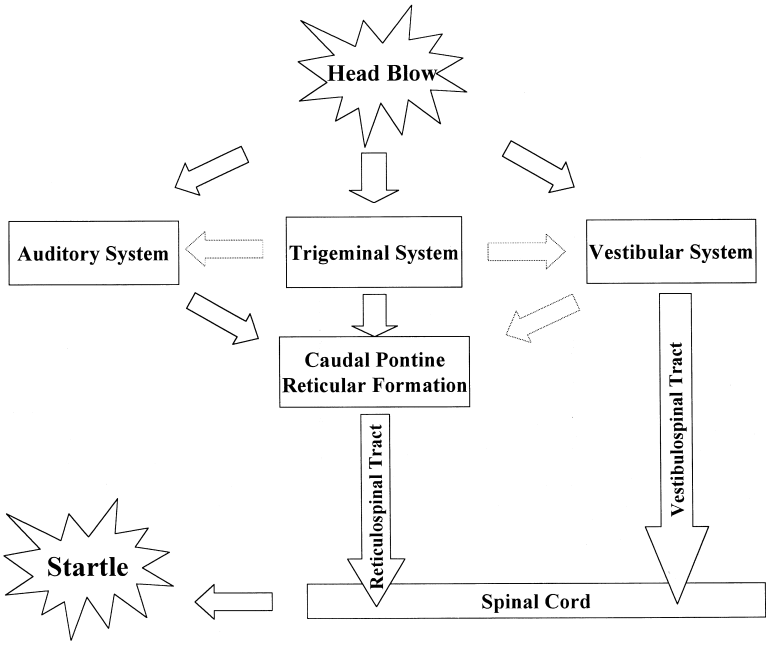


Fig. 5. Proposed circuits for trigeminal, acoustic and vestibular startle responses, showing convergence of information in the PnC and spinal cord (based on Ref. [55]).

of the trigeminal, contrasting with the smaller neurons found elsewhere in Pr5 and Sp5O [83]. Terminals of these Sp5O projection neurons surround the soma and proximal dendrites of giant neurons in the PnC [30,39,57]. Unfortunately, recordings from these large Sp5O and cochlear root neurons have not been reported, so their physiological properties are not known.

In vestibular nuclei, the neurons projecting to PnC are concentrated in the ventromedial-most part of the lateral vestibular nucleus in a narrow band [30]. These are large neurons, not quite as large as the giant Deiter's cells of the dorsal and lateral parts of the lateral vestibular nucleus. They are located amid the lowest threshold sites for electrically evoked startle in the ventral-most part of the lateral vestibular nucleus [55].

The R2 component of eyeblink in humans and rodents also uses a polysynaptic pathway from the spinal trigeminal nuclei passing through the pontine reticular formation, but the critical reticular formation neurons and nuclei for eyeblink are not yet known [63,65]. The effects of pontine reticular formation lesions on startle responses evoked by purely tactile or vestibular stimulation alone have not been tested either.

PnC giant neurons project directly and indirectly to motoneurons in the brain stem and spinal cord. Each giant neuron sends a large axon that branches and makes thousands of terminal contacts near hundreds of motoneurons and interneurons in rats and cats [27,57,61,71]. In this way, an integrated startle response appears to be organized by a small number of command neurons in a cluster, with rapid cross-modal input and with rapid, diffuse outputs [90].

4.2. Motor circuits for trigeminal and vestibular startle reflexes

An early study concluded that the response to vestibular stimulation appeared to involve activation of reticulospinal neurons in cats [66]. Stimulation of the vestibular nucleus evokes a startle-like response at EMG latencies that are about equal to those for PnC, and about 1 ms shorter than the stimulation of Pr5 or cochlear nuclei [55]. This suggests that the vestibular nucleus stimulation can activate startle via a more direct route than the synaptic relay through the PnC and reticulospinal tract. Furthermore, stimulation of the VN and medulla together shows that the summation between sites is interrupted at ISIS of 0–0.6 ms, whether the VN stimulus is presented first, or the medulla stimulus is presented first. This symmetric collision-like effect (found using either EMG responses or whole-body startle response) suggests that the two sites are connected by continuous axons, along the lateral vestibulospinal tract [55,89]. Therefore, the vestibulospinal tract can elicit startle as well as the reticulospinal tract.

Both reticulospinal and lateral vestibulospinal tracts descend lateral to the medial longitudinal fasciculus in the medulla, and then through the spinal cord in the medial part of the ventral columns. Both tracts include very fast-conducting axons (80–120 m s^{-1} in cats) [85,86]. Both tracts terminate heavily on interneurons in layers 7 and 8 at all spinal levels, with weak projections to layer 9 motoneurons at some levels [79]. This suggests that the hindlimb startle responses are summed in ventral spinal cord interneurons and motoneurons. More work is needed to define which neurons in the spinal cord respond to reticulospinal

and vestibulospinal input from acoustic, tactile and vestibular stimuli that can evoke startle.

The pathways for trigeminal startle are less clear, although it is clear that some of the trigeminally evoked startle is mediated through the PnC [14]. The latencies of hindlimb EMG responses are about 1 ms longer following stimulation of Sp5O sites versus medial medulla sites [55]. Stimulation of these two sites in combination resulted in strong summation, but an asymmetric collision effect indicates that there is a synaptic relay connecting the two sites. The synaptic connection is strong with a short delay (0.4 ms) implying a monosynaptic connection. This connection may occur in the PnC or in the vestibular nucleus, which also receives trigeminal input [13].

Trigeminal stimuli for eyeblink reflexes in cats and guinea pigs appear to relay through spinal trigeminal nucleus caudalis, as well as nucleus oralis [65]. The coordination of tactile stimuli from the body for startle with those from the head is not yet determined.

Fig. 5 shows the proposed connections mediating whole-body or hindlimb startle. Three sensory systems, acoustic, trigeminal and vestibular, are activated by strong mechanical stimuli impacting the body surface. In each modality, primary sensory neurons activate large secondary neurons in primary sensory nuclei of the hindbrain. Acoustic stimuli activate cochlear root neurons and anteroventral cochlear nucleus neurons that relay to PnC giant neurons (largely via other auditory nuclei, such as superior olivary nuclei and VLTg not shown). These giant neurons send large axons in the reticulospinal tract to directly activate layer 7 and 8 interneurons (and some motoneurons) to activate muscles throughout the body. Vestibular stimuli activate large vestibular nucleus neurons that send large axons in the vestibulospinal tract to activate layer 7 and 8 interneurons (and some motoneurons) to activate muscles in a similar way. Finally, trigeminal stimuli may use either or both motor pathways to affect startle.

These circuits for the mammalian startle reflex have many similar principles with those for fast escape reflexes in many lower vertebrates and invertebrate species, such as earthworm, squid, insects, and teleost fish [22]. That is, multisensory inputs converge on giant neurons found in the hindbrain of lower vertebrates or caudal head ganglia of higher invertebrates. These giant neurons, or command cells, connect via large axons to activate hundreds of motoneurons in the spinal cord of vertebrates or ventral nerve cord of higher invertebrates, resulting in a fast motor response involving most of the body.

5. Possible coevolution of hindbrain systems mediating startle

To optimally protect the body during and immediately after impact stimuli, startle systems must minimize response latency. The three modalities that elicit startle activate fast mechanoreceptors whose primary axons enter the brain stem via cranial nerves V and VIII. The spinal branch of the trigeminal tract passes caudally into Pr5 and Sp5O near cochlear and vestibular nuclear complexes in the caudal pons and rostral medulla. By contrast, olfactory and visual modalities that do not elicit startle use slower G-coupled receptors, and enter the brain via the forebrain (cranial nerves I and II), a long distance from startle effector systems in the hindbrain and spinal cord.

The most critical primary nuclei for startle are found in the caudal pons and rostral medulla surrounding the key integrating neurons in the PnC and the vestibular nucleus. Each sensory system uses large neurons, fast axons, and a few strong synapses to elicit startle quickly. Converging inputs from the three mechanoreceptor systems are summed at high-threshold PnC giant neurons located close to these inputs, and in spinal cord interneurons.

In this way, information from each system about the strength of stimulation, time of arrival at the body surface and onset transients can be combined to maximize the reliability of the startle response decision. This arrangement allows for fast processing of the cross-modal information for startle, as well as rapid communication between these systems. In our view, the critical survival value of startle in protecting against blows may have shaped the anatomical evolution of these systems together in the hindbrain to ensure a minimum-latency protective response to life-threatening impact stimuli.

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