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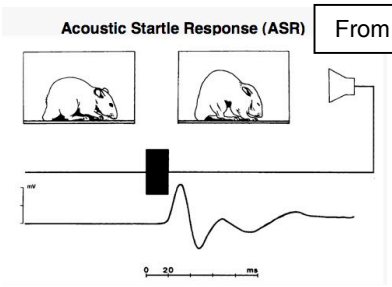
Acoustic Startle and Prepulse Inhibition

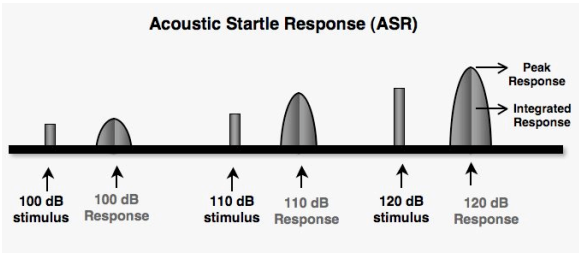
Introduction and Basics

Acoustic Startle Reflex

When we hear a loud, abrupt and unexpected sound, we startle, a phenomenon that is common to all mammals [4]. The response consists of a rapid and involuntary extension and then flexion of a series of muscles. Although the startle response is a reflex, it can be modulated by many different stimuli. Startle reactions tend to be higher in the presence of threats, fear and pain [5-11] and are conversely decreased by anxiolytics [6, 12-14].

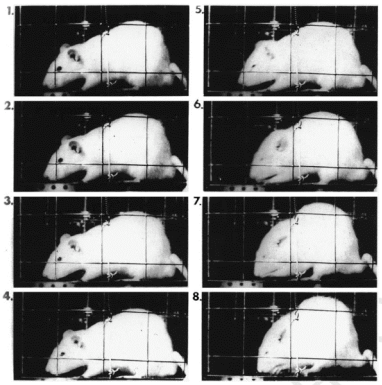


From [3]



The pharmacology and circuitry of this reflex is virtually identical in rodents and humans [15-23]. Startle response is measured in rodents using automated startle chambers or "stabilimeter chambers", with detectors recording whole-body reaction. In humans, the movements of oculomotor muscles (eye-blink reflex assessed using electromyographic recording of orbicularis oculi muscle) are most typically used .

The picture below shows still photos of the actually startle response in a rat [3].



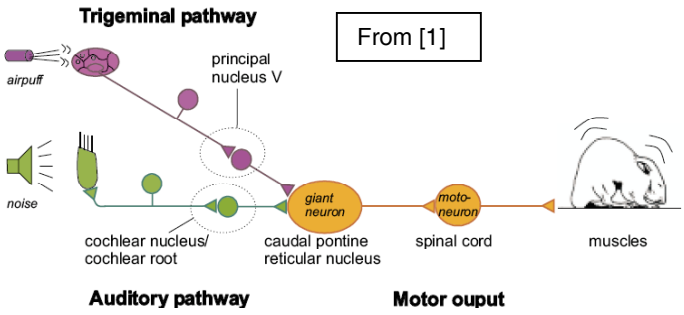
From [3]

Acoustic Startle Circuit

In humans, changes in electrical activity in neck muscles can occur within 9 msec after the onset of an auditory stimulus and within 14 msec in jaw muscles. In rats, startle occurs within 5 msec in the neck and 8 msec in the hindleg. The very short latency of the acoustic startle reflex (ASR) indicates that a simple neural pathway must mediate it. In 1982, Davis et al [24] proposed that acoustic startle in the rat was mediated by 3 (or at most 4) synapses - 1) cochlear root neurons; 2) neurons in the nucleus reticularis pontis caudalis and 3) motoneurons in the facial motor nucleus (pinna reflex and perhaps the eyeblink) or spinal cord (whole body startle) see also [4, 11, 18, 21, 25-30]

However, this simple neural pathway may not be able to account for the relatively long latency of the eyeblink reflex (35 msec) and for this reason other pathways have been suggested.

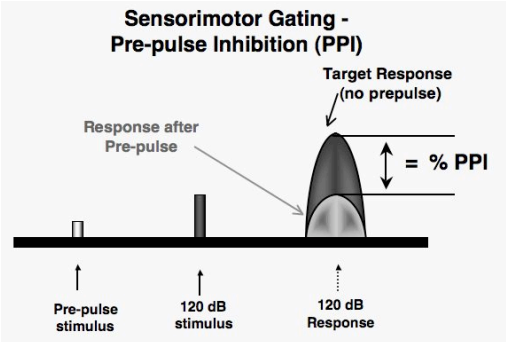
The cochlear root neurons (in both rodents and humans) are a small group of very large cells (35 µm in diameter) embedded in the cochlear nerve. These neurons receive direct input from the spiral ganglion cells in the cochlea, making them the first acoustic neurons in the central nervous system.



Tactile Stimuli (such as a sudden air puff) can also induce a startle reaction [29] and can integrate with auditory stimuli [3, 15].

[11, 18, 21, 26-29]

Prepulse Inhibition (PPI) – Sensorimotor Gating



Prepulse Inhibition (PPI) is a neurological phenomenon in which a weak prestimulus (prepulse) inhibits the reaction to a subsequent strong, startling stimulus (pulse) [31-37]. The stimuli are usually acoustic, but tactile and visual (light and airpuff) prepulse stimuli are also used. The reduction of the startle amplitude reflects the ability of the nervous system to temporarily adapt to a strong sensory stimulus when a preceding weaker signal is given and has also been called sensorimotor gating. PPI is detectable in numerous species ranging from mice to humans. Different prepulse-to-pulse intervals, or lead intervals, or interstimulus intervals are used ranging from 20-480 msec. Lead interval counts from the start of prepulse to the start of the pulse (onset to onset interval). Typical durations are about 20 ms for prepulse and 40 ms for pulse. Prepulse is typically set 3-16 dB louder than background. Maximum inhibition is typically observed at 40-120 ms interval in rodents, but this may vary.

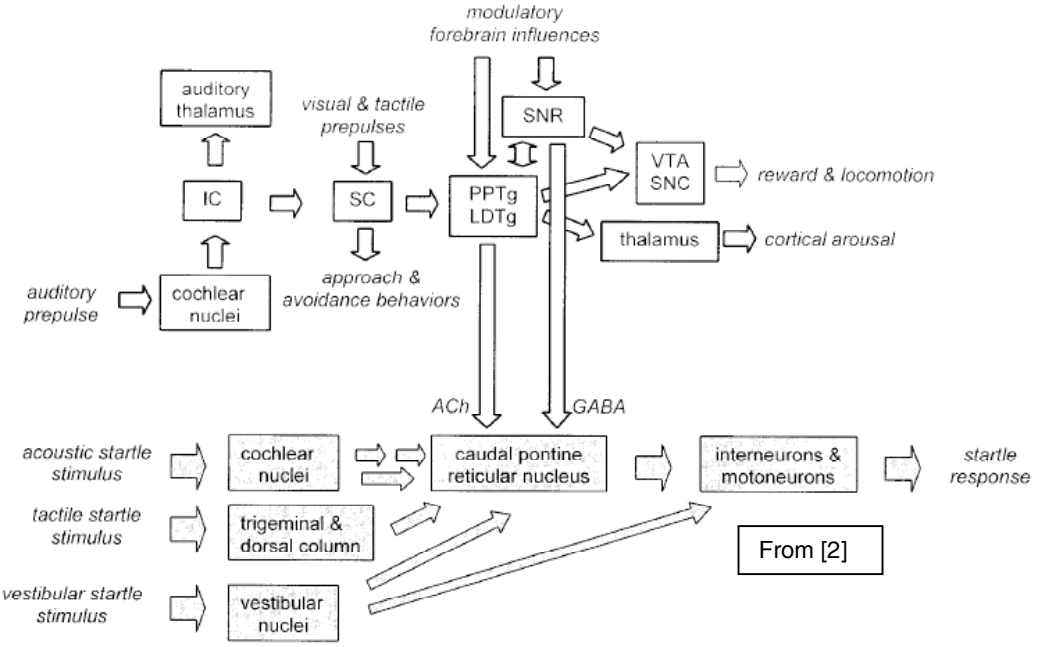
Deficits of prepulse inhibition (and ASR) have been demonstrated in a wide range of neurodegenerative, psychiatric and affective disorders [23, 38-64]

Prepulse Facilitation (PPF)

The converse of prepulse inhibition, known as prepulse facilitiation occurs when increased response to the target stimulus is noted after prior presentation of a non-startling stimulus. This generally occurs when the lead time (or inter-stimulus interval) between the prepulse and the target pulse exceeds 500 ms.

PPI Circuit

The circuitry and pharmacology of PPI is more complex than those of the basic ASR [2, 28, 65-69]. These are also much more controversial. Below are 2 samples of the main brain regions thought to be involved in PPI from 2 different groups.



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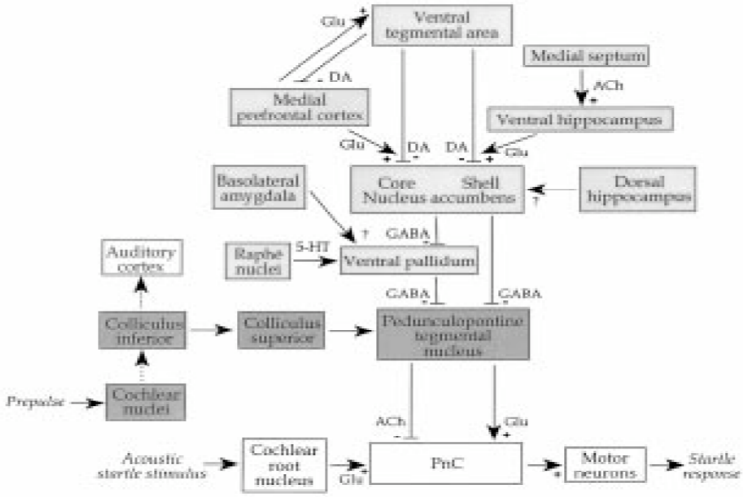


From [4]

Procedure

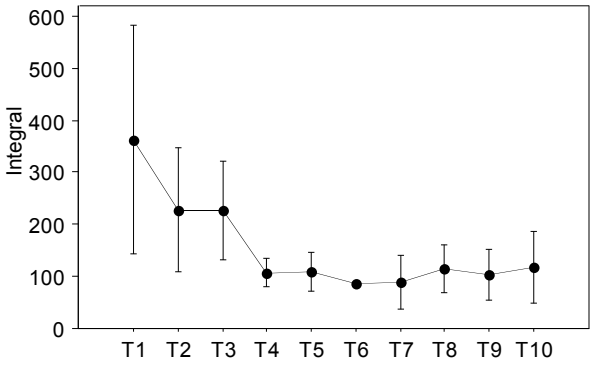
Body weight

The animals should first be weighed. Grossly different body weights can confound both ASR and PPI since the force of the muscle reaction is what is being measured. Analysis of startle by weight or inclusion of weight as a co-variant or other form of weighting/controlling for means is necessary to ensure valid results.

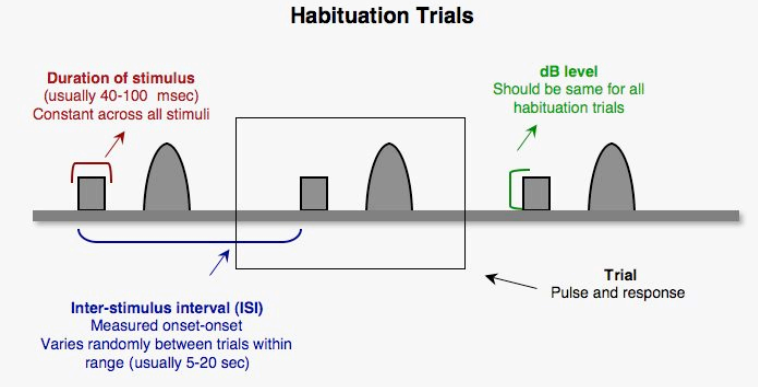
Acclimatization

It is important to acclimatize the subjects to the test environment [70]. The amount of time required depends on the species strain and many other variables and can only be precisely determined empirically but 5-15 min is a good estimate.

Habituation



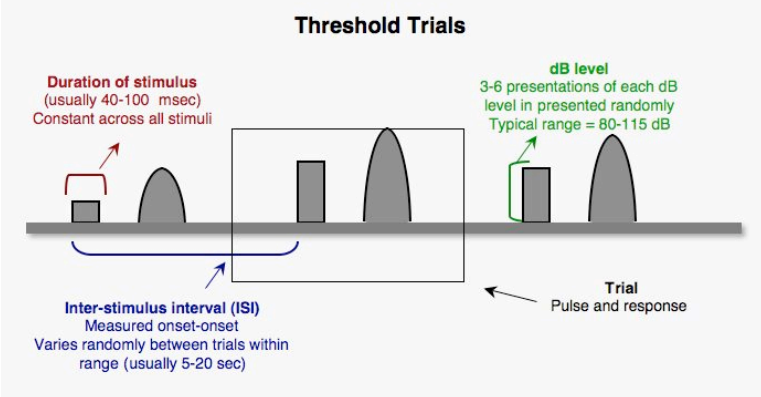
Several (5-15) pulses of the maximum to be used (usually 110 or 120 db) should be presented [71-73]. Generally these pulses are about 40 msec in duration. This serves several purposes. Firstly, the amount and rate of habituation (or facilitation in rare cases) are important measures. Secondly, it serves to ensure a stable baseline and it reduces variability. All sound stimuli should be presented with random time intervals (inter-trial interval, or ITI) between each presentation, or the subjects will rapidly learn to predict the impending sound. This point is somewhat controversial, as may groups provide an ITI consistent (and thus predictable)



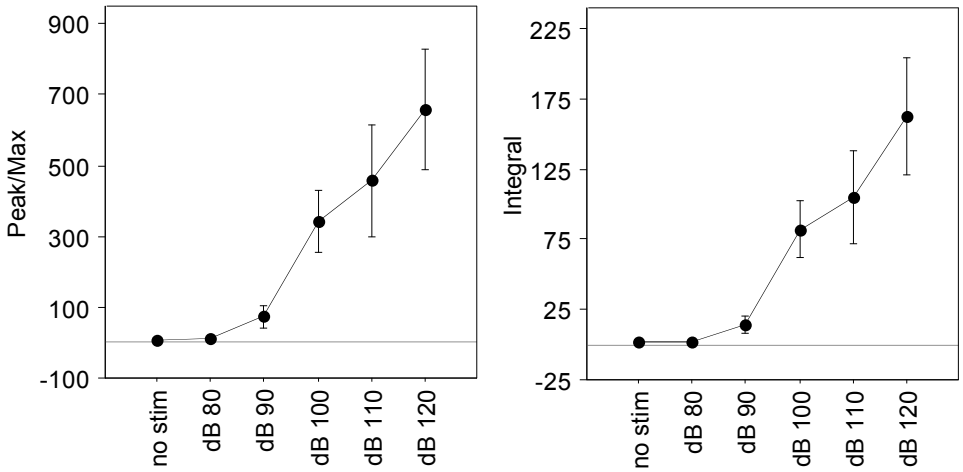
General refs [1, 16, 17, 49, 52, 74-87]

Threshold

Next, the startle threshold should be established. A “no stim” (or 0 dB, or baseline) trial should always be included to ensure that movement, weight or other confound is not altering the apparent startle response. At least 3-5 instances of each dB levels should be presented and averaged. These should be presented in random order, with random intervals. These should NEVER be presented in ascending or descending order. Generally these pulses are about 40 msec in duration – the same values that you use during your habituation and PPI.



General refs [88-90]



PPI

There are several parameters that can be varied [91-93]. The duration and intensity (dB) of the target pulse will impact the PPI results. The inter-stimulus interval (ISI) between the prepulse and the target pulse is also a factor.

Each prepulse should be presented at least 3-6 times. Be sure to include the same number of presentations of "no stim" (0 db target pulse) and the target pulse (i.e. 110 dB) alone.

Calculating PPI

%PPI = [pulse-alone – (prepulse + pulse score)]/pulse-alone score

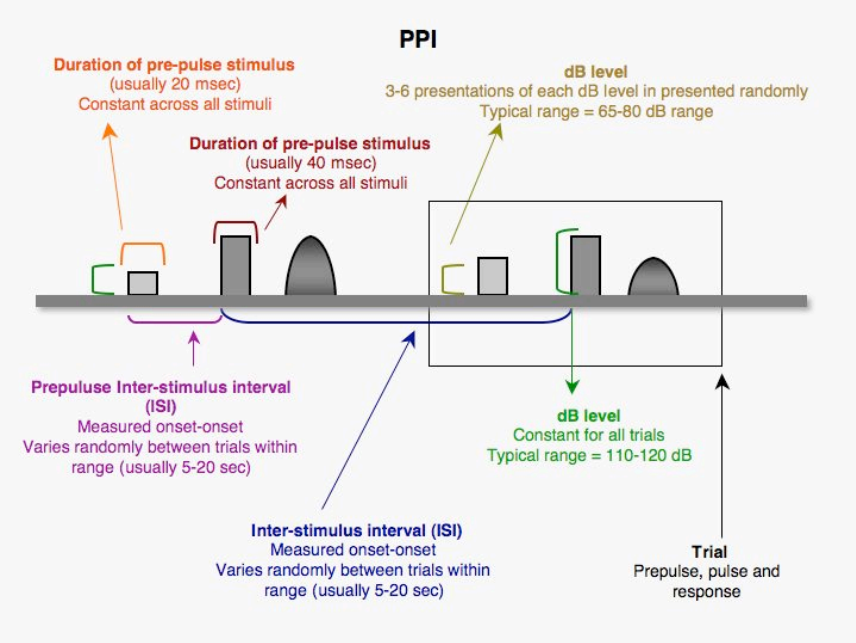
General refs [22, 28, 65, 67, 69, 79, 91, 94-107]

Sample PPI protocol

Pulse alone trials (P) consisted of a single white noise burst (120 dB, 40ms). The prepulse + pulse trials (such as PP69P, PP73P, PP81P) consisting of a prepulse of noise (20 ms at 69, 73, or 81 dB respectively) followed 100 ms after prepulse onset by a noise pulse (120 dB, 40 ms).

No-stimulus (NS) trials consisted of background noise only. Sessions were structured as follows: 1) 10- min acclimation at background noise level; 2) five P trials; 3) ten blocks each containing all five trials (P, PP69P, PP73P, PP81P, NS) in pseudorandom order; 4) five P trials. Inter-trials intervals were pseudorandomly distributed between 12-30 sec. The maximum force intensity for each trial was recorded as startle level. The average percent reduction in startle intensity between pulse and prepulse +pulse trials at all three prepulse levels was defined as the PPI level. The percentage PPI induced by each prepulse

intensity is calculated as (100-[100□startle amplitude on pre-pulsetrial]/[startle amplitude on pulse alone]).



Determination of target pulse.

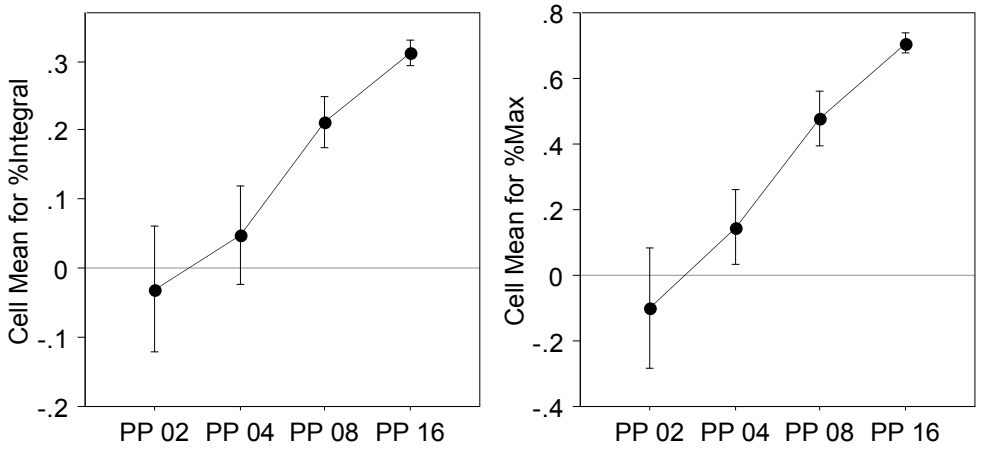
Generally, the target pulse is around 110-120 dB, but pulses as low as 90 dB have been used. Establishing the ASR threshold first ensures that you will not have a floor effect (i.e. that startle response to the target pulse is already too low to see an effect).

Inter-stimulus Interval (ISI)

Generally an ISI of 60-200 msec has been used, and in some cases even greater ranges. Generally, and ISI of between 40-100 msec produces the maximal PPI in mice [108] (however strains are likely to vary). Be aware of the optimum range for your species, strain etc from the literature or determine it empirically. Your ability to detect differences between groups may depend on this factor, since the most robust PPI may result in a ceiling effect (or floor effect, depending on how you think about it). Longer intervals (500 msec or longer) will generally result in facilitation. [109]

Prepulse duration

The prepulse duration should be from 20-40 msec – there is no evidence that changing prepulse duration within that range alters PPI (or PPF) [110]



Reviews

[4, 111, 112]

Measuring the ASR and PPI

[113, 114]

Factors Affecting Startle and PPI

Sex

[47, 115-123]

Gonadal Hormones / Estrous/ Menstrual Cycle

[117, 120, 124-130]

Age and Development

[79, 119, 121, 131-136]

Strain

[116, 132, 137-148]

Stress and other Hormones

[30, 139, 148-150]

Ambient lighting

[41, 151-155]

Hearing Loss

[156-160]

Circadian

[161-163]

Human ASR and PPI deficits
[23, 38-64, 164-166]

Relationship to P50 (evoked potential)
[167]

Other
[168-171]

Relationship to other disorders and traits (anxiety, depression, psychiatric attention etc)
[41, 123, 150, 164, 166, 172-182]

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