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Assessing Prepulse Inhibition of Startle in Mice

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[Abstract] Animal models are an important tool for studying neuropsychiatric disorders. However, a major challenge for researchers working with laboratory rodents is trying to reproduce 'core' symptoms of complex human disorders such as schizophrenia. Despite this challenge, however, it is still conceivable to use animal models designed to reproduce some of the disease's 'endo-phenotypes'. One example is the prepulse inhibition (PPI) of the startle reflex. PPI is a form of startle plasticity and is characterized by a normal reduction in startle magnitude that occurs when an intense startling stimulus (or pulse) is preceded by a weaker pre-stimulus (or prepulse). The PPI paradigm is commonly used to evaluate sensorimotor gating and it has been described in numerous species including humans and rodents. Deficits in PPI have been observed in subjects with schizophrenia and other neuropsychiatric diseases, as well as in established animal models of these disorders. The PPI paradigm is therefore largely used to explore genetic and neurobiological mechanisms underlying the sensorimotor gating phenotypes found in these disorders. Thus, it is necessary to set up reliable and reproducible protocols to study PPI in mice.

Keywords: Prepulse inhibition of startle, PPI, Animal models, Schizophrenia, Sensorimotor gating

[Background] Sensorimotor gating refers to the ability of a sensory event to suppress a motor response (Cryan and Reif, 2012). One form of sensorimotor gating that has been widely studied in humans and rodents is the prepulse inhibition (PPI) of startle. The startle reflex consists of involuntary contractions of whole-body musculature elicited by sufficiently sudden and intense stimuli. Specifically, the acoustic startle response is characterized by an exaggerated flinching response to an unexpected strong auditory stimulus. PPI is a form of startle plasticity and it is characterized by a normal reduction in startle magnitude that occurs when an intense startling stimulus (or pulse) is preceded by a brief, low intensity prestimulus (or prepulse) (Graham, 1975; Hoffman and Ison, 1980). The PPI paradigm is commonly used to evaluate sensorimotor gating and it has been described in numerous species, including humans (Schwarzkopf *et al.*, 1993) and mice (Carter *et al.*, 1999; Frankland *et al.*, 2004). Impaired PPI is observed in schizophrenia (Braff *et al.*, 2001; Swerdlow *et al.*, 2008), as well as other neuropsychiatric disorders including obsessive-compulsive disorder (Ahmari *et al.*, 2012), Tourette's syndrome (Swerdlow *et al.*, 2001), Huntington's disease (Swerdlow *et al.*, 1995) and bipolar disorder (Perry *et al.*, 2001). In patients with psychotic disorders, deficits in sensorimotor gating are associated with cognitive fragmentation and psychotic symptoms (Kapur, 2003). As these deficits have been found both in psychotic patients as well as in animal models (Swerdlow and Light, 2016), the PPI paradigm is largely

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used in the study of neuropsychiatric diseases and has proven a useful tool for studying and characterizing the effects of several anti-psychotics (Xue *et al.*, 2012), and for exploring the mechanisms underlying psychotic-like behaviors (Geyer, 1999; Ouagazzal *et al.*, 2001).

Materials and Reagents

1. Mice (C57BL6/N mice purchased from Janvier Labs, Le Genest-Saint-Isle, France)
   Note: If pharmacological treatments are applied before PPI performance, the reagents will depend on the control or drug solutions prepared. Depending on the treatments applied prior to the testing, the animals can be housed in either single or collective cages.
2. 70% ethanol

Equipment

1. SR-LAB startle apparatus with digitized electronic output (SR-Lab, San Diego Instruments, catalog number: 2325-0400) (Figure 1)
2. Digital sound level meter (FLIR Systems, Extech, catalog number: 407730)

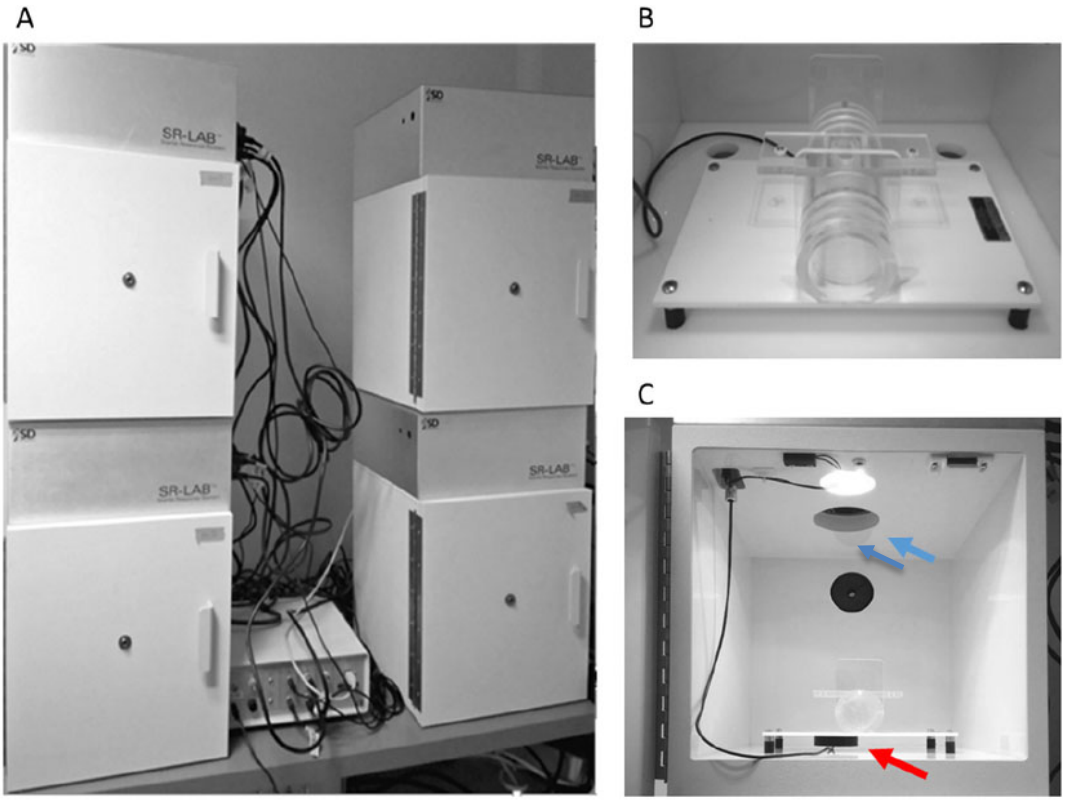

Figure 1. SR-LAB startle apparatus. A. Each experimental apparatus consists of an outer, lighted and ventilated, chamber that serves to prevent external noise or vibrations interfering with experiment. B. Inside the chamber a stabilimeter consisting of a Plexiglas cylinder is

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secured to a platform. C. A piezoelectric accelerometer-indicated by the red arrow-mounted under the cylinder transduces animal movements that are then digitized, rectified, and recorded by a computer and interface assembly. A loudspeaker-indicated by the blue arrow-generates the startling acoustic stimuli, according to the desired settings.

Software

1. SR-Lab Analysis software (SR-Lab San Diego Instruments, catalog number: 2325-0400)

Procedure

A. Designing the protocol

Here, we describe the experimental design used in our lab to study PPI response in mice (Busquets-Garcia *et al.*, 2017), but the protocol can be modified by adjusting the pulse and prepulse intensities, the number of trials, inter-trial intervals *etc.*, appropriate for exploring different experimental questions.

1. Begin the session with a 5-min acclimation period. During the acclimation period, the constant background noise of 70-dB white noise is presented for the animal to adapt to the animal holder, startle box and background noise.
2. The session then proceeds through the presentation of 90 different trials (Figure 2):

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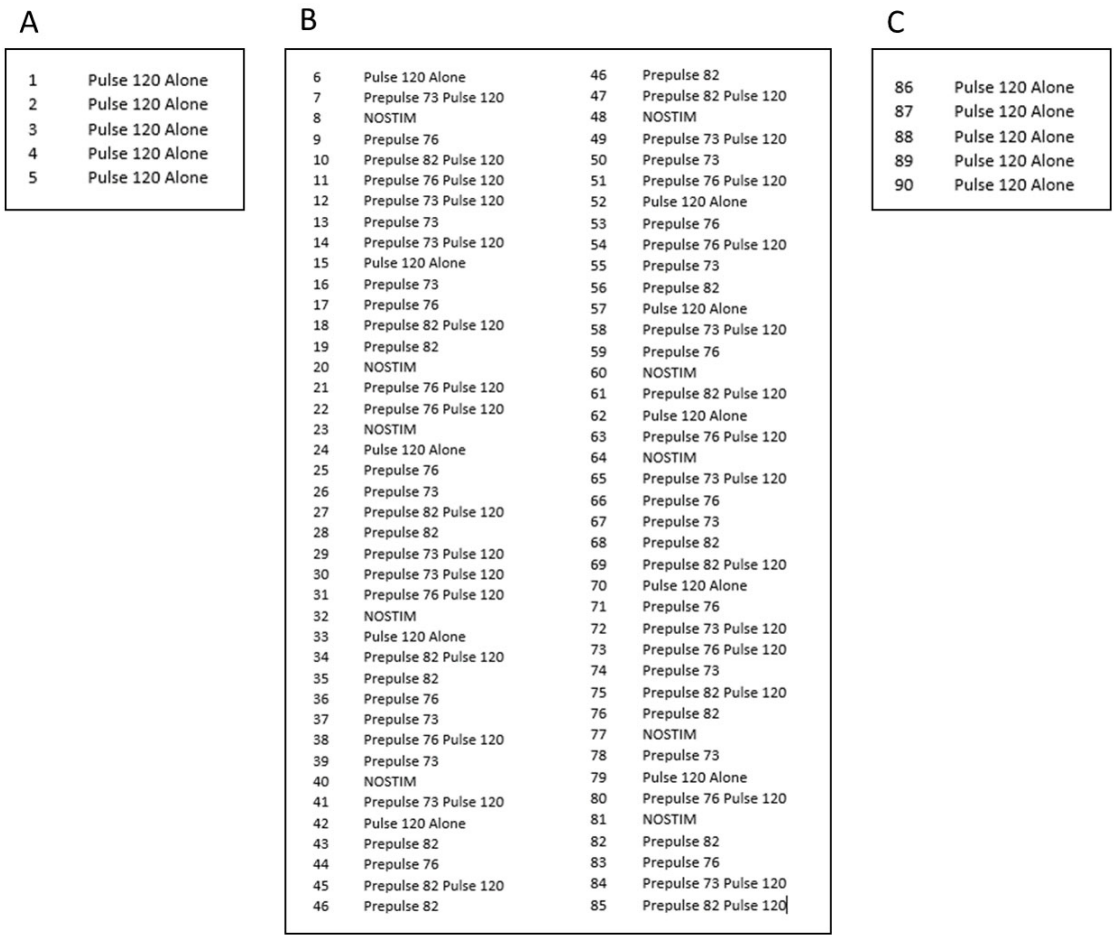

A

1	Pulse 120 Alone
2	Pulse 120 Alone
3	Pulse 120 Alone
4	Pulse 120 Alone
5	Pulse 120 Alone

B

6	Pulse 120 Alone
7	Prepulse 73 Pulse 120
8	NOSTIM
9	Prepulse 76
10	Prepulse 82 Pulse 120
11	Prepulse 76 Pulse 120
12	Prepulse 73 Pulse 120
13	Prepulse 73
14	Prepulse 73 Pulse 120
15	Pulse 120 Alone
16	Prepulse 73
17	Prepulse 76
18	Prepulse 82 Pulse 120
19	Prepulse 82
20	NOSTIM
21	Prepulse 76 Pulse 120
22	Prepulse 76 Pulse 120
23	NOSTIM
24	Pulse 120 Alone
25	Prepulse 76
26	Prepulse 73
27	Prepulse 82 Pulse 120
28	Prepulse 82
29	Prepulse 73 Pulse 120
30	Prepulse 73 Pulse 120
31	Prepulse 76 Pulse 120
32	NOSTIM
33	Pulse 120 Alone
34	Prepulse 82 Pulse 120
35	Prepulse 82
36	Prepulse 76
37	Prepulse 73
38	Prepulse 76 Pulse 120
39	Prepulse 73
40	NOSTIM
41	Prepulse 73 Pulse 120
42	Pulse 120 Alone
43	Prepulse 82
44	Prepulse 76
45	Prepulse 82 Pulse 120
46	Prepulse 82
46	Prepulse 82
47	Prepulse 82 Pulse 120
48	NOSTIM
49	Prepulse 73 Pulse 120
50	Prepulse 73
51	Prepulse 76 Pulse 120
52	Pulse 120 Alone
53	Prepulse 76
54	Prepulse 76 Pulse 120
55	Prepulse 73
56	Prepulse 82
57	Pulse 120 Alone
58	Prepulse 73 Pulse 120
59	Prepulse 76
60	NOSTIM
61	Prepulse 82 Pulse 120
62	Pulse 120 Alone
63	Prepulse 76 Pulse 120
64	NOSTIM
65	Prepulse 73 Pulse 120
66	Prepulse 76
67	Prepulse 73
68	Prepulse 82
69	Prepulse 82 Pulse 120
70	Pulse 120 Alone
71	Prepulse 76
72	Prepulse 73 Pulse 120
73	Prepulse 76 Pulse 120
74	Prepulse 73
75	Prepulse 82 Pulse 120
76	Prepulse 82
77	NOSTIM
78	Prepulse 73
79	Pulse 120 Alone
80	Prepulse 76 Pulse 120
81	NOSTIM
82	Prepulse 82
83	Prepulse 76
84	Prepulse 73 Pulse 120
85	Prepulse 82 Pulse 120

C

86	Pulse 120 Alone
87	Pulse 120 Alone
88	Pulse 120 Alone
89	Pulse 120 Alone
90	Pulse 120 Alone

Figure 2. Representative session using the described experimental design. The first five trials consist of five pulse-alone trials (A), the intermediate 80 trials are divided into 10 blocks of randomized pulse-alone trials, prepulse-alone trials, combinations of prepulse-pulse trials and no-stimulus trials (B) and the session is concluded with a final block of five consecutive pulse-alone trials (C). Prepulse intensities (73 dB, 76 dB and 82 dB) are above the 70 dB background.

a. The first five trials consist of five pulse-alone trials where 120 dB of white noise is presented in isolation for a duration of 20 msec (*i.e.*, with no prepulse). These trials serve to habituate and stabilize the animals to the startle response.
b. Subsequently, ten blocks of trials are presented. Each block consists of one pulse-alone trial, three prepulse-alone trials (+3, +6, or +12 units above the background of 70 dB), three combinations of prepulse-pulse trials, and one no-stimulus trial (*i.e.*, background only) (Table 1). The 8 trials are presented in a randomized order within each block, with the inter-trial interval (ITI) varying randomly between 10 and 30 sec, intended to minimize habituation to startle across trials.

   Notes:

   i. The advantage of randomized ITIs is in the fact that the animal cannot predict the time when the next stimulus presentation will occur. For example, attention to the prepulse

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can increase the animal's efficacy in suppressing startle responses. ITIs below 10 sec should be avoided in order to exclude effects caused by muscle fatigue and refractory periods of muscle responses.

ii. *The intensities of the prepulse should be kept at levels above the background noise but also low enough that they do not elicit a significant startle response on their own, the margin being approximately 2-20 dB above background levels (e.g., +3, +6 or +12 dB above a background of 70 dB). It is important to note that sensitivity to the prepulse may also vary between strain, gender or age of the animals.*

Table 1. Representation of the different types of trial used in the behavioral protocol

Trial	Description
Pulse alone trials	20 msec in duration of 120 dB intensity white-noise.
Prepulse trials	20 msec prepulses of 73 dB, 76 dB and 82 dB intensities.
Prepulse–pulse trials	20 msec prepulses (73 dB, 76 dB and 82 dB) presented before the onset of pulse-alone stimuli.
NOSTIM trials	No stimuli, but mouse movements are recorded as a measure of basal motor activity in the cylinder.

c. The session is concluded with a final block of five consecutive pulse-alone trials, as in the first block.

Note: Stimulus rise-time, duration, and intensity are variables that affect startle reflex magnitude (Graham, 1975; Hoffman and Searle, 1968). All the parameters should be carefully decided after taking into account the strain, age, sex and genetic background of the animals, since different lines can exhibit different responses to the startle stimuli (Willott et al., 1995 and 2003).

B. Running the experiment

1. Calibrate the loudspeakers and the sensitivity of the transducer platform of the startle chambers (Figure 3). Follow manufacturer's guidelines for effective sound and movement calibration.

Note: Calibration of the sound and the movement sensors is very important for obtaining valid test results. Consequently, these must be routinely calibrated before each experiment.

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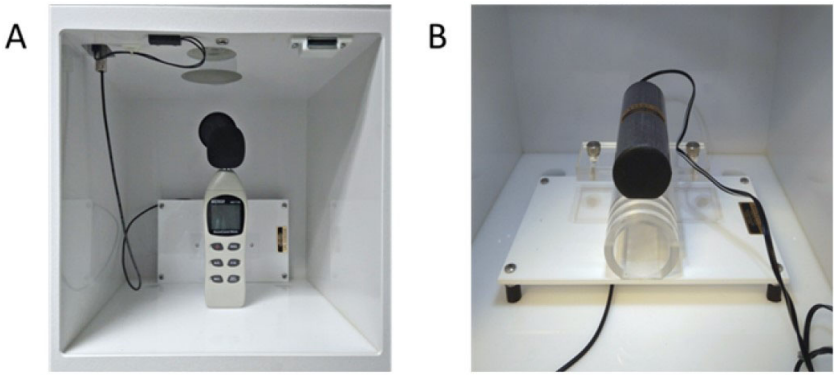

Figure 3. Representative images of loudspeakers (A) and movement sensitivity detector (B) used for the calibration of the startle chambers

2. Having created your experimental protocol (A1, A2), you can create a study database using the SR-LAB startle apparatus software, defining both the experimental sessions and the subjects that will be tested.
3. Transport the mice to the testing room. You can simultaneously test as many mice as the number of chambers you have available (software compatible with up to a maximum of 16 chambers). For housing conditions, see Note 1. Take care not to stress the mice before starting the experiment and, to that end, make no changes to the home cage (*e.g.*, bedding) for at least 24 h before the experiment. Illumination and noise levels in the testing room should be comparable to those in the housing rooms in order to minimize environmental effects on the behavioral outcome. Tubular animal enclosure minimizes stress from being restrained while animal remains centered over the sensor for consistently reliable results.
4. In each experimental session, place the mouse in the cylinder inside the testing chamber and secure the door shut.
5. Run the experimental session according to the experimental design described above. The session will stop automatically at the end of the protocol (after approximately 35-40 min).
6. Remove each mouse from the chamber at the end of the experimental session and return it to its home cage. Wipe clean the animal holders and chambers with water and allow to dry before introducing the next animal.
7. Select the next session on the screen and repeat the procedure for all the animals.
8. At the end of all the sessions, clean the cylinders and chambers with 70% ethanol and leave them to dry. Save the data obtained for a subsequent detailed analysis of acoustic startle and acoustic prepulse inhibition responses.

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Data analysis

Reactivity scores obtained on the first and last blocks of five consecutive pulse-alone trials can be analyzed separately to evaluate startle habituation. The data obtained from the remaining 80 trials are categorized into three different subsets according to their relevance to distinct behavioral constructs.

First, startle reactivity (S) is assessed from the reactivity scores obtained in the pulse-alone trials (excluding the first and last blocks of five consecutive pulse-alone trials). The 100 millisecond response window after the presentation of the 120 dB pulse is analyzed by the software and the maximal response peak amplitude is used to determine the acoustic startle response as a control index for the animal's reaction to the startle pulse (Figure 4A).

Second, reactivity on prepulse-pulse trials (PPiS) relative to the pulse-alone/startle trials (S) is used to evaluate prepulse inhibition (PPI) (Figure 4B). The amount of prepulse inhibition is calculated as a percentage score for each acoustic prepulse trial type using the following formula:

% PPI = 100 x (S - PPiS)/S (Figure 4B)

Third, to measure prepulse-elicited reactivity (PP), data from prepulse-alone trials are included.

The output of a typical experiment should show increasing PPI levels with increasing prepulse intensities, with relatively low variability (Figure 4C). Well-established effects of particular drugs on PPI should be reproducible when using the same strain, sex, and drug dosages. Startle response data typically show more variability and less reliability than PPI response data.

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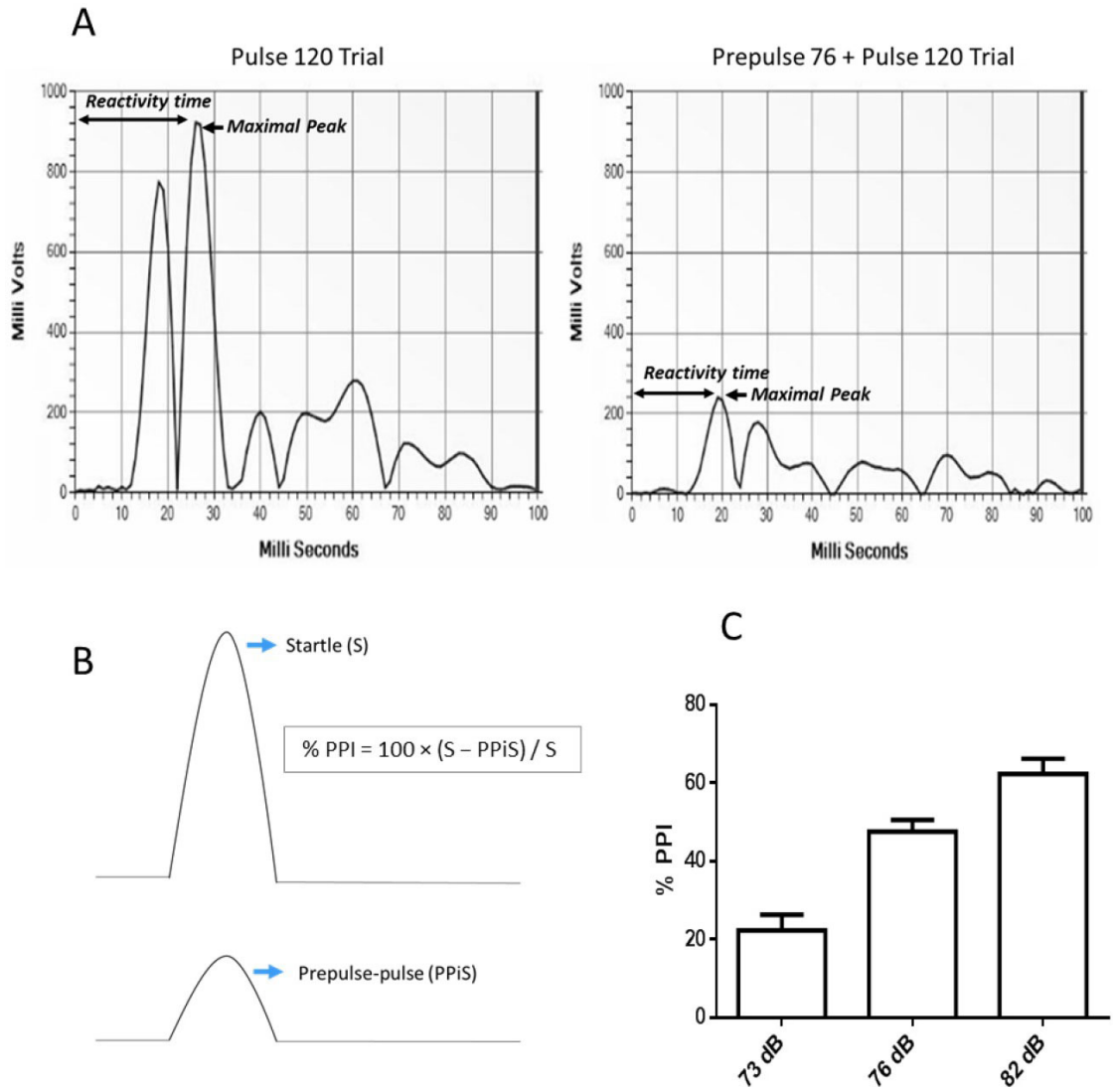

Figure 4. Expected results of a typical PPI experiment. A. Software output of a 100 millisecond response window after the presentation of a pulse-alone and a prepulse-pulse trial. The arrows indicate the maximal response peak amplitude, which is used to determine the acoustic startle response and the maximal response time as an index of the animal's reactivity to the stimuli. B. Reactivity on prepulse-pulse trials (PPiS) relative to pulse-alone/startle trials (S) is utilized to evaluate prepulse inhibition (PPI). C. Percent prepulse inhibition (%PPI) is shown for naïve wild-type mice with a BL6N background produced in our institute. As expected, PPI levels increase with increasing prepulse intensity (above background), and variability is low.

Notes

1. In all PPI experiments performed in our institute, animals were housed in collective cages of 4-5 animals per cage. While social isolation can alter startle variables in rats, the effects of isolation on startle measures in mice have not been well characterized. Therefore, the use of mice that have been separated and single-housed in startle experiments is not ideal.

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2. All sessions of the experimental protocol were performed in the morning (from 9 AM to 2 PM).
3. **Strain:** Strain differences in startle reflex and PPI have been described in mice (Bullock *et al.*, 1997; Tarantino *et al.*, 2000; Willott *et al.*, 2003). This protocol was tested in several mouse lines. We found similar results between the C57/BL6N mice and the wild-type animals with a BL6N background produced in our institute, although each batch of mice can vary slightly in their responses.
4. **Sex:** Both male and female mice have been used in the protocol of startle reactivity and PPI. If used on the same experimental day, the cleaning process of the testing chambers must be performed meticulously in order to avoid effects on the behavioral outcome.
5. **Age:** Age is an important variable in measures of acoustic startle and PPI. Age-related hearing loss, which can alter startle reactivity and PPI levels, has been reported for many inbred strains including the C57BL/6 (Willott *et al.*, 1995). Moreover, studies have shown that early adolescent mice can display altered startle reactivity and PPI compared to adult animals (Pietropaolo and Crusio, 2009).
6. Different psychotogenic drugs (*e.g.*, cannabinoids, amphetamine *etc.*) can be used as positive controls (*i.e.*, PPI alteration) for the test.

Recipes

The current protocol does not contain any recipes. In case any psychotogenic or other drug is used as a positive control for the test, the preparation should be done according to relevant protocols and manufacturer's guidelines.

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