

## Enhanced Prepulse Inhibition Predicts Treatment Response in PTSD

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### Abstract

Alterations in the functional relationship between a hyperactive amygdala and hypoactive ventral medial prefrontal cortex in posttraumatic stress disorder (PTSD), suggests an underlying faulty inhibitory neural mechanism. Prolonged exposure (PE) and sertraline are treatments that are thought to normalize interactions between these brain regions; with PE potentially working to strengthen inhibitory learning and selective serotonin reuptake inhibitors (SSRIs) potentially acting to promote serotonergic neurotransmission, suggesting that PE may lead to greater changes in inhibition. The present study examined changes in inhibition from pre- and post-treatment in individuals treated with sertraline to those treated with PE, and individuals who responded more to treatment to those who responded less to treatment. Prepulse inhibition (PPI) was used to examine inhibitory changes from pre- and post-treatment in 49 individuals with chronic PTSD. Regardless of treatment modality, there was a decline in automatic inhibition (30 ms), from pre- to post-treatment. Better pre-treatment attentional inhibition (120 ms) of PPI was associated with better treatment response, regardless of treatment modality ( $d=0.95$ ). Better inhibition may serve as a pre-treatment, general prognostic marker for better treatment response, highlighting the importance of enhancement strategies that strengthen inhibitory processes prior to starting either pharmacotherapy or psychotherapy for PTSD.

**Keywords:** Neurotransmission; Post-Traumatic Stress Disorder (PTSD); Depression; Anxiety; Psychotherapy

### Introduction

Inhibitory deficits are implicated in the neural circuitry of post-traumatic stress disorder (PTSD). According to the neurocircuitry model of PTSD [1-3] the ventral medial prefrontal cortex (vmPFC) fails to engage in a top down inhibition of the amygdala's over responsivity to fear [4,5]. This loss of control is thought to disrupt the vmPFC in inhibiting the trauma memory and subsequently leading to impaired extinction of fear in PTSD [6,7]. Psychotherapy [8,9] and pharmacotherapy [10,11] for PTSD are thought to normalize responding in this neural circuitry, with psychotherapy potentially working to strengthen the inhibitory control of the vmPFC, and pharmacotherapy potentially acting to decrease amygdala hyperactivity, suggesting inhibition ought to improve with successful treatment. Therefore, studying changes following treatment may help implicate inhibitory processes as a critical mechanism observed in treatment response in PTSD. At present, evidence is limited as to whether inhibition improves with successful treatment using SSRIs or psychotherapy. Although the field of PTSD has begun to indirectly explore inhibition, the study of inhibition and PTSD treatment is essentially nonexistent.

One common measure of inhibition is prepulse inhibition of startle [12]. PPI is a form of startle modulation, which occurs when a non-startling prepulse precedes the startling pulse by a short interval (e.g. 30ms-120 ms), resulting in inhibition of the startle reflex [13]. The neural circuitry of PPI is thought to project from the cochlear root nucleus, dorsal cochlear nucleus to the inferior colliculus, the superior colliculus to the pontine tegmental nucleus, and end at the nucleus reticularis pontine caudalis [14]. The startle reflex is thought to tap into the defensive response system that mediates fight and flight actions [15]. PPI is thought to occur through a sensorimotor gating system that functions as an attentional filter to protect limited capacity systems from being overloaded with incoming sensory information [16]. PPI is proposed to index early stages of lower level, automatic processing

(30, 60 ms) and voluntary, controlled attentional processing (120 ms); providing a sensitive measure of inhibitory dysfunction.

Although the fronto-striatal network implicated in PTSD [17] also engage the neural substrates that modulate PPI [18-20] the PPI studies in PTSD are, at present, equivocal. Three studies show reduced PPI in individuals with PTSD compared to controls [21-23]. However, accumulating evidence suggests no differences in PPI across PTSD and control groups [24-28], although sample characteristics and experimental confounds in a subset of these studies may potentially affect the results (i.e., self-selection, noise bursts). Notably, the use of a non-optimal signal to noise ratio (SnR; the difference between background noise intensity and prepulse intensity) might help explain the null findings in PPI across anxiety disorders [29]. Using a normative sample with variations of trait anxiety and PTSD, [30] reported a large association between anxiety and PPI strengthens as SnR approaches +15dB. Given these issues, a review by [31] concluded that whether or not individuals with PTSD exhibit impaired PPI has not yet been settled. Furthermore, there are no published studies examining PPI from pre- to post-treatment in chronic PTSD.

Strengthening inhibitory processes in key neural circuits involving the vmPFC may underlie successful treatment for PTSD [32] suggesting selective serotonin reuptake inhibitors (SSRIs) and psychotherapies such as prolonged exposure (PE) may normalize inhibitory deficits over

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the course of treatment. SSRIs are the best-studied pharmacotherapy for PTSD [3-35]. SSRIs are thought to work through enhanced serotonergic transmission that result in broad neurochemical changes in the network of regions including the prefrontal cortex and amygdala [34,36]. Preliminary evidence suggests SSRIs show an increase in activity in brain regions such as the vmPFC that are thought to be associated with executive functioning and inhibition in PTSD [10,11,37], though these studies are limited by small samples and lack of control groups. Indirect evidence from animal studies points to a potential link between SSRIs and enhanced inhibition of the vm PFC over the amygdala [38,39]. Across human and animal studies, serotonergic agents have been shown to modulate PPI in some [40,41] but not all studies [42-44]. As noted in the effects of increased central serotonergic activity on prepulse inhibition and habituation of the human startle response [44], the discrepant finding may be due to differences in dose, specificity in regard to PPI effects across species, for the serotonergic system, and binding characteristics with serotonin receptors. Accordingly, the effects of serotonin on PPI for PTSD are largely still unknown.

PE, an empirically supported treatment for PTSD [35], is a form of cognitive behavioral exposure-based therapy that is thought to work through inhibitory learning processes associated with extinction learning [45-48]. There is preliminary evidence, although not directly looking at inhibition, showing functional improvements in the inhibitory-related, prefrontal network following psychosocial PTSD treatments [49,50]. Mechanistically, the neural circuits involved in regulating fear via extinction (i.e., amygdala, mPFC, hippocampus) are also thought to modulate PPI [51]. Specifically, the neural circuitry of PPI is largely influenced by top-down modulation via the projection from the amygdala to the pontine tegmental nucleus through the nucleus accumbens as studied by Li et al. It is well-established that PPI is enhanced by attention and fear conditioning [51-54], suggesting that PPI may also be enhanced by top-down modulation during extinction.

More broadly, evidence suggests a potentially common biological mechanism for both extinction and mood regulation processes [55], suggesting the mechanism of action for SSRIs and exposure-based treatments may be similar. Taken together, both SSRIs and PE are effective treatments for chronic PTSD and are thought to potentially affect the network of regions involved in fear and inhibitory learning [3,9]. However, one treatment may lead to greater changes in inhibitory processes. Though large-scale comparison studies are lacking, a comparison of pre- to post-treatment effect sizes show that PE typically produces larger effects than SSRIs [35]. Thus, individuals with PTSD treated with PE may show stronger changes in inhibition than those treated with an SSRI.

The current study examined changes in inhibition, as assessed using PPI, from pre- to post-treatment for individuals with chronic PTSD. Two main questions were examined. First, do distinct forms of treatment, PE versus an SSRI, specifically sertraline, differentially improve PPI? Given that not only are there larger effect sizes associated with PE over sertraline but that exposure-based therapies are thought to work through strengthening inhibitory processes, we hypothesized that individuals treated with PE would show greater improvement in PPI from pre- to post-treatment than those treated with sertraline. Second, does successful treatment improve PPI deficits? Specifically, are reductions in PTSD severity associated with improvement in inhibition from pre- to post-treatment? Given the effectiveness of both treatments and similar effects on the network of neural regions implicated in fear and inhibitory learning, it was hypothesized that those with stronger treatment response, as defined as a larger change in PTSD severity from pre- to post-treatment, would show a greater improvement in inhibition than those with less strong of a treatment response.

## Method

### Participants

Participants were 49 men (25.5%) and women (74.5%) with primary DSM-IV chronic PTSD. Participants were recruited from an NIMH-funded treatment trial at two large metropolitan areas through community advertisements and local referrals. Inclusion criteria for the treatment trial were being between the ages of 18 and 65 years of age with current, chronic DSM-IV PTSD using the Posttraumatic Symptom Scale-Interview Version [56] at least 12 weeks post-trauma. Participants were excluded from the study if they had a current diagnosis of schizophrenia or delusional disorder, reported medically unstable bipolar disorder, depression with psychotic features, or depression severe enough to require immediate psychiatric treatment (e.g., actively suicidal), or reported a current diagnosis of alcohol or substance dependence within the previous three months, had an ongoing intimate relationship with the perpetrator, were unwilling to discontinue current psychotherapy or antidepressant medication, or had a medical contraindication for the initiation of sertraline (e.g., pregnancy). Given the role of auditory processing, participants were excluded if their hearing was above 20 dB at 1 kHz. No participants were excluded for auditory problems. This study was approved by the institutional review boards of University of Washington and Case Western Reserve University. Refer Table 1 for characteristics of the sample.

### Materials

#### Auditory stimuli

The startle stimulus consisted of a 50 ms burst of 105 dB noise with a 0 instantaneous rise/fall time. The prepulses consisted of 25 ms, non-startling tones (75 dB, 1000 Hz, 4 ms rise/fall times) at 30 ms, 60 ms, and 120 ms interstimulus intervals before the onset of the startle stimulus. These prepulse intervals were used because 30 ms and 60 ms are thought to reflect automatic processes [57,58] and the 120 ms prepulse interval is thought to reflect more strategic attention [59,60]. Intensity levels of

Characteristics	Total Sample (n=49)		PE (n=29)		SER (n=20)	
	M	SD	M	SD	M	SD
Age	37.69	12.8	37.08	12.61	40.95	13.05
Gender (% Female)	74.5		81.5		65.0	
<b>Race</b>						
Caucasian (%)	66.7		71.4		61.1	
African American (%)	20.5		19.0		22.2	
Asian (%)	5.1		9.5		0.0	
Other (%)	7.7		0.0		16.7	
	M	SD	M	SD	M	SD
Education level (yrs)	15.05	3.42	15.8	3.81	14.05	2.61
Cognitive ability (Shipley)	62.01	14.09	64.34	14.39	58.62	13.50
Years since trauma	12.5	12.77	13.08	12.00	13.32	14.13
<b>Trauma Type (%)</b>						
Child Sexual Assault	22.4		24.1		20.0	
Child Physical Assault	8.2		10.3		5.0	
Sexual Assault	30.6		31.0		30.0	
Physical Assault	26.5		24.1		30.0	
Motor Vehicle Accident	6.1		10.3		0.0	
Natural Disaster	4.1		0.0		10.0	
Death of Loved One	2.0		0.0		5.0	

Table 1: Summary of participant characteristics.

the startle probes and non-startling tones were calibrated with a sound level meter (Digital-display sound-level meter, Model: 33-2055).

### Startle trials

A series of startle stimuli trials were presented either alone or proceeded by prepulses. There were four types of startle stimuli trials: 1) 50 ms 105 dB noise burst presented alone; 2) 50 ms 105 dB noise burst, followed after 30 ms by a 25 ms 75 dB tone; 3) 50 ms 105 dB noise, followed after 60 ms by a 25 ms 75 dB tone; and 4) 50 ms 105 dB noise, followed after 120 ms by a 25 ms 75 dB tone. The four types of startle stimuli trials were repeated 20 times each, for a total of 80 repetitions. The order of the four trial types were randomized with the constraint that the same type of trial could not occur more than twice in succession. The recording session was initiated by a startle-alone trial on the first and last trial. Between trials or inter-trial intervals ranged from 15 s to 35 s (mean 25 s). In summary, there were a total of 80 startle trials that consisted of two blocks of 40 each, over a period of 20-30 min. Stimulus presentation was controlled using Eprime software v 1.0 (Psychology Software Tools, Inc.) on a 17-inch Dell monitor.

### Physiological recording startle responses

Physiological recording of orbicularis oculi electromyogram (EMG) were controlled by Coulbourn Instruments Labline LLC (Model v.15-17) and acquired by Windaq software 0.1-720 v.2.72. A set of 4 mm, silver/silver chloride sensors (EMG) were placed below the left eye, directly below the pupil and 13 mm apart to measure contraction of the orbicularis oculi muscle, and a ground electrode was placed on the center of the forehead. EMG was filtered with low frequency cutoffs of 90 Hz and high frequency cutoffs of 1000 Hz.

### Analyses of startle response

The EMG responses in each type of trial were averaged across the 40 trials. Startle trials preceded by prepulses reflect a reduction in magnitude produced by a prepulse, with startle magnitude on the no prepulse trials serving as a reference. Both were used to compute percent startle modulation scores [61]. Startle responses were measured by the peak amplitude occurring 20 ms to 100 ms after stimulus onset, relative to a 50 ms average baseline preceding probe onset [62]. Although both percent and arithmetic difference scores can be utilized to assess PPI [62] proportion of difference is the method least affected by differences in control reactivity and thus was used instead [63]. Prepulse inhibition was calculated using the proportion of difference method, defined by percent change scores from baseline ITI startle:  $[(\text{mean prepulse startle} - \text{mean ITI startle}) / \text{mean ITI startle}] \times 100$ . A negative prepulse inhibition score indicates that eyeblink activity was reduced in the paired stimulus condition, while a positive score indicates that eyeblink activity was increased. To correct for positive skewness, natural log transformations was used, consistent with other PPI studies [23]. Participants with less than 1 mV of activity on the trials with startle stimuli presented alone were designated as eyeblink nonresponders and these participants were removed from analyses [63]. Consistent with previous PPI studies [25] six participants were excluded for poor electrode impedances or equipment failure and five participants were excluded for participant movement resulting in unstable data (e.g., startle not greater than baseline).

### Treatments

#### Prolonged exposure

Prolonged exposure [64] consisted of 10 weekly 90-120 min individual sessions with study therapists that were either Master's

or Ph.D. level trained clinical psychologists. PE consists of psycho education, breathing retraining, imaginal exposure focusing on revisiting the trauma memory followed by processing of major themes, and *in vivo* exposure focusing on approaching feared situations and places. Treatment standardization was achieved through weekly supervision, joint cross-training sessions, and outside treatment fidelity ratings. Assessment of treatment adherence and therapist competence for PE was conducted for 10% of the cases by an outside expert. For this sample, fidelity for PE was high, with 92.3% adherence to imaginal exposure, *in vivo* exposure, and processing components. Therapist competence in PE was evaluated using a 3-point scale (1=Inadequate, 3=Adequate or Better). PE therapist competence was good ( $M=2.73$ ,  $SD=0.32$ ).

#### Sertraline

Sertraline consisted of 10 weekly sessions with a board certified psychiatrist who monitored response to medication and offered general support only. Psychiatrists started with 25 mg/day for one week, and then the dose was titrated each week by 50 mg until the maximum dose of 200 mg/day was met at Session 5, based on a standard treatment algorithm and manual [65]. Final average dose for this sample was 153.15 mg/day ( $SD=42.00$ ). Similarly, treatment adherence was monitored by pill counts and medication diaries. For this study, evaluated by a rater who viewed 15% of the videotapes of sertraline sessions, fidelity for sertraline was high, with 98% of essential elements, including a discussion of dose, side effects, and client concerns covered during sessions and no protocol violations observed.

#### Procedure

During the informed consent procedure, in addition to providing consent to participate in the treatment study, participants completed a separate consent process for this research study. Potentially interested participants were told that that they would complete the study twice; with the participants completing the study before session 1 and following session 10 of acute treatment. An independent evaluator (IE) who was blind to treatment condition administered standardized diagnostic interviews (PSS-I, SCID-IV). After the consent procedure and pre-treatment assessment, hearing was assessed by presenting the series of 30 and 60 dB tones used for PPI.

Participants were oriented to psychophysiological monitoring procedures. Next, physiological monitoring sensors were attached. To help improve participant attention [23] participants viewed a silent video that showed various scenic panoramas, which ran for the duration of the task. Participants heard soft and loud sounds that were intermittently delivered through the headphones. Following the assessment at pre-treatment, participants were paid \$20/hour. The study was repeated again at post-treatment using the same counterbalancing order. At the end of this visit, participants were debriefed on the study purpose and paid \$20/hour for their participation.

#### Data Analysis

Random effects modeling was conducted to compare individuals in PE to those in sertraline and those who responded more to treatment to those who responded less to treatment on changes in inhibitory functioning, as measured by PPI, from pre- to post-treatment. To measure treatment response, change scores from pre- to post treatment on PSS-I (to examine changes in inhibition as part of treatment) was grand mean centered to provide an interpretable zero point [64]. Specifically, PPI at three lead intervals (30, 60, 120 ms) were examined. The best-fitting models were for random intercept, fixed slopes models,



specifying a covariance structure of variable components, using a Hurvich and Tsai are Criterion (AIC) index and restricted maximum likelihood (REML). Convergence issues occurred when modeling PPI, consistent with repeated observations within a participant are negatively correlated over time [64]. Thus, modeling the covariance structure of the repeated measures, which accommodate this negative within-subject correlation as well as the clustering of the repeated measures, was used [64]. PPI exhibited this pattern with a within-subject correlation of  $r=-0.074$ , and subject-to-subject variability at each time-point of 1501.33 (SE=450.11),  $\chi^2(1)=11.12$ ,  $p<0.001$ .

## Results

Means and standard errors for PPI (30 ms, 60 ms, 120 ms) at pre- and post-treatment can be seen in Table 2.

### Treatment modality PE vs. sertraline PPI changes over time

To compare two treatment modalities from pre- to post-treatment, models were fit for each short lead intervals of PPI (30 ms, 60 ms, 120 ms) as the dependent variables. For the short lead interval of 30 ms, the fixed effect of time predicted PPI at post-treatment,  $F(1, 33.02)=4.25$ ,  $p=.047$ ,  $B=-24.39$ ,  $SE=11.83$ ,  $d=0.67$ , showing a decline in automatic PPI inhibitory processes from pre- to post-treatment. No other effects were significant for 30 ms, 60 ms, or 120 ms lead intervals, such that there was no differential effect between PE and sertraline on changes in PPI.

### Treatment response PPI changes over time

To examine clinical response, defined as change in pre-treatment interviewer-rated PTSD severity (PSS-I) to post-treatment, models were similarly fit for each of the short lead intervals of PPI (30 ms, 60 ms, 120 ms) as the dependent variables. At 30 ms, mirroring the above analysis, there was an effect of time,  $F(1, 33.02)=4.25$ ,  $p=0.047$ ,  $B=-24.39$ ,  $SE=11.83$ ,  $d=0.67$ , where percent inhibition on 30 ms short lead interval decreased from pre- ( $M=13.43$ ,  $SE=7.24$ ) to post-treatment ( $M=-7.60$ ,  $SE=7.54$ ). There was also a trend toward an effect of response,  $F(1, 25.84)=3.85$ ,  $p=0.06$ ,  $B=1.04$ ,  $SE=0.53$ ,  $d=0.77$ . No other effects were significant.

For 60 ms lead interval, again, there was a trend toward an effect of response,  $F(1, 30.1)=3.93$ ,  $p=0.06$ ,  $B=1.15$ ,  $SE=0.58$ ,  $d=0.72$ . No other effects were significant.

Notably, at 120 ms, this effect achieved significance, with PPI predicting response at 120 ms short-lead interval,  $F(1, 23.34)=5.29$ ,  $p=0.031$ ,  $B=1.16$ ,  $SE=0.51$ ,  $d=0.95$ , suggesting that better pre-treatment PPI, particularly at 120 ms, strongly coincided with stronger improvement of PTSD symptoms from pre- to post-treatment. (Figure 1) shows estimated 120 ms PPI for average change in PTSD severity from pre- to post treatment (Mean), in comparison to those who made better than average response (Mean + 1 SD) and those who made worse than average response (Mean - 1 SD).

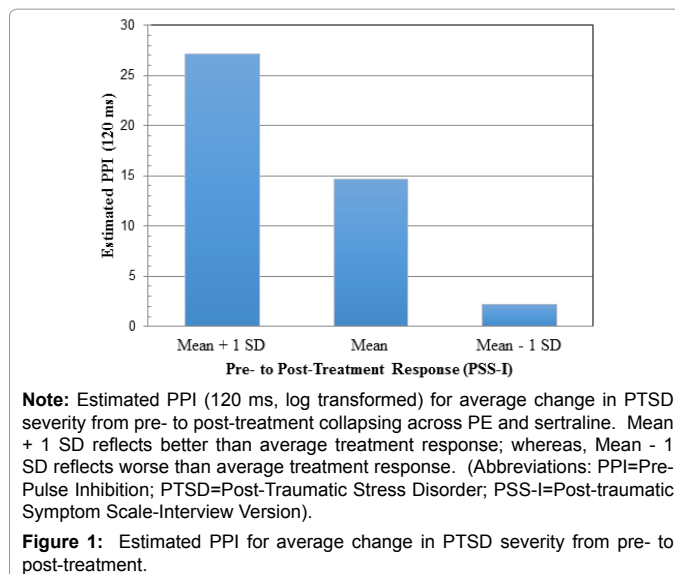
## Discussion

This is one of the first studies to directly examine changes in inhibitory

Variables	Pre-treatment		Post-treatment	
	M	SE	M	SE
PPI (% Change Score)				
30 ms	13.43	7.24	-7.60	7.54
60 ms	18.26	7.60	5.00	9.29
120 ms	16.43	6.81	4.18	6.64

N=49. PPI=Pre-pulse Inhibition.

Table 2: Pre-treatment and post-treatment PPI.



processes in PTSD following psychotherapy and pharmacotherapy. As predicted, PE and sertraline modulated inhibitory processes from pre- to post-treatment. Although PE and SER did not differentially change PPI from pre- to post-treatment; more efficient PPI, specifically at the more attentional processing level (120 ms), was associated with better treatment response, pointing to a potential pre-treatment biomarker for overall treatment response. Thus, fundamental inhibitory processes of better inhibition of startle were associated with treatment response to both PE and sertraline, suggesting a critical process implicated in PTSD treatment response.

There was a general pattern of decreased early sensory gating (across PE and sertraline) from pre- to post-treatment, suggesting a decline in automatic inhibitory processes following psychotherapy and pharmacotherapy. This finding is in accord with the physiological dysregulation in PTSD through disturbances in early sensory flooding [22] and a faulty neural inhibitory network between the prefrontal regions and amygdala [2,3] implicated in the pathophysiology of PTSD. Further, these findings point to a final common pathway in engaging the prefrontal and amygdala neural network across PE and sertraline [7]. Some suggest that a top down modulation of amygdala activity is thought to underlie exposure therapy whereas a bottom up modulation by the amygdala is likely to underlie sertraline [66,67]. In a meta-analysis comparing cognitive behavioral therapy and antidepressants for depression, CBT involved similar brain changes as those seen with antidepressants following treatment [68]. In summary, PE and sertraline may converge on a final pathway in engaging the prefrontal and amygdala neural network, which may account for decreased early sensory gating seen in both treatments over time.

Better overall strategic attentional inhibition (120 ms) was associated with better PTSD treatment response, suggesting individuals with the ability to inhibit attention responded better to treatment, regardless of treatment modality. The size of the effects across all lead intervals were large but the findings for 30 ms and 60 ms short-lead intervals were at a trend level probably due to sample size limitations. These findings extend the work by [69]. where higher pre-treatment activity of the frontal network during an inhibitory control task in individuals with PTSD was related to better treatment outcome. The authors posited that increased efficiency or reduced demand on inhibitory control networks may predict better treatment outcome, as the ability to inhibit

perseveration of previous behavioral associations reduces interference with new associations learned in therapy. Conversely, poorer treatment response was related to a lower inhibitory control. [70,71] argues that anxious individuals exhibit key deficits in inhibitory learning and enhanced fear generalization that are thought to enhance extinction learning in exposure therapy. Consequently, these individuals may make out poorly in treatment or may be less likely to remit completely. If treatments for PTSD work in normalizing inhibitory deficits [35], those with better inhibition at pre-treatment may have an advantage over those with worse inhibition.

The strong association between better PPI and treatment response points to the possibility of using a biomarker strategy in facilitating treatment response in PTSD. Across the anxiety and traumatic-stressor related disorders, [72] points out that a proportion of anxious individuals will fail to remit and may even remain symptomatic following treatment. One clinical implication may be that biomarkers may reflect targets to strengthen inhibitory control prior to starting either pharmacotherapy or psychotherapy for PTSD. As deficits in inhibition may interfere with one's ability to benefit from exposure therapy [70] enhancement strategies have the potential to optimize exposure therapy by focusing on general factors that are not directly targeted in CBT. Patient matching, particularly augmenting inhibitory learning before psychotherapy and pharmacotherapy for those with clear pre-treatment deficits, could result in significantly more inhibitory learning, accelerate therapeutic gains, and ultimately better treatment response. As there are few studies that have examined markers of treatment recovery in PTSD, these findings are preliminary and need replication.

## Limitations

Several limitations are worth noting. There was no waitlist or placebo condition, and the design was such that it did not include an untreated group given the efficacy of PE and sertraline for PTSD [35]. Changes in inhibition might be due to the passage of time; however, it is well established that chronic PTSD symptoms do not substantially improve on their own in waitlist conditions, relaxation, placebo, or supportive control conditions [73,74,35]. Arguing against the effects of time alone. Also, comparison groups such as other inhibition-related disorders (e.g., ADHD) that might be expected to show similar modulations in inhibition were not included; and thus it is unknown whether the pattern of findings are specific to PTSD or not. It also remains to be determined whether the inhibitory deficits existed prior to PTSD or whether they developed with the disorder. Future research should utilize prospective pre-trauma exposure designs, to provide a better understanding of the relationship between trauma exposure and changes in inhibitory modulation over time. Although multi-level modeling does not require complete data on all participants on all outcome measures, whether missing data were ignorable or non-ignorable was examined because of the limitations of the sample size and inability to use pattern mixture modeling [75]. Finally, this study used a subsample of individuals from a larger randomized clinical trial, who opted to participate in this study. Accordingly, they may differ from those in the larger trial on some unmeasured third variable, as they are not a random subset of the trial [76-78].

## Conclusion

Taken together, better inhibitory processes may play a critical role in the response to PTSD treatment. Individuals who made clinical improvements across both PE and sertraline also had better pre-treatment inhibition, potentially highlighting the importance of

sensory gating relevant from irrelevant information in enhancing the prefrontal-amygdala network in PTSD. Future work should consider targeting improving sensory gating in PTSD using novel therapeutic interventions. In conclusion, successful sensory gating may be implicated in treatment recovery and may not only help advance our theories of therapeutic change but also serve as a pre-treatment marker of treatment response in PTSD.

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