Alterations in Inhibition Underlying Treatment Effects and Recovery in PTSD

Aileen M. Echiverri-Cohen

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Reading Committee

Lori A. Zoellner, Chair

Robert Kohlenberg

Theodore Beauchaine

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Abstract

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Aileen M. Echiverri-Cohen

Chair of Supervisory Committee:
Professor Lori A. Zoellner
Psychology Department

Inhibitory deficits expressed as difficulty ignoring irrelevant stimuli in the pursuit of goal-directed behavior may be crucial in our understanding of information processing in posttraumatic stress disorder (PTSD) and may serve as a fundamental mechanism of the disorder. If inhibitory deficits underlie the cognitive abnormalities in PTSD, then inhibition should improve with treatment; however, no published studies have examined changes in inhibition following PTSD treatment. Evidence of inhibitory processes as central to extinction suggests that exposure-based treatments may act directly on the inhibitory deficits implicated in PTSD, with selective serotonin reuptake inhibitors (SSRIs) facilitating serotonergic neurotransmission to bring about neurochemical changes in the fear circuitry. Accordingly, the present study examined changes in inhibition at pre-and post-treatment in individuals with chronic PTSD. Two inhibitory measures, attentional blink, a task that examines the temporal sequence of inhibition, and prepulse inhibition of startle, a behavioral measure that indexes the strength of inhibition, were used to

study inhibition pre- and post-treatment. Specifically, this study examined whether inhibition changes with 10 weeks of prolonged exposure, a variant of an exposure-based treatment, or sertraline, the best-studied SSRI, for chronic PTSD. Treatment modality and treatment responder were examined to ascertain whether they change inhibition differentially. In addition, pre-treatment inhibitory deficits were examined as a predictor of change in trauma-related symptoms. Finally, individual difference factors such as age, sex, and education were examined as predictors of changes in inhibition. Individuals who made greater improvements with prolonged exposure showed faster improvements in inhibition on the critical inhibitory lag of the attentional blink task than sertraline, showing a large effect for this interaction, and pointing to potentially different mechanisms of treatment response in PTSD. Related to this, better inhibitory functioning on PPI, with a large effect at trend level, was associated with better treatment response, consistent with prepulse inhibitory functioning potentially serving as pre-treatment biomarker for treatment response. Finally, age contributed to slower improvements in a critical inhibitory lag of the attentional blink task over time, suggesting older individuals are associated with making less changes in inhibitory processes. Thus, differential modulation in fundamental attentional inhibitory processes by treatment responders suggests differential specificity in how prolonged exposure and sertraline normalize inhibitory processes. Further, prolonged exposure and sertraline may use specific pathways in how they bring about therapeutic change, however ultimately converge on a final common pathway in reducing amygdala reactivity.

TABLE OF CONTENTS

Page

LIST OF FIGURES

LIST OF TABLES

INTRODUCTION

Failure of inhibitory processes involved in the voluntary suppression of information (i.e., stimuli classified as irrelevant for an ongoing task; Harnishfeger & Bjorklund, 1993; Harnishbeger, 1995) have been implicated in the development, maintenance, and treatment of posttraumatic stress disorder (PTSD; Vasterling, Duke, Brailey, Constans, Allain & Sutker, 2002). Given that preliminary work suggests that treatment recovery is associated with improvement in cognitive deficits in inhibition (e.g., Vermetten, Vythilingam, Southwick, Charney, & Bremner, 2003), treatment outcome in PTSD should be related to measures of inhibition; however, no study has directly examined this relationship.

Many researchers and theorists (e.g., Blechert, Michael, Vriends, Margraf, & Wilhelm, 2007; Rothbaum & Davis, 2003) conceptualize PTSD as an overgeneralization of stress responding to non-fearful stimuli. Although pre-existing inhibitory deficits may increase the likelihood of this overgeneralization, over time this overgeneralization may lead to a breakdown of inhibitory processes associated with executive functioning (Bremner et al., 1993; Sutker, Davis, Mark, Uddo, & Ditta, 1995). Specifically, there is accumulating evidence from neuroimaging studies that the medial prefrontal cortex (mPFC) assumes an inhibitory role in emotion and cognition (Whalen et al., 1998; Bush, Luu, & Posner, 2000, Kerns, Cohen, MacDonald, Cho, Stenger, & Carter, 2004). PTSD is characterized by functional abnormalities between the mPFC and amygdala (Gilboa et al., 2004; Lanius et al., 2001). Specifically, reduced activity in the mPFC and greater activity in the amygdala in PTSD is thought to reflect a potential failure of the mPFC to inhibit an overactivated amygdala (e.g., Morgan, Grillon, Southwick, Davis, & Charney, 1996; Bremner, Narayan, Staib, Southwick, McGlashan, & Charney, 1999; Quirk & Beer, 2006). Thus, abnormalities in the functional relationship of these

brain regions associated with a wide range of executive functions may reflect inhibitory dysfunctions in behavioral performance and clinical symptoms in PTSD.

Although major neurobiological models address inhibitory dysfunction in PTSD (e.g., inescapable shock, van der Kolk, Greenberg, Boyd, & Krystal, 1985; kindling, Friedman, 1988), one of the earliest models connecting impaired inhibitory control to the prefrontal cortex and amygdala was a neuropsychological model posited by Kolb (1987). Kolb proposed that PTSD results from excessive stimulation in brain structures including the amygdala that, in turn, promotes sensitization and disrupts activity in the frontal executive systems responsible for inhibiting cortical and subcortical structures. Expanding upon Kolb's original hypothesis, others have argued further for deficient inhibitory control by the mPFC over the amygdala in PTSD (Rau, DeCola, & Fanselow, 2005; Pitman, Shin & Rauch, 2001; Charney, 2004).

Both sensitization, an increase in reactivity to potent stimuli after repeated exposure over time (e.g., Groves & Thompson, 1976), and kindling, repeated subthreshold stimulation leading to increased reactivity (e.g., Goddard, McIntyre, & Leech, 1969), have been posited to account for deficient top-down control by the mPFC on the amygdala. Accordingly, the functional connectivity network made up of the prefrontal cortex and subcortical structures, such as the amygdala (Gilboa et al., 2004), may reflect neural substrates of inhibition. The functionally deficient inhibitory networks are presumed to have a negative effect on information processing (Bremner et al., 1993). The mPFC and anterior cingulate are involved in a range of executive functions including error monitoring, and detecting failures of the executive system in carrying out goal-directed processing of information (Hajcak & Simons, 2008, Lavie, Hirst, de Fockert, & Viding, 2004). Consequently, a functionally deficient mPFC may indicate a dysfunction in inhibitory mechanisms necessary for regulating information processing. This is consistent with

findings of individuals with PTSD having difficulty filtering trivial stimuli and attending to relevant aspects of the environment (e.g., McFarlane, Weber, & Clark, 1993; Paige, Reid, Allen, & Newton, 1990; Vasterling, Brailey, Constans, & Sutker, 1998). Taken together, the mPFC carries out executive functions necessary for inhibition and, if impaired, as thought in individuals with PTSD, may lead to impairment in executive functioning.

This failure to inhibit prepotent responses, or highly practiced responses, in PTSD may contribute to impaired performance seen across cognitive domains (Vasterling & Brailey, 2005). Consistent with this, there is strong support for this type of dysfunction in individuals with PTSD on performance-based behavioral tasks using trauma-neutral stimuli. Individuals with PTSD are slower, less accurate, and make more errors compared to controls on Stroop tasks (counting/color; Shin et al., 2001; Bremner et al., 2004; Klumpers Tulen, Timmerman, Fekkes, Loonen, & Boomsma, 2004), continuous performance tasks (Semple, Goyer, McCormick, Compton-Toth, Morris, & Donovan, 1993; Semple et al., 1996; 2000; Kimble, Kaloupek, Kaufman, & Deldin, 2000; Felmingham et al., 2007; Vasterling et al., 2002), go/no-go tasks (Mackenzie et al., 2002; Metzger, Orr, Lasko, & Pitman, 1997; Navalta, Polcari, Webster, Boghossian, & Teicher, 2006; Weber, Bush, & McNally, 2005), working memory updating (Clark et al., 2003; Shaw et al., 2002; Galletly, Clark, McFarlane, & Weber, 2001; Beers & De Bellis, 2002; Vasterling et al., 1998), and oddball tasks (e.g., Bryant et al., 2005; Metzger et al., 1997; Araki et al., 2005).

There is also evidence that poor executive performance results from decreased activity in the mPFC and other brain structures implicated in inhibitory processing. Individuals with PTSD show increased perseveration in object-alternation tasks that recruit the mPFC (Koenen et al., 2001). In addition, event related potential (ERP) and positron emission tomography (PET)

studies show a correspondence between decreased cognitive activation in the prefrontal region (e.g., decreased P3 amplitude, decreased regional cerebral blood flow) and decreased reaction time or decreased accuracy on response tasks in individuals with PTSD compared to those without psychopathology (e.g., Boudarene & Timsit-Berthier, 1997; McFarlane, et al., 1993; Galletly et al., 2001; Clark et al., 2003; Shaw et al., 2002; Semple et al.; 1996; Vasterling et al., 1998, 2002; Koso & Hansen, 2006; Navalta et al., 2006; Beers et al., 2002). However, many of these studies suffer from low sample sizes, lack of comparison groups to control for trauma exposure, or failure to control for such things as history of psychotropic treatment and substance use. Nevertheless, the initial pattern of results suggests that deficient inhibitory processes underlie, at least in part, the poor cognitive performance in tasks using trauma-neutral stimuli and the decreased activity in the prefrontal brain regions observed in individuals with PTSD.

Two relevant measures of inhibition are attentional blink (AB; Raymond, Shapiro, & Arnell, 1992), a behavioral measure assessing reduced ability to direct attention to multiple stimuli in a visual stream, and prepulse inhibition of startle (PPI; Braff & Geyer, 1990), a psychophysiological measure evaluating the strength of inhibition in gating irrelevant information. The AB is a cognitive paradigm that is thought to be linked to inhibitory processes by directing attentional resources to one target thereby affecting the processing of the subsequent target (Raymond et al., 1992). Using a rapid serial visual presentation sequence (RSVP) in which target (T) stimuli (e.g., letters) are embedded in a stream of distractor (D) stimuli (e.g., numbers; Raymond, et al., 1992), participants are instructed to identify the first and second targets from a set of possible targets that are separated by intervening distractors also referred to as a lag (L). Individuals typically show high rates of correct identification of both targets under a Lag 1 condition (e.g., no intervening distractors between targets); however, individuals typically show

lower rates of correct identification of the second target under Lag 2 and 3 conditions (e.g., one or two distractors presented between targets). With more than two intervening distractors, participants are again able to correctly identify both targets under Lag 4 and 5 conditions. This is termed an "attentional blink," referring to a deficit in the ability to identify a second target of a pair of stimuli presented closely in time. This is thought to happen because the presentation of two or more distractors allows the participant to recover from the impairment in attention. Accordingly, when plotting accuracy of identification of the second target (T2), a U-shaped pattern emerges as a function of length of lag.

Cognitive models of AB that explain this U-shaped pattern fall into two categories: early (attentional gating model; Weighselgartner & Sperling, 1987; inhibition model, Raymond, et al., 1992) or late selection (two-stage processing model; Chun & Potter, 1995, interference model; Shapiro, Raymond, & Arnell, 1994). Both highlight the limitations in processing two targets close in time within a stream of stimuli (Peterson & Juola, 2000). Early selection refers to the recruitment of attentional resources in the early stage of visual processing initiated by the processing resources needed in the identification of the first target that leads to poor identification of the second target. In contrast, with late selection, attentional resources are recruited by an item in the distractor position immediately following the first target leading to limited resources in processing the second target. Although more studies are consistent with late selection (e.g., Vogel, Luck, & Shapiro, 1998, Vogel & Luck, 2002; Di Lillo et al., 2005) than early selection theories (e.g., Giesbrecht & Kingstone, 2004), others show that attentional mechanisms may operate at multiple levels of perception. Indeed, recent studies have adopted a connectionist model that suggests that both perceptual and post-perceptual level selection in AB can occur (Bowman & Wyble, 2007; Giesbrecht et al., 2009), depending on task demands (e.g.,

Lavie et al., 2004; Vogel, Woodman, & Luck, 2005), with early-stage perceptual factors and late-stage central capacity limitations both modulating AB.

Overall, AB measures the ability to direct attention to multiple stimuli and assesses temporal cognitive processing, providing a solid cognitive index of inhibitory processing. AB has not been examined in PTSD. Yet, there is evidence of AB deficits in disorders including schizophrenia (Li, Lin, Yang, Huang, Chen, & Chen, 2002; Wynn, Breitmeyeer, Nuechterlein, & Green, 2006), attention deficit hyperactivity disorder (Armstrong & Munoz, 2003; Hollingsworth, McAuliffe, & Knowlton, 2001; Li, Lin, Chang, & Hung, 2004; Mason, Humphrey, & Kent, 2005), and dysphoric mood (Rokke, Arnell, Koch, & Andrews, 2002). These studies typically show a deep, protracted u-shaped curve, suggesting a slower recovery from the impairment in attention that may result from limited attentional resources.

Similarly, inhibitory processes that drive AB may be related to those influencing prepulse inhibition of startle (PPI; Filion, Kelly, & Hazlett, 1999). PPI is a form of startle modulation which occurs when a non-startling prepulse precedes the startling pulse by a short interval (e.g, 30 - 120 ms), resulting in inhibition of the startle reflex (Blumenthal, 1999). 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 (Graham, 1975). PPI is proposed to index early stages of lower level, automatic processing and voluntary, controlled, attentional processing. These levels of processing follow different time courses, such that automatic processing occurs before 120 ms (Wu, Krueger, Ison, & Gerrard, 1984; Wynn , Schell, & Dawson, 1996), whereas controlled processing occurs at or after 120 ms (Blumenthal, 1999; Dawson, Hazlett, Filion, Nuechterlein, & Schell, 1993; Filion et al., 1999). Greater PPI is presumed to be associated with more effective information processing (e.g., Bitsios,

Giakoumaki, Theou, & Frangou, 2006; Giakoumaki, Bitsios, & Frangou, 2006); whereas, lower PPI is thought to reflect reduced efficiency in filtering information. Thus, impaired PPI may reflect a reduced ability to inhibit sensory information, as well as a failure of sensorimotor gating. Accordingly, PPI has been used to study inhibitory deficits across various forms of psychopathology (e.g., schizophrenia; Swerdlow, Light, Cadenhead, Sprock, Hsieh, & Braff, 2006; obsessive compulsive disorder; Swerdlow, Benbow, Zisook, Geyer, & Braff, 1993).

The PPI studies in individuals with PTSD are at present equivocal, though there is general evidence pointing to reduced PPI compared to controls (Grillon, Morgan, Southwick, Davis, & Charney, 1996; Grillon, Morgan, Davis, & Southwick, 1998; Ornitz & Pynoos, 1989). Specifically, Grillon et al. (1996) examined PPI in combat veterans with PTSD and found a lower PPI compared to a no psychopathology control group and a trend toward lower PPI compared to a trauma-exposed group (Grillon et al., 1996). Reduced PPI in PTSD compared to controls was replicated in another investigation by the same group (Grillon et al., 1998). In contrast, two studies (Butler, Braff, Rausch, Jenkins, Sprock, & Geyer, 1990; Morgan, Grillon, Lubin, & Southwick, 1997) showed no differences in PPI across PTSD and control groups. However, both studies had notable confounds. Butler et al. (1990) removed 35% of the sample from their analyses based on a conservative criteria for identifying startle non-responders (less than 120 uV in the 116dB group). Morgan et al.'s study utilized a sample of female assault victims without isolating the effects of elevated estrogen, which has been associated with reduced PPI responding (Swerdlow, Hartman, & Auerbach, 1997). Thus, not controlling for phase of menstrual cycle may have accounted for these negative findings.

AB and PPI are thought to be functionally linked, with AB potentially indicating the duration of inhibition and PPI potentially reflecting the strength of inhibition (Cornwell,

Echiverri, & Grillon; 2006). Given that the mPFC is implicated in fear inhibition during treatment (Milad & Quirk, 2002) and in impaired top-down control of the amygdala (Milad et al., 2009), increased inhibitory processes may underlie treatment recovery (Rauch, Shin, Whalen, & Pitman, 1998). Accordingly, the potential effects of pharmacological agents such as selective serotonin reuptake inhibitors (SSRIs) and exposure-based psychotherapies, such as prolonged exposure, on the relationship between the mPFC and the amygdala suggest that inhibitory deficits may be normalized over the course of treatment. Therefore, inhibitory processes ought to improve following successful treatment.

Generally, the preponderance of work suggests that selective serotonin reuptake inhibitors (SSRIs) are effective in treating PTSD (e.g., Brady et al., 2000; Davidson, Rothbaum, van der Kolk, Sikes, & Farfel, 2001; Davidson et al., 2003; Marshall, Beebe, Oldham, & Zaninelli, 2001; Rothbaum, Ninan, & Thomas, 1996). Of all the SSRIs, sertraline (SER) is the best studied for PTSD (Fabre et al., 1995; Davidson et al., 2003, 2001). Although there is no direct evidence of inhibitory changes, indirect evidence from animals and humans of the mPFC and amygdala after SSRI administration points to a potential link between SSRIs and enhanced inhibition. Animal studies show initial evidence of functional changes in the brain implicated in inhibition from pharmacotherapy. For instance, there is a growing body of evidence to suggest that SSRIs enhance neurotransmission of serotonin to metabolize stress hormones (e.g., Heym & Koe, 1998; Hashimoto et al., 1999; Inoue et al., 1996; Geyer et al., 1988), down-regulates noradrenergic neurotransmission (Koe, Koch, Lebel, Minor & Page, 1987), and reduces immobility or inactivity (Koe, Weissman, Welch, & Browne, 1983). There are no animal studies to date that have examined the chronic effects of SSRIs in animal models of PTSD. Still, the pattern of evidence in animal research offers a modicum of support for improvement in

inhibitory processes with SSRI administration. Although there are no human studies in PTSD that have examined the effects of SSRIs directly on inhibitory functioning from pre- to post-treatment, SER is thought to facilitate serotonergic transmission by blocking the reuptake of serotonin transporter, resulting in neurochemical changes in the prefrontal-amygdala circuitry (Brady et al., 2000; Davidson et al., 2001).

Preliminary evidence suggests SSRIs show an increase in activation in brain regions such as the mPFC that are thought to be associated with executive functioning and inhibition (Seedat et al., 2004; Sachinvala et al., 2000; Vermetten et al., 2003), though the studies are limited by small and uncontrolled samples. Specifically, using single photon emission computed tomography (SPECT), Seedat et al. (2004) examined a sample of two civilians and nine combat veterans with PTSD before and after eight weeks with the SSRI, citalopram. There were no pre-treatment differences in regional cerebral blood flow (rCBF) in the anterior cingulate between those individuals who showed a significant reduction in PTSD symptoms and those that did not. At post-treatment, there was decreased rCBF in the left medial temporal cortex in the PTSD group, regardless of whether they responded to treatment. In addition, they found a correlation between PTSD symptoms and activation of the mPFC, such that higher activation of the mPFC was related to less PTSD symptoms at post-treatment. Similarly, in another SPECT study, Sachinvala et al. (2000) compared 17 veterans undergoing group therapy for PTSD, with 12 of these individuals also on anti-depressants (5 SSRI, 7 tricyclic anti-depressant) to 8 healthy controls. At post treatment, they found increased rCBF activity of the anterior cingulate regions, regardless of treatment status. Finally, in a sample of 23 patients with PTSD, executive functioning was examined following nine to twelve months of treatment with the SSRI, paroxetine (Vermetten et al., 2003). Long-term administration of paroxetine was associated with

an increase in verbal memory and improvement in PTSD symptoms. In summary, SSRIs appear to have effects that may at a global level improve inhibitory functioning; however, none of these studies used measures that examined inhibition directly. Extrapolating from the existing data, treatment with an SSRI may help extinguish learned fear responses by facilitating neurotransmission of serotonin (Rauch et al., 1998). Accordingly, SSRIs ought to improve inhibitory functioning in individuals with PTSD.

Psychotherapeutic interventions such as exposure therapy, cognitive therapy, stress inoculation training, and eye movement desensitization and reprocessing (EMDR) also reduce PTSD symptoms (e.g., Foa, Dancu, Hembree, Jaycox, Meadows, & Street, 1999; Resick, Nishith, Weaver, Astin, & Feuer, 2002; Rothbaum, Astin, & Marsteller, 2005), with the efficacy of exposure-based psychotherapies being well established (Institute of Medicine, 2007). Prolonged exposure (PE), a form of exposure therapy, is a theory-based treatment that uses principles of extinction to create an inhibitory association that suppresses the conditioned response (CR; Bouton 1991; 1988; 2004; Bouton & Bolles, 1985). Indeed, the excitatory association acquired during fear learning, which is a process by which individuals' learn the association between the conditioned stimulus (CS) and the unconditioned stimulus (UCS), is robust. It is theorized that extinction inhibits this excitatory learning by making the meaning of the CS ambiguous (Bouton, 1991; 1993, 2004, Bouton & Bolles, 1985). However the inhibitory association, or new learning brought about through extinction, is gated by context, so that context is the occasion setter that determines whether one learning or another is activated, making this learning fragile. Exposure-based treatments principally rely on extinction processes (Craske, Kircanski, Zelikowsky, Mystkowski, Chowdhury, & Baker, 2008), the subsequent goal being to consolidate inhibitory learning in therapy by creating multiple contexts that

disambiguate the original fear association between the CS and UCS. Similar to the pharmacotherapy and PTSD literature, no studies have examined changes in inhibitory functioning directly with psychotherapy in PTSD. Yet, there is preliminary evidence for improved inhibitory functioning with psychotherapy. Given the role of the mPFC in the inhibitory learning that occurs during extinction in animals (Milad et al., 2002), the mPFC is also believed to play a similar role in the inhibitory learning that occurs in exposure therapy in humans (Nutt & Malizia, 2004).

Three preliminary studies, although not directly looking at inhibition, show functional improvements in the inhibitory-related, cortico-prefrontal circuitry following psychosocial PTSD treatments (Felmingham et al., 2007; Levin, Lazrove, & van der Kolk, 1999). Felmingham et al. (2007) presented eight individuals with PTSD with a symptom provocation task using stimuli made up of fearful and neutral facial expressions before and after eight sessions of imaginal exposure and cognitive restructuring. Although there was no differential amygdala activity at either pre-treatment or six month follow-up, these individuals showed increased rostral anterior cingulate cortex (rACC) activity during fear processing from pre-treatment to follow-up. Further, increased changes from pre-treatment to follow-up on anterior cortex activity were correlated with a reduction in PTSD symptoms (Felmingham et al., 2007). Similarly, a functional magnetic resonance imaging study (fMRI; Kim, 2006) examined individuals with PTSD treated with PE before and after treatment. Notably, there was in increase in activation of the Broca's area from pre- to post-treatment, presumably reflecting cognitive processing of the traumatic experience and improvement in PTSD. Finally, Levin et al. (1999) presented a case study of a man who was abused as a child and treated with three, weekly EMDR sessions from pre- to post-treatment. Although on an antidepressant during EMDR, the authors found that increased resting anterior

cingulate gyrus and left frontal lobe activity coincided with decrements in PTSD symptoms from pre to post-treatment. Thus, evidence from three preliminary studies, albeit inconsistent, suggests that psychotherapy may improve inhibitory functioning in PTSD.

Taken together, both SER and PE are effective treatments for chronic PTSD (Foa et al., 1999; Brady et al., 2000) and both are thought to potentially affect the fear circuitry involved in inhibitory learning (Felmingham et al., 2007; Rauch et al., 1998). Despite this, and with no trial to date directly comparing these two treatments, one treatment may be more superior in leading to greater changes in inhibitory processes. A comparison of pre- to post-treatment effect sizes showed PE typically produced larger effects (e.g., Foa et al., 2005) than SER (e.g., Brady et al., 2000; Friedman, Davidson, & Stein, 2009). Further, the Institute of Medicine (2007) report also concluded that while there were enough efficacy studies in support of exposure therapy as a treatment for PTSD, there were not for SSRIs. Thus, individuals with PTSD treated with PE were expected to produce more sustained and stronger changes in inhibition than with SER.

Further, if inhibitory processes are a critical mechanism in PTSD treatment, regardless of treatment modality, individuals with PTSD should show concomitant improvement in inhibition and PTSD symptoms following treatment. Indeed, both psychotherapy (e.g., Felmingham et al., 2007) and pharmacotherapy (Rauch et al., 1998; Sachinvala et al., 2000; Seedat et al., 2004) for PTSD are thought to strengthen the inhibitory control of the mPFC over a hyperactive amygdala, resulting in a reduction of PTSD symptoms as well as improvement in overall functioning (e.g., Bryant et al, 2005; Ohtani & Matsuo, 2006). Therefore, PE and SER may ultimately work towards the same goal of restoring the functional integrity of the brain structures implicated in inhibition, which may be sufficient to bring about overall symptom reduction in PTSD.

Regardless of the general effects of treatment modality and treatment response on inhibition, the effects may be specific to certain individual characteristics. Pre-treatment inhibitory deficits may be able to predict not only improved PTSD symptoms but also improved anxiety, depression, and functioning following treatment. As discussed above, both PE and SER have the potential to improve inhibitory functioning in individuals with PTSD. Thus, if treatments work to normalize inhibitory processes, then individuals with reduced inhibitory functioning at pre-treatment may be more likely to show greater treatment gains in PTSD and overall functioning than those individuals with greater inhibitory functioning at post-treatment.

Individual difference factors, specifically gender, age, and education may also contribute to improvement in inhibition over the course of treatment. There are wide individual differences in PPI across women and men, with women showing worse sensorimotor gating than men on PPI (Swerdlow et al., 1999; Swerdlow, Filion,.Geyer, & Braff; 1995; Swerdlow, Auerbach, Monroe, Hartston, Geyer, & Braff, 1993). Similarly, inhibitory processes are sensitive to age differences, with older individuals exhibiting deficits in inhibitory measures including Stroop and negative priming (Swerdlow et al., 1993) and eye movement tasks (Butler & Zacks, 2006). Impaired inhibitory processes have also been observed during tests measuring inhibition (go/no go) in individuals with lower education attainment (Spinella & Miley, 2004). Thus, because these individuals may be more likely to have problems with inhibition and potentially more room for improvement in inhibitory functioning, being female, being older, and having less years of education may predict improvement in inhibitory functioning from pre- to post-treatment.

The current study examined inhibitory changes, as assessed using AB and PPI, at pre-and post-treatment for individuals with chronic PTSD. Individuals with chronic PTSD were part of a larger PTSD treatment trial at the University of Washington (R01MH066347) and Case Western

Reserve University (R01MH066348) that compared ten weeks of pharmacotherapy using sertraline to 10 weeks of psychotherapy using PE. Interviewers blind to PTSD treatment condition assessed PTSD, depression, trait anxiety, dissociation, broader functioning, and treatment drop-out at pre- and post-treatment, and at three-month follow-up.

Four main questions were examined. First, do different forms of treatment, prolonged exposure versus sertraline, differentially improve AB and PPI deficits? Given that not only are there larger effect sizes associated with PE over SER (Friedman et al., 2009), but that exposure-based therapies also parallel the processes involved in extinction that aim to strengthen inhibitory processes (Craske et al., 2008), it was hypothesized that individuals with PTSD treated with PE would show greater improvement in their performance on AB and PPI from pre- to post-treatment than those treated with SER. Second, does successful treatment improve AB and PPI deficits? Specifically, are reductions in PTSD severity associated with improvement in inhibition from pre- to post-treatment. Second, given the effectiveness of both treatments (Foa et al., 1999; Brady et al., 2000) and similar effects on the fear circuitry involved in inhibitory learning (Heym et al., 1998; Felmingham et al., 2007), 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. Third, does pre-treatment inhibition predict changes in trauma-related outcomes over time? If treatments for PTSD work in increasing inhibitory processes, then those individuals with reduced inhibition at pre-treatment may experience greater improvement in PTSD and broader psychopathology symptoms following treatment. As such, it was hypothesized that poorer pre-treatment inhibition measured by decreased inhibition on AB and PPI would predict greater reductions in anxiety, depression, and social functioning from pre- to post-treatment and from

pre- to follow-up. Fourth, do pre-treatment factors of gender, age and education predict increased inhibitory functioning from pre- to post-treatment? Given that differences across pre-existing demographic factors of age, gender, and education are consistently found in relation to inhibition, it was hypothesized that individuals who are older, female, and with less education would show greater improvement in inhibition on AB and PPI from pre- to post-treatment.

METHOD

Participants

Participants were 49 men (25.5%) and women (74.5%) with primary DSM-IV chronic PTSD. All participants were recruited directly from an ongoing PTSD treatment trial (R01MH066347/R01MH066348) through community advertisements and local referrals.

Inclusion criteria for the treatment trial were current PTSD diagnosis based on DSM-IV criteria with at least 12 weeks post-trauma, and be between the age of 18 and 65 years. 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). Participants in PE were asked to discontinue other current trauma-focused psychotherapy. Participants in SER were cross-titrated from any current antidepressant medications to SER. Further, given the role of auditory and visual processing, participants were excluded if their hearing was above 20 dB at 1 kHz or did

not report normal or corrected-to-normal visual acuity. No participants were excluded for either visual or auditory problems. See Table 1 for characteristics of the sample.

Design

The study consisted of individuals with chronic PTSD from pre-to post-treatment, comparing modality (PE vs SER) and treatment response (change in interviewer-rated PTSD severity from pre- to post-treatment). The dependent variables were percent accuracy for attentional blink and percent inhibition of startle for PPI.

Measures

Structured Clinical Interviews. A trained independent evaluator (IE), who was blind to treatment condition, administered the diagnostic interviews and self-report measures. To ensure inter-rater reliability, IEs were trained to a reliable standard of 80% agreement on the Posttraumatic Symptom Scale-Interview (PSSI-I) and Structured Clinical Interview for the DSM-IV (SCID-IV) by joint discussions before beginning assessments. Cross-site training and reliability rating of 10% of the interviews were conducted to minimize rater drift and ascertain reliability.

Posttraumatic Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, & Rothbaum, 1993) is a semi-structured interview that assesses DSM-IV PTSD diagnosis. It yields total symptom severity and symptom cluster severity. It shows good inter-rater reliability (r = .93-.95) and convergent validity with other PTSD measures (Foa, Friedman, & Keane, 2000). Inter-rater reliability was assessed by randomly re-coding 10% of the PSS-I audiotape recordings. In the present study, reliability coding of 10% of the cases yielded good reliability (ICC = .83).

Structured Clinical Interview for the DSM-IV (SCID-IV; First, Spitzer, Gibbon, & Williams, 2002) is a semi-structured diagnostic interview that was used to assess current and past comorbidity and to determine primary diagnostic status of PTSD. An earlier version (SCID-III-R) shows adequate inter-rater agreement for disorders across samples (Segal et al., 1993). Inter-rater reliability was assessed by randomly re-coding 10% of the SCID-IV audiotape recordings. For this study, reliability coding of 10% of the cases yielded good agreement for any current mood disorder (K = .70) and any current anxiety disorder (K = 1.00).

Self-report Measures. Self-report instruments were collected to assess depression, anxiety, dissociation, functioning, and cognitive ability. See Table 2.

Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) is a 21-item inventory that assesses cognitive and physical symptoms of depression. Its concurrent validity with other depression scales is high (Beck, Steer, & Garbin, 1988).

State-Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983) is a 40-item measure that assesses anxiety as a temporary state and enduring trait. The state subscale was used to assess the participant's anxiety at that moment, whereas trait anxiety was used to evaluate the participant's general level of anxiety. It shows high convergent validity (Spielberger et al., 1983).

Dissociative Experiences Scale (DES; Bernstein & Putnam, 1986) is a 28-item self-report inventory of trait dissociation or the general tendency to experience depersonalization, derealization, and altered perceptions during everyday events. DES was scored using the total mean score across all the subscales (depersonalization, derealization, and altered perceptions; Bernstein & Putnam, 1986). It shows good convergent validity (Van Ijzendoorn & Schuengel, 1996).

Sheehan Disability Scale (SDS; Sheehan, 1986) assesses disruption caused by symptoms in work, social activities, and home life. SDS uses an 11-point scale to evaluate disability in each of these three areas, ranging from 0 (*not at all*) to 10 (*very severely*). A global functional impairment score reflecting total impairment in work, social, and home functioning was used. The scale shows adequate reliability and construct validity (Leon, Shear, Portera, & Klerman, 1992).

Shipley Institute of Living Scale (Shipley, 1967) is a 60-item, self-administered test that assesses cognitive functioning in areas of verbal intelligence and abstract reasoning ability. Scores from the verbal intelligence and abstract reasoning subscales yield a composite score for the full scale (Paulson & Lin, 1970). The composite score of the two subscales was used to assess the effects of general cognitive ability. The measure shows good convergent validity with the Weschler Adult Intelligence Scale, (Kaufman, 1990).

Materials

Attentional blink. To provide a behavioral measure of temporal inhibition, a visual AB task was used (Raymond et al., 1992). Specifically, AB was made up of sequences with one or two visual targets (T) embedded in a stream of 16 to 20 distractors (D), referred to as rapid serial visual presentation (RSVP). The target set (T1, T2) consisted of letters (ACEJKRTY), and the distractor set consisted of numerals (23456789). AB was assessed using dual target trials that involved identification of two targets, where T1 was separated from T2 by 1, 2, 3, 4, or 5 serial positions, which was defined as the lag length (L1 - L5). Lag length was defined as the interval with 1 to 4 distractors separating a target from a distractor.

AB presentation was controlled by Eprime software v 1.0 (Psychology Software Tools, Inc.) and presented on a 17-inch Dell monitor. All stimuli were presented in size 48 Times New

Roman font, measuring 10 mm wide and 10 mm tall in white text against a black background. The response keys on the computer keyboard were labeled to aid with identification. All the stimuli within the RSVP sequence were displayed for 16 ms, followed by a 25-30 ms interstimulus interval (ISI). Generation of the targets and distractors were similar to the paradigm used by Cheung, Chen, Chen, Woo, and Yee (2002). The distractors in the RSVP sequence were arranged in a random order, under the constraint that the same distractor cannot appear in the previous four serial positions in the RSVP sequence. The letters were randomly drawn from the target set, and designated T1 and T2. No letter could appear more than once in a block of four consecutive sequences, and a distractor always followed T2. The overall task consisted of 124 sequences, with two separate versions. The first four sequences were practice trials, and the remaining 120 sequences were used for data collection.

Prepulse inhibition. To provide a physiological measure of inhibition, PPI was used (Graham, 1979). 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 (Wu et al., 1984; Wynn et al., 1996) and the 120 ms prepulse interval is thought to reflect more strategic attention (Filion et al., 1993, Hazlett, Dawson, Nuechterlein, & Filion, 1993; McDowd, Filion, Harris, & Braff, 1993).

Intensity levels of the startle probes and non-startling tones were calibrated with a sound level meter (Digital-display sound-level meter, Model: 33-2055). Stimulus presentation was controlled using Eprime software v 1.0 (Psychology Software Tools, Inc.) on a 17-inch Dell monitor. A series of startle stimuli trials were presented either alone or preceded 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.

Physiological recording of orbicularis oculi electromyogram (EMG) were controlled by Coulbourn Instruments Labline LLC (Model v15-17) and acquired by Windaq software 01-720 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.

Treatments

Prolonged exposure (PE; Foa, Hembree, & Dancu, 2002) consisted of 10 weekly 90-120 min individual sessions with study therapists that were either Master's or Ph.D. level trained clinical psychologists. Session 1 involved an overview of the treatment program, rationale for exposure, and instructions on breathing retraining. Session 2 consisted of psychoeducation about common reactions to trauma, and development of an *in vivo* exposure hierarchy that involves setting up a list of avoided trauma-related activities, situations, and places. Sessions 3-9 focused on imaginal exposure to the trauma memory and continued *in vivo* exposure. Clients are

instructed to revisit the trauma as vividly as possible for a duration of 45-60 min. After imaginal exposure, the therapist and client discussed major themes of the imaginal exposure, and *in vivo* and imaginal exposure exercises were assigned for practice between sessions. Session 10 consisted of imaginal exposure followed by relapse prevention and termination. Master's and doctoral level clinical psychologists received formal training with experts in PE (Drs. Edna Foa, Lori Zoellner, and Norah Feeny). Treatment standardization was achieved through weekly supervision, joint cross-training sessions, and outside treatment fidelity ratings. Specifically, assessment of treatment adherence 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 in PE.

Sertraline (SER) consisted of 10 weekly sessions with a board certified psychiatrist who monitored response to medication and offered general support based on a modified treatment manual used in previous medication studies (Marshall & Lockwood, 2002). In the first session (45 min), the study psychiatrist reviewed the client's trauma history and discussed the role of medication in reducing PTSD symptoms. Subsequent sessions ran 15-30 min where current symptoms and side effects were assessed. The final session included medication management and termination, with the encouragement for those who respond to stay on the medication for at least one year (Davidson et al., 2001). 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, as indicated by a standard titration algorithm used in previous clinical trials (i.e., 50 - 200 mg; Brady et al., 2000; Davidson et al., 2001). Sertraline was titrated up based on the client's tolerance and was reduced or discontinued for clients that experienced significant side effects. Similarly, treatment adherence was evaluated by an outside rater who viewed 15% of the

videotapes of SER sessions. For this study, fidelity for SER was high, with 98% of essential elements, including a discussion of dose, side effects, client concerns about the medication, and compliance, covered during sessions.

Procedure

Participants were assessed for initial eligibility including the presence of Criterion A trauma exposure, presence of PTSD symptoms, and other inclusion/exclusion criteria via telephone screening. Potentially eligible participants were invited for an in person assessment. An independent evaluator (IE) who was blind to treatment condition, administered standardized diagnostic interviews (PSS-I, SCID-IV). Participants also completed pre-treatment self-report measures (BDI, STAI, DES). During the informed consent procedure, in addition to providing consent to participate in the treatment study, participants indicated their interest in being contacted to participate in a research study involving psychophysiological responses in PTSD. Potentially interested participants were contacted, provided an overview of the study, and scheduled for a session. Participants were told that that they would complete the study twice; before and after treatment, with the participants completing the study before session 1 and following session 10 of acute treatment. After providing a description of the nature of the study and completing a separate informed consent process for the study, the participant's vision was assessed using a standard Snellen eye chart (1962) and, after fitting the individual with Bose headphones (Model TP-1A,) hearing was assessed by presenting the series of 30 and 60 dB tones used for PPI.

Across participants, to control for order effects, the administration of the PPI and AB tasks was counterbalanced. To set up the AB task, participants sat in a dimly lit room at a viewing distance of 35 cm away from the monitor. Next, participants were instructed to identify

the letters and ignore the numbers from a stream presented in rapid succession. Following the stream of letters and numbers, participants entered the target letters on the keyboard. If no second target was present, participants pressed a key labeled 'NO' on the keyboard to ensure that participants were always entering two responses. Participants started with a practice block of six trials. Participants were given a 1 min break halfway through the AB task.

For the PPI task, participants were oriented to psychophysiological monitoring procedures. Next, physiological monitoring sensors were attached. Participants heard soft and loud sounds that were intermittently delivered through the headphones. To help improve participant attention (Ornitz et al., 1989), participants viewed a silent video that showed various scenic panoramas, which ran for the duration of the task.

Following the assessment at pre-treatment, participants were paid $20/hour for their time. AB and PPI were 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 Reduction

AB. To assess the main AB effect, the percent accuracy of T2 identification was calculated across lags on trials in which T1 was correctly identified (Raymond, Shapiro, & Arnell, 1992), reflecting the probability of correct T2 identification given accurate identification of T1. Accurate identification was defined as correct responding with the correct letters and order in the RSVP out of number of trials in the lag. For example, if T1 is "A" and T2 is "J", the correct responses are "A then J" and not "J then A".

PPI. 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 (Braff, Geyer, & Swerdlow, 2001).

Startle responses were measured by the peak amplitude occurring 20-100 ms after stimulus onset, relative to a 50 ms average baseline preceding probe onset (Balaban, Losito, Simons, & Graham, 1986). Although both percent and arithmetic difference scores can be utilized to assess PPI (Braff et al., 2001), proportion of difference is the method least affected by differences in control reactivity and thus was used instead (Blumenthal, Elden, & Flaten, 2004). Prepulse inhibition was calculated using the proportion of difference method, defined by percent change scores from baseline ITI startle: [((mean prepulse startle -mean ITI startle)/mean ITI startle) x 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. 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 (Blumenthal et al., 2004). Consistent with previous PPI studies (Grillon et al., 1998), six participants were excluded for poor electrode impedances or equipment failure and 5 participants were excluded for participant movement resulting in unstable data (e.g., startle not greater than baseline).

Evaluation of Assumptions and Data Screening

For the main analyses, assumptions including normality of residuals and homoscedasticity of residuals were assessed through data screening procedures (Tasca & Gallop, 2009). Across both AB and PPI, accuracy of data entry was evaluated using frequencies of categorical measures and descriptive statistics (mean, standard deviation, range) of continuous measures. Normality assumptions were assessed through skewness and kurtosis. AB

demonstrated appropriate skewness given the expected skewed nature of the U-shaped curve of the AB effect. In contrast, PPI showed significant positive skewness and was corrected using natural log transformations, consistent with other PPI studies (Ornitz et al., 1989). To reduce outlier status, univariate and multivariate outliers were examined separately at pre- and post-treatment to isolate the correlated observations that often result in consecutive measurements in longitudinal studies (Tasca & Gallop, 2009). Univariate outliers were evaluated by running scatterplots of standardized residuals of measures, in addition to the inspection of z-scores where cases with standardized residual values exceeding 3.29 in absolute value were identified as potential outliers (Tabachnick & Fidell, 2001). The outliers for the repeated measures, were determined by getting the absolute value of the correlation of the observed values and the subject-specific predicted values. The lower 5^{th} percentile of the correlation coefficients were linked back to the subjects corresponding to potential multivariate outliers. Where there were potential outliers, variable transformation or changing scores on the variable for the outlier so that it is less deviant, were considered to minimize variability within groups (Tabachnick & Fidell, 2001). Missing data was addressed using restricted maximum likelihood (REML) within a random effects modeling and mixed model regressions analytic approach assuming that the missing data is independent of outcome variables (Gallop & Tasca, 2009).

Evaluating Possible Covariates

A bivariate correlation matrix was conducted across all variables to evaluate possible covariates. Covariates were included in the analysis if it was theoretically correlated with the outcome variables (Tabachnick et al., 2001). Age and education are demographic variables known to be related to executive functioning (Hasher & Zacks, 1988; Posner & Snyder, 1975;

Spinella & Miley, 2004) were examined as possible covariates to help and reduce error variance and obtain a more powerful test (Tabachnick & Fidell, 2001). Based on the small correlations between the potential covariates and inhibition measures, no covariates were included in the main analyses. However for the exploratory analyses examining pre-treatment inhibition as a predictor of changes in psychopathology, age showed significant correlations with pre-treatment inhibition and was therefore included as a covariate for AB.

Power Analysis

Power analyses were based on a general linear model framework based on the observed effects seen with each of the four specific aims. The general linear model framework provides slightly more conservative power estimates compared to longitudinal model frameworks such as mixed effects modeling. The increase in power for mixed effects models depends on with magnitude of the magnitude of the within subject correlation such that power ranges between the estimates derived in the general linear model framework to 100% power.

Power in the present study was most constrained by the first hypothesis, comparing two treatment modalities (PE vs SER) on AB and PPI from pre-to post-treatment, and the third hypothesis, examining the ability of pre-treatment inhibition (AB: L1, L2, L3, L4, L5; PPI: 30 ms, 60 ms, 120 ms) to predict changes from pre- to post-treatment and follow-up on psychopathology and functioning.

For the first hypothesis, with respect to the treatment modality x time interaction, the sample size of two groups (SER: 29 and PE: 20) yielded 77.1% power to detect a significant interaction when the interaction is a disordinal effect. A disordinal effect means the treatment effect is in opposite directions between the two treatments with effect sizes of 0.8 for each treatment contrast and the two levels of the predictor.

For the third hypothesis of estimating predictors of trauma-related outcomes, with a maximum of five predictor variables (L1, L2, L3, L4, L5), a sample of 49 participants provided a minimum 80% power to detect a large effect (Cohen's d = 0.8).

Thus, power was adequate across main analyses to detect large, clinically relevant effects.

Main Analyses

Random Effects Modeling. Random effects modeling is a widely-accepted data analytic technique in longitudinal research designs because it affords modeling individual change and variances (Tasca & Gallop, 2009). This approach allows for examination of both within-subject (level 1) and between-subject (level 2) factors in a participant's response. The combination of the level 1 and level 2 factors is translated into a mixed linear model with fixed and random coefficients with person-specific parameters corresponding to a random intercept and a random slope. Random effects modeling is appropriate for data that have a nested or hierarchical structure by modeling the within-subject correlation using random effects, and missing data that are inherent in longitudinal treatment data (Gibbons et al., 1993). Random effects modeling is superior to other data analytic techniques that are typically used in repeated measurement studies. Unlike analysis of variance techniques that violate the assumption of sphericity (i.e., equivalent error variances and correlations between two measurements across time) resulting in inflated Type 1 error rates, ignore within subject correlation for hierarchical data resulting in understestimating the variance in the model, and rely on group averages and group variance, random effects modeling does not (Tasca & Gallop, 2009).

For the treatment modality and treatment response analyses, estimation of random effects modeling through SPSS version 18 was used to examine the difference in linear rates of change between treatment and response in inhibition scores from pre- to post-treatment.

The random intercept model equation for treatment modality is

y_{ij} (post-txt AB/PPI) = β_{oi} (intercept; pre-txt AB/PPI) + β_{1i} (slope; time)+ e_{ij}

β_{oi} (intercept) = Y_{00} + Y_{01} (treatment modality : SER/PE) + u_{oi}

β_{1i} (slope) = Y_{00} + Y_{01} (treatment modality : SER/PE) + u_{oi}

The random intercept model for responder status is

y_{ij} (post-txt AB/PPI) = β_{oi} (intercept; pre-txt AB/PPI) + β_{1i} (slope; time)+ e_{ij}

β_{oi} (intercept) = Y_{00} + Y_{01} (responder status) + u_{oi}

β_{1i} (slope) = Y_{00} + Y_{01} (responder status)

For the mixed effects models, all available data from participants were used. In contrast to repeated measures that rely on a completer sample for analysis, mixed effects modeling uses all the available data where individuals missing values at various time-points are retained as long as there is one outcome point. Mixed effects modeling accounts for the within-subject correlation attributable to the repeated measures by either specificity, subject-specific effects (i.e., random effects), or modeling the errors to address the correlation of the repeated measures. The model estimated random effects for treatment and response and differential rates of change per treatment response between treatments were assessed by the treatment x time x response interaction. Hurvich and Tsai's Criterion (AIC) was chosen over the -2 Restricted Log

Likelihood index as it corrects the -2 Restricted Log Liklihood for small sample sizes like in the present study (Fields, 2001). A random intercept, fixed slopes model specified a covariance structure of variable components, as is often the result of small sample size and small number of repeated measures per participant or small levels of variance (Gallop & Tasca, 2009). Restricted maximum likelihood (REML) was used as it yields unbiased estimates of the random effects variances (Twisk, 2006).

The best-fitting model for treatment modality, time, and AB was a random intercept model. This was evaluated by fitting nested structures of the most complex covariance structure for multilevel models, where the specified random effect, (i.e., random intercept and random slope) using an unstructured covariance design with random intercept and random slope terms, were allowed to be correlated. The correlated random terms accounts for a possible relationship between where an individual starts and their rate of change. If the correlation is not significantly different from zero, under parsimony, then the next less complex structure using a variance components structure was fitted to the model where the correlation of the random intercept and random slope term was set to 0. This structure allows for subject-to-subject variability in their group average intercept and group average slope but assumes where a person starts is independent of how they change. If there is not sufficient subject-to-subject variability in rate of change, the parsimonious structure is the least complex structure corresponding to a random intercept model. Under the random intercept model, the covariance structure between the repeated measures is modeled as a compound symmetry structure which is analogous to the simplistic repeated measures ANOVA model for clustered data. Guidelines in assessing the parsimonious covariance structure for the random effects terms was based on Gallop and Tasca (2009).

Data Analytic Strategy

Treatment Modality and Time. To compare individuals treated with sertraline to those treated with prolonged exposure on changes in inhibitory functioning, as measured by AB and PPI, from pre- to post-treatment, random effects modeling was conducted comparing change in inhibition in SER and PE. Specifically, the dependent variables were AB at Lags 1-5 and PPI at three lead intervals (30, 60, 120 ms) were examined.

Responder Status and Time. Next, to compare individuals who responded more to treatment to those who responded less to treatment on changes in inhibitory functioning, as measured by AB and PPI, from pre- to post-treatment, random effects modeling was conducted. To measure treatment responder status, change scores from pre to post treatment on PSSI to examine changes in inhibition as part of treatment, was grand mean centered to provide an interpretable zero point (Gallop & Tasca, 2009). Specifically, AB at Lags 1-5 and PPI at three lead intervals (30, 60, 120 ms) were examined.

Predictors of Trauma-Related Symptoms. To examine the ability of pre-treatment inhibitory functioning, as measured by AB and PPI, to predict changes in trauma-related psychopathology (i.e., anxiety, depression, dissociation), disability, and treatment dropout from pre- to post-treatment and from pre-treatment to 3-months follow-up, mixed model regressions were used to examine change scores in anxiety (STAI-T), depression (BDI), dissociation (DES), functioning (SDS), and treatment drop-out from pre- to post-treatment and pre- to follow-up as dependent variables and pre-treatment scores on lags 1-5 in AB and short lead intervals 30, 60, 120 ms in PPI as independent variables were performed. The dependent variables were PTSD severity (PSS-I), depression (BDI), trait anxiety (STAI-T), dissociation (DES), functioning

(Sheehan), and treatment drop-out scores at pre-treatment and post-treatment, and pre-treatment and three month follow up.

Individual Difference and Changes in Inhibition. Similarly, to examine pre-treatment individual difference predictors (e.g., gender, age, education) of improvement in inhibitory functioning, mixed model regressions were conducted using scores on AB at Lags 4 and 5 and PPI at two lead intervals (30, 60 ms) as dependent variables and pre-treatment variables including gender, age, and educational attainment as independent variables. The choice was made to examine these specific AB lags and short lead intervals in PPI because it is thought that these lags and short lead intervals, respectively, better represent the construct of inhibition (Raymond et al., 1992; Filion, Dawson, & Schell, 1993).

RESULTS

Means and standard errors for AB and PPI at pre- and post-treatment can be seen in Table 3. In Table 4, pre-treatment correlations between AB (lags 1-5) and PPI (30 ms, 60 ms, 120 ms) can be seen. There were no strong associations between AB and PPI.

Does Treatment Modality (PE vs. SER) Differentially Change Inhibition over Time (pre-treatment, post-treatment?)

To examine the first a priori hypothesis comparing two treatment modalities from pre- to post-treatment, models were fit for each of the lags in AB (Lags 1, 2, 3, 4, and 5) and short lead intervals of PPI (30 ms, 60 ms, 120 ms) as the dependent variables, with treatment modality (PE vs SER), time (pre-treatment, post-treatment), treatment modality x time interaction.

Attentional Blink. The best-fitting model was a random intercept model using the log likelihood criteria. Despite the simplicity of the random intercept model, it accounts for both subject-to-subject differences with respect to outcome, as well as the within-subject correlation.

The relationship between treatment modality, time, and AB showed significant variance in intercepts across participants, Lag 2: var(u_{0j}) = .02, $\chi^2(1) = -24.29$, $p < .05$, Lag 3: var(u_{0j}) = .04, $\chi^2(1) = -65.93$, $p < .05$, Lag 4: var(u_{0j}) = .01, $\chi^2(1) = -119.45$, $p < .05$, Lag 5: var(u_{0j}) = .01, $\chi^2(1) = -131.09$, $p < .05$. In this model, on average, the effect of time (i.e., fixed effects) significantly predicted AB at post-treatment for lags 3-5, the lags affected by the AB effect (lag 3: $F(1, 34.31) = 6.02$, $p < .05$, $d = 0.84$; $B = .04$, $SE = .02$, $t(34.31) = 2.45$, $p < .05$, lag 4: $F(1, 35.5) = 7.7$, $p < .05$, $d = 0.93$, $B = .04$, $SE = .01$, $t(35.5) = 2.78$, $p < .05$, lag 5: $F(1, 40.03) = 6.42$, $p < .05$, $d = 0.80$, $B = .04$, $SE = .02$, $t(40.03) = 2.53$, $p < .05$), suggesting that, across treatment modality, participants showed increased accuracy on lags 3-5 from pre-treatment to post-treatment.

To examine if the time effect findings were consistent across treatment modalities, we examined treatment modality, time, and the interaction term in the model. The interaction of treatment term predicted AB for lags 1 and 4 at trend levels, $F(1, 35.9) = 3.95$, $p = .06$; $B = -.06$, $SE = .03$, $d = 0.66$, $t(35.9) = -2$, $p = .06$); $F(1, 34.1) = 3.38$, $p = .08$, $d = 0.63$; $B = -.05$, $SE = .03$, $t(34.1) = -1.84$, $p = .08$), because they were not significant, further breakdown of the interactions were not conducted, although the pattern is consistent with individuals treated with psychotherapy showing increased accuracy at post-treatment than at pre-treatment.

Taken together, there was an increase of AB accuracy on lags 3, 4, and 5 from pre- to post-treatment, indicating a clear pattern of increased inhibitory functioning on critical AB lags from pre- to post-treatment for both PE and SER. Inclusion of the treatment modality x time interaction indicated some, albeit at a trend level, differences between PE and SER from pre- to post-treatment.

Prepulse Inhibition of Startle. In contrast, the relationship between treatment modality, time, and PPI showed negligible variance in intercepts across participants. The effect of time

marginally predicted PPI for 30 ms, $F(1, 32.14) = 3.62$, $p = .07$, $d = 0.67$; $B = -34.45$, $SE = 16.69$, $t(30.26) = -2.06$, $p = .05$), but not for 60 ms or 120 ms, providing some support, at a trend level, for a decline in automatic PPI inhibitory processes from pre-to post-treatment, regardless of treatment modality. There were no strong presences of treatment modality x time interactions.

Taken together, accuracy on lags 3-5 in AB, but not percent inhibition for PPI, increased from pre- to post-treatment.

Does Inhibition Change with Successful Treatment over Time (pre-treatment, post-treatment)?

To examine the second a priori hypothesis examining clinical responder status, defined as change in pre-treatment interviewer-rated PTSD severity (PSS-I) to post-treatment, models were fit for each of the lags in AB (Lags 1, 2, 3, 4, and 5) and short lead intervals of PPI (30 ms, 60 ms, 120 ms) as the dependent variables, with treatment response, time (pre-treatment, post-treatment), treatment response x time interaction.

Attentional Blink. Similar to the previous models, the parsimonious random effect structure was when the intercept was allowed to randomly vary for treatment response and time and AB, Lag 2: $var(u_{0j}) = .02$, $\chi^2(1) = -20.06$, $p < .05$, Lag 3: $var(u_{0j}) = .03$, $\chi^2(1) = -61.5$, $p < .05$, Lag 4: $var(u_{0j}) = .01$, $\chi^2(1) = -108.78$, $p < .05$, Lag 5: $var(u_{0j}) = .01$, $\chi^2(1) = -115.87$, $p < .05$. Consistent with the analysis above, time significantly predicted AB for lags 3, 4, and 5 (Lag 3: $F(1, 33.58) = 6.2$, $p < .05$, $d = 0.86$; $B = .04$, $SE = .02$, $t(33.58) = 2.49$, $p < .05$; Lag 4: $F(1, 35.2) = 7.45$, $p < .05$, $d = 0.92$; $B = .04$, $SE = .01$, $t(35.2) = 2.73$, $p < .05$, Lag 5: $F(1, 36.84) = 5.28$, $p < .05$, $d = 0.76$, $B = .04$, $SE = .01$, $t(36.84) = 2.30$, $p < .05$), such that regardless of treatment response, accuracy on lags 3-5 increased from pre- to post-treatment. In contrast, there were no significant effects of treatment response or response x time interactions.

Prepulse Inhibition of Startle. Convergence issues occurred when modeling PPI, where the outcome did not conform to the parsimonious covariance structure for the random effects under a random effects modeling framework. This is quite common when repeated observations within a participant are negatively correlated over time (Gallop & Tasca, 2009). Because this structure cannot account for the negatively correlated within-subject data, 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 (Gallop & Tasca, 2009). PPI exhibited this pattern with a within-subject correlation of r = -.074, and subject-to-subject variability at each time-point of χ^2 = 1501.33 (*SE* = 450.11), $\chi^2(1) = 11.12$, $p < 0.001$). After adjusting for negatively correlated values of PPI, time predicted changes in PPI for 30 ms at trend level, $F(1, 33.02) = 4.25$, $p = .05$, $d = 0.72$, $B = -24.39$, $SE = 11.83$, $t(33.02) = -2.06$, $p = .05$), regardless of treatment response, percent inhibition on 30 ms short lead interval marginally decreased from pre- to post-treatment. Responder status predicted PPI, at a trend level, across all lead intervals, at 30 ms, $F(1, 25.84) = 3.85$, $p = .06$, $d = 0.77$, $B = 1.04$, $SE = .53$, $t(25.84) = 1.96$, $p = .06$), 60 ms, $F(1, 30.1) = 3.93$, $p = .06$, $d = 0.72$, $B = 1.15$, $SE = .58$, $t(30.1) = 1.98$, $p = .06$), and 120 ms, $F(1, 23.34) = 5.29$, $p < .05$, $d = 0.95$, $B = 1.16$, $SE = .51$, $t(23.34) = 2.30$, $p < .05$), suggesting that better PPI at 30, 60, and 120 ms coincided with greater improvement in PTSD symptoms. In contrast, there were no significant treatment response x time interactions.

Thus, inhibition, measured by AB, increased more from pre- to post-treatment. In addition, for PPI, there was some evidence, albeit at a trend level, to suggest that better percent inhibition in PPI (30 ms. 60 ms, 120 ms) was associated with a greater reduction in PTSD symptoms.

Does Inhibition Change Differentially across Treatments (PE vs. SER) with Successful Treatment over Time (pre-treatment, post-treatment)?

Finally, to examine the relationship among treatment modality (PE vs. SER), treatment response, and time from pre- to post-treatment, the three-way interaction terms (treatment modality x treatment response x time) were added to the models. As before, random intercept models were fit for each of the lags in AB (Lags 1, 2, 3, 4, and 5) and short lead intervals of PPI (30 ms, 60 ms, 120 ms) as the dependent variables, with treatment modality, treatment response, time (pre-treatment, post-treatment), and their interaction terms.

Attentional Blink. For lag 3 only, there was a significant treatment modality x treatment response x time, $F(1, 30.69) = 6.83$, $p < .05$, $d = 0.94$. See Figure 1. For PE, changes in accuracy in lag 3 from pre- to post-treatment was faster for individuals that showed greater treatment response ($B = .002194$, $SE = .003$, $t(30.69) = 2.61$, $p < .05$). Whereas, for SER, changes in accuracy in lag 3 from pre- to post-treatment was slower for those individuals that showed greater treatment response ($B = -.006239$, $SE = .002$, $t(30.52) = -2.81$, $p < .05$). To further clarify these relationships, contrast statements showed rate of accuracy in lag 3 of AB increased over the course of treatment with more response to PE ($M = .0270$, $SE = .022$) and rate of accuracy in lag 3 of AB decreased over the course of treatment with more response to SER ($M = .0358$, $SE = .022$).

Prepulse Inhibition. In contrast, there were no treatment modality x treatment response x time interactions for PPI across all short lead intervals (30, 60, 120).

Thus, there was evidence from AB that the rate of inhibitory changes from pre- to post-treatment between the two treatment modalities differed depending on responder status. Specifically, accuracy on lag 3 of AB increased more in those who made more improvements

from PE than those that made less improvements from PE; whereas the opposite was the case for individuals treated with SER, with accuracy on lag 3 of AB decreasing more in those who made more improvements from SER than those who made less improvements in SER.

Does Pre-Treatment Inhibitory Functioning (AB and PPI) Predict Changes in PTSD, Depression, Trait Anxiety, Dissociation, Functioning, and Treatment Drop-out?

To examine the ability of pre-treatment inhibition to predict changes in PTSD (PSS-I), broader psychopathology (BDI, STAI-T, DES), general functioning (SDS), and treatment drop-out from pre- to post-treatment and from pre- to three-month follow-up, separate mixed model regressions were run for PPI (30, 60 ms) and AB (lags 3-5). Table 5 shows zero-order correlations among measures over time. Tables 6 and 7 displays unstandardized regression coefficients (B) and standard errors of variables for change from pre-treatment to post-treatment and pre-treatment to three-month follow-up, covarying for age. There were no strong associations between pre-treatment inhibitory processes (AB, PPI) and changes in psychopathology symptoms, functioning, and treatment dropout from pre-treatment to post-treatment. Similarly, covarying for age, there were no strong relationships between pre-treatment inhibitory functioning (AB, PPI) and changes in psychopathology symptoms, functioning and treatment dropout from pre-treatment to three-month follow-up. Thus, lower pre-treatment inhibitory functioning as measured by AB and PPI was not predictive of improvement in broader psychopathology, general functioning, and treatment drop-out.

Do Individual Difference Factors Predict Pre- to Post-treatment Changes in Inhibition?

To examine the predictive value of pre-treatment individual difference predictors on changes in inhibition from pre- to post-treatment (AB: lags 4, 5; PPI: 30, 60 ms), mixed model regressions were run using three predictor variables: age, gender (male = 0; female = 1), and

education. Table 8 shows zero-order correlations among measures over time. Table 9 displays unstandardized regression coefficients (B), and standard errors of variables for change from pre-treatment to post-treatment. Only older age predicted changes in AB from pre- to post-treatment at lag 4: $F(1, 33.85) = 4.95$, $p < .05$, $d = 0.76$; $B = .002$, $SE = .001$, $t(33.85) = 2.22$, $p < .05$; such that older individuals with PTSD showed slower changes in inhibition from pre- to post-treatment. Contrast statements showed that for each additional year rate of improvement in inhibition slowed down (Lag 4: $M = -.05$, $SE = .04$). In contrast, gender, and education were weakly related to changes in inhibition, either for AB or PPI, from pre- to post-treatment. Thus, older age, but not gender or education, was a predictor of slower improvements in inhibitory functioning over the course of therapy.

DISCUSSION

Inhibition is implicated as a key mechanism of change because of the putative inhibitory effects of exposure therapy and selective serotonergic reuptake inhibitors in reducing chronic fear responses in PTSD. Despite this, little work has been done in comparing inhibitory changes associated with treatment response in these treatments. This is the first study to directly examine changes in basic inhibitory processes in PTSD from pre- to post-treatment, using these therapies. Notably, the present findings point to potential differential mechanisms of treatment response for exposure therapy and SSRIs. Specifically, individuals that showed greater reduction in PTSD symptoms from PE showed a faster increase in inhibition measured by attentional blink from pre- to post-treatment than those treated with SER, potentially highlighting the role of the alteration of temporal attention inhibition in exposure therapies. Generally, different effects were found for attention blink and pre-pulse inhibition. The AB paradigm showed improvements of inhibition from pre- to post-treatment, arguing for common factors associated with improved

attentional inhibitory functioning with PTSD treatment. Alternatively, the PPI paradigm showed that better inhibitory functioning, albeit at a trend level, was associated with better treatment response, pointing to a potential biomarker for treatment response. Finally, among the individual difference factors, old age contributed to slower improvements in inhibitory functioning on AB, suggesting modulations in attentional inhibitory processes are less likely in older individuals.

Differential modulation in fundamental attentional inhibitory processes by treatment responders suggests differential specificity in how PE and SSRIs normalize inhibitory processes. Individuals who showed more symptom improvements with PE showed faster improvement in inhibitory processes from pre- to post-treatment on a key inhibitory lag of AB, suggesting greater improvements in temporal processing across time. In contrast, with sertraline, individuals who showed more symptom improvement in PTSD symptoms made slower changes in inhibitory processes from pre- to post-treatment, indicating less improvement in temporal attention over the course of treatment. Further, there was a large effect for this interaction. This potential differential mechanism of treatment response between PE and SER was specific to lag 3 which places the most stress on temporal attention when close proximity of irrelevant distracters inhibit processing of relevant stimuli in a rapid visual stream (Olivier et al., 2008). When trying to understand AB effects, AB is one of many executive functioning tasks where individuals with PTSD show impairment in redirecting attention in the presence of distracters. Deficient inhibition of relevant and irrelevant stimuli may underlie these deficits through a process where relevant and irrelevant stimuli are simultaneously activated, which in turn, increases the likelihood of retrieval interference and retrieval failures (Vasterling et al., 1998). Further, difficulties in differentiating relevant from irrelevant information may contribute to understanding reexperiencing and hyperarousal symptoms in PTSD. Indeed, cognitive intrusions,

using neutral stimuli, were associated with re-experiencing symptoms (Vasterling, 2000), suggesting that failure to inhibit intrusions of irrelevant information may not be restricted to emotionally threatening content. Similarly, hypervigilance symptoms may be associated with difficulties in differentiating relevant from irrelevant information by utilizing cognitive processing resources that prohibit one's ability to rule out maladaptive behaviors (Lee, Vaughn, & Armstrong, 1999). Taken together, deficient temporal attention may be particularly relevant in the reexperiencing and hyperarousal symptoms of PTSD because of their role in increasing demands on attentional allocation (Keller, Hicks, & Miller, 2000) and subsequently may be more responsive to treatments that directly target deficits in temporal attention. Indeed, PE is thought to utilize extinction to dampen chronic fear responses by strengthening prefrontal functioning (Felmingham et al., 2007; Porto, Oliveira, Mari, Volchan, Figueira, & Ventura, 2009), presumably through correcting pathological elements of fear structures and changing pathological beliefs (Jaycox, Foa & Morral, 1998). As a consequence, PE may directly target reexperiencing and hyperarousal symptoms related to increased distractibility, poor memory, and concentration problems associated with the disorder (Uddo et al., 1993; Wolfe & Charney, 1991), in addition to "freeing" up attentional resources to differentiate between maladaptive and adaptive behaviors (Lee et al., 1999) and to differentiate between remembering and reexperiencing of the trauma (Jaycox et al., 1998). Thus, PE may act in improving functioning of the prefrontal-amygdala circuit and subsequently regulating rexperiencing and hyperarousal symptoms in PTSD.

Consistent with this, differential modulation of inhibition across treatments in responders points to potentially different mechanisms of treatment response in PE and SER. As discussed before, PE is thought to act on the mPFC, anterior cingulate and other cortical areas that have

inhibitory inputs and ultimately decrease amygdala responsiveness, in addition to mediating extinction of fear responding (Quirk & Beer, 2006; Akirav & Maroun, 2007) suggesting PE may have an additive effect of changing pathological beliefs related to the trauma over SER. In addition, exposure therapy uses extinction principles in facilitating inhibitory learning (Rauch et al., 2003) subsequently inhibiting fear responses in PTSD. Therefore it may be more specific in directly targeting inhibitory processes (Craske et al., 2008) than SER that facilitates serotonin neurotransmission and is thought to bring about more broad changes in functioning (Brady et al., 2001; Davidson et al., 2001). Indeed, pharmacological therapies are heavily criticized to ameliorate target symptoms but not necessarily the underlying cause of the disorder, to suggest that it may not inhibit the original fear learning (Brady et al., 2001). PE and SER may use specific pathways on how they bring about therapeutic change, however ultimately follow a final common pathway in reducing amygdala reactivity (Rausch et al., 2003).

This final common pathway may help explain the general pattern of increased attentional inhibitory control from pre- to post-treatment being modified by therapeutic modality and treatment response. Specifically, exposure therapy is thought to bring about therapeutic change through a top down modulation of amygdala activity whereas sertraline may influence bottom up modulation by the amygdala (Porto et al., 2009; Brady et al., 2001). In a fMRI study examining predictors of treatment recovery of cognitive behavioral therapy (CBT) for MDD, Siegle and colleagues (2006) found reduced subgenual cingulate cortex activity at pre-treatment for treatment responders of CBT for depression. The authors proposed that responders of CBT were those individuals with high emotional reactivity; therefore, emotion regulation strategies, a treatment component of CBT, may have facilitated control and regulation over their emotions. Similarly, in MDD, DeRubeis et al. (2008) reviewed studies that compared CBT and

antidepressants and found that CBT involved similar brain changes as those seen with antidepressants following treatment. They argued for the superiority of CBT in strengthening prefrontal regions leading to the acquisition of emotion regulation skills where symptom improvement continues long after treatment ends. In contrast, antidepressants purportedly address amygdala hyperactivity but confer risk upon termination and may not offer protection like CBT in maintaining treatment gains. These studies provide preliminary support for a top-down pathway of strengthening prefrontal regions to reduce amygdala reactivity in CBT, leading to therapeutic change. In summary, although PE and SER appear to converge on a final pathway in reducing amygdala reactivity, which may account for increased temporal attentional inhibition over time, PE produced earlier attentional inhibitory gains, and more sustained and stronger changes in inhibition than SER, arguing for treatment specific effects in normalizing inhibitory deficits in PTSD.

Using the AB paradigm, temporal attentional inhibition improved over time. Individuals with PTSD showed increases in inhibition on AB from pre-treatment to post-treatment, with accuracy on AB on critical inhibitory lags improving over time. Although there was this effect of time on inhibition, as stated above, the effect of time was modified by the interaction with treatment modality and treatment response. Nevertheless, these findings bolster the argument for commonalities between PE and SER, particularly in light of the effectiveness of both treatments (e.g., Foa et al., 1999; Brady et al., 2000), similar neural changes to the fear circuitry of PTSD (Heym et al., 1998; Felmingham et al., 2007), and potential common pathways discussed above. One alternative explanation is that time or repeated practice could lead to subsequent improvement in inhibition as well. Time and repeated practice with attentional tasks has been

shown to modify attentional processes (Nakatani, Baijal, & van Leeuwen, 2009). This explanation cannot be ruled out without a control or waitlist group as part of the study design.

Better inhibitory functioning on PPI was associated with better treatment response, suggesting that better prepulse inhibition may be a potential biomarker for treatment response. The size of the effects here were large but the findings were at a trend level probably due to sample size. Indeed, identifying biomarkers are a promising approach to understanding disorders and treatment response (Deutsch et al., 2009; Ritsner & Gottesman, 2009; Van Lieshout & Szatmari, 2009). Biomarkers are measureable indicators of a biological process that is directly linked to the clinical manifestation of a disorder (Beauchaine; 2009; Ritsner et al., 2009). According to this definition, for PPI to qualify as a biomarker, measurable deficits in this tasks must be linked to an identifiable abnormal neural network and associated with the pathophysiology of PTSD.

The present study examined inhibitory failures in basic processes of sensory gating processes (Graham, 1975; 1979; Filion, Dawson, & Schell, 1998; Fendt, Li, Yeomans, 2001) that purportedly result from disruptions in the fear circuitry in PTSD (Kolb, 1987; Morgan, Grillon, Lubin & Southwick, 1997). Thus, inhibitory deficits measured by PPI presume a common biological basis of a disrupted neural circuitry involving the prefrontal regions and amygdala (Campeau and Davis, 1995; Hitchcock and David, 1996; Fendt et al., 2001). Abnormalities in PPI show close associations to PTSD symptoms, with abnormal PPI, or disturbances in early sensory flooding, being implicated in PTSD (Grillon et al., 1998; Ornitz et al., 1989). As there are few studies that have examined biomarkers of treatment recovery, the findings are preliminary and need further replication. Taken together, better PPI may represent a potential

viable biomarker of treatment recovery and has the potential to advance our understanding of who responds to treatment.

An exploratory hypothesis examined whether pre-treatment inhibition may be better at predicting broader changes in trauma-related psychopathology. Given that deficient AB and PPI are associated with depression (AB; Rokke et al., 2002), anxiety (PPI; Ludewig, Ludewig, Geyer, Hell, & Vollenweider, 2002) and poor functioning (AB; Domeney & Feldon, 1998), pre-treatment inhibition was expected to predict changes in psychopathology and global functioning. However, pre-treatment inhibition seemed to play less of a role in regard to changes in psychopathology and functioning symptoms from pre- to post-treatment and pre-treatment to follow-up. Individuals with PTSD may vary in their level of inhibitory function at pre-treatment, with some showing lower levels and others showing higher levels of inhibitory function (Swerdlow, Talledo, Sutherland, Nagy, & Shoemaker, 2006). Therefore, only individuals with worse pre-treatment inhibitory function may be more likely to make an impact on broader, secondary symptoms (Domeney et al., 1998).

Regardless of treatment modality and treatment response effects on inhibition, there may be specific individual characteristics that may predispose some individuals to show greater changes in inhibition from pre to post treatment. Exploratory analyses with regard to pre-treatment demographic variables showed age but not gender or education predicted improvement in inhibition. Specifically, older individuals with PTSD showed slower improvement in inhibitory functioning in lag 4 of AB from pre- to post-treatment, with rate of improvement in inhibition slowing down for each additional year. Inhibitory deficits that come with older age may be more resistant to improvement during treatment. Inhibitory deficits and cognitive decline are linked to old age suggesting that inhibitory processes and cognitive decline may run parallel

and may not be regained. Indeed, older age is related to loss of inhibition function (Woodruff-Pak, 1997), and may be associated with general slowing of cognitive operations (Salthouse, 1986), or may be related to education in attentional resources or working memory capacity (Salthouse, 1988). Inhibitory theories on aging posit that cognitive decline may be a direct consequence of deficits in inhibitory function (Hasher & Zacks, 1988; Posner & Snyder, 1975) with inhibitory processes declining with age. Indeed, older individuals fail to suppress irrelevant information on inhibitory measures including Stroop and negative priming (Swerdlow et al., 1993) and eye movement tasks (Butler & Zacks, 2006). Thus, improvement in inhibitory processes may be less likely in older individuals.

The present findings point to a potential mechanism underlying treatment response particularly for PE, highlighting the role of temporal inhibitory attention processes. Future directions for treatment may involve the development of novel therapeutic applications that target attentional inhibitory processes. Attentional training, for instance, is associated with altering attentional mechanisms by improving performance on tasks involving executive control (Sturm, Willmes, Orgass & Hartje, 1997). It has also shown promise as a therapeutic approach in improving attention allocation and reducing clinical symptoms across anxiety disorders (Amir, Weber, Beard, Bomyea, & Taylor, 2008; Schmidt, Richey, Buckner, & Timpano, 2009). Pharmacological interventions, such as D-cycloserine, may similarly target inhibition by consolidating inhibitory learning in therapy, resulting in enhancing treatment response (Hoffman et al., 2006; Ressler et al., 2004). In addition, the association between better PPI and treatment response points to the possibility of using a biomarker strategy in facilitating treatment response in PTSD. One clinical implication may be that biomarkers may reflect targets for pharmacotherapy or psychotherapy to strengthen treatment response in PTSD. In turn, using a

biomarker approach may elucidate mechanisms underlying inhibitory therapeutic change and identify components for the development of more targeted interventions.

Several limitations are worth noting. The sample size for the present study was small. Large effects were observed but they may potentially be not stable, thus merit replication in larger samples. There was no control condition in the present study, therefore does not permit the isolation of the effects from pre- to post-treatment beyond time. However, the design was designed to specifically examine differential treatment effects between PE and SER. Related to this, other comparison groups (other inhibition-related disorders) 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. Also, conclusions can only be made on the short-term effects of these treatments and cannot speak to the long term, maintenance of symptom improvement. It also remains to be determined whether the inhibitory deficits existed prior to PTSD or whether it developed with the disorder. Although multi-level modeling analytic methods do not require complete data on all participants on all outcome measures, these analytic methods assume the missing data is missing at random (MAR). MAR assumes that the missingness is not related to the outcome. In the case where missingness is information (i.e., not randomly missing), the robustness of the analytical results may be in question. Future research may assess potential informativeness of the missing data with methods such as the pattern-mixture model approach (Hedeker & Gibbons, 1997). Finally, AB and PPI are theoretically indexes of inhibition, however, are also affected by other functions (e.g., vigilance, attention) and as such the role of other functions cannot be ruled out. Similarly, the construct validity of commonly used inhibition tasks, including AB, are not yet well established (Friedman &

Miyake, 2004) and further construct validation work is needed to understand the specific types of inhibitory processes deficient in PTSD.

Taken together, inhibitory processes, particularly attentional ones, may play a critical role in the response to PTSD treatment. The present findings suggest that individuals who made more clinical improvements showed faster improvement in inhibition over the course of exposure therapy, potentially highlighting the importance of irrelevant and relevant discrimination in attention in modifying the dysfunctional prefrontal-amygdala circuit in PTSD. Further, the interaction showed a large effect size and may be a mechanism of treatment response. The present study supports the utility of novel therapeutic interventions that target attention in PTSD. Although requiring replication with larger sample sizes, the findings from the current study also move the field forward in line with the new movement set by the Research Domain Criteria (RDoC) in developing a new research nosology that will refine our current diagnostic criteria by investigating more basic, bottom-up mechanisms (Sanislow et al., 2010). In conclusion, irrelevant and relevant discrimination in attention may be an important mechanism to recovery with PE treatment and may help advance our theories of therapeutic change in PTSD.

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Table 1

Summary of Participant Characteristics

Characteristic	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	
Race						
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	
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*
Trauma Type (%)						
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 2

Psychopathology and Functioning Measures at Pre-treatment, Post-treatment, and Follow-up

Psychopathology	Pre-treatment		Post-treatment		Follow-up	
	M	*SE*	*M*	*SE*	*M*	*SE*
PTSD (PSS-I)	28.04	*1.01*	11.16	*1.58*	10.21	*1.61*
Depression (BDI)	25.76	*1.42*	10.49	*1.87*	11.35	*1.85*
State Anxiety (STAI-S)	56.53	*1.79*	42.41	*2.18*	39.41	*2.58*
Trait Anxiety (STAI-T)	60.05	*1.5*	43.53	*2.06*	43.99	*2.44*
Dissociation (DES)	14.43	*2.02*	11.15	*2.08*	10.71	*2.25*
Func Impair (Sheehan)	18.32	*1.01*	11.18	*1.46*	4.51	*1.75*

Note. n =49. Func Impair=Functional Impairment.

Table 3

Pre-treatment and Post-treatment AB and PPI

	Pre-treatment		Post-treatment	
	M	*SE*	*M*	*SE*
AB (% Accuracy)				
Lag 1	.96	*.01*	.95	*.01*
Lag 2	.80	*.03*	.82	*.03*
Lag 3	.79	*.03*	.83	*.03*
Lag 4	.86	*.02*	.89	*.02*
Lag 5	.90	*.02*	.94	*.01*
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*

Note. *n* =49. AB = Attentional blink, PPI = Prepulse Inhibition.

Table 4

Pearson Coefficients between Measures of Inhibition

	1.	2.	3.	4.	5.	6.	7.
AB							
1. Lag 1							
2. Lag 2	.46*						
3. Lag 3	.38*	.81*					
4. Lag 4	.29*	.72*	.8*				
5. Lag 5	.32*	.54*	.6*	.74*			
PPI (%)							
6. 30 ms (%)	.07	.01	-.13	-.1	-.1		
7. 60 ms (%)	-.07	-.09	-.17	-.16	-.03	.75*	
8. 120 ms (%)	-.004	.02	-.08	-.14	-.04	.78*	-.59*

* $p \leq .05$.

Table 5

Correlations between AB and PPI, Psychopathology, Functioning, Treatment Drop-out, from Pre to Post-treatment and Pre to Follow-up (Completers only)

	Pre-treatment to Post-treatment (n = 46)						Pre-treatment to Three-month Follow-Up (n = 46)				
Variable	PTSD (PSSI)	Dep (BDI)	Anx (STAI)	Diss (DES)	Functioning (SDS)	Drop-out	PTSD (PSSI)	Dep (BDI)	Anx (STAI)	Diss (DES)	Functioning (SDS)
AB											
Lag 1	-.13	.01	.01	-.02	-.18	.11	-.11	-.16	-.17	-.14	-.25*
Lag 2	.05	.13	.01	.03	-.03	.06	.05	-.01	.05	.04	-.07
Lag 3	.02	.11	.04	-.03	-.02	.05	.002	-.05	.02	.09	-.02
Lag 4	.03	.12	.08	-.05	-.01	.03	-.18	-.19	-.14	-.06	-.21
Lag 5	.06	.12	.16	-.01	.05	-.05	-.28*	-.34*	-.25*	-.15	-.35
PPI											
30 ms	.18	.05	.16	.03	-.13	-.18	.01	-.11	.06	.07	-.11
60 ms	.21	.19	.17	.13	-.15	-.4*	.25	.16	.24	.3	.14
120 ms	.11	.07	.05	.01	-.30*	-.16	.02	-.2	-.06	.06	-.18

Note. *p < .05. With the exception of treatment drop-out, change scores (pre-treatment – post-treatment, pre-treatment -3 month follow-up) were calculated for all other psychopathology and functioning measures. Dep = Depression, Anx = Anxiety, Diss = Dissociation.

Table 6

Parameter Estimates, Standard Errors for Pre-treatment AB and PPI Predicting Psychopathology, Functioning, from Pre to Post-treatment, Covarying for Age

	Pre-treatment to Post-treatment																			
Var	PTSD				Depression				Trait Anxiety				Dissociation				General Functioning			
	B	*SE*	*T*	*Sig*	*B*	*SE*	*T*	*Sig*	*B*	*SE*	*T*	*Sig*	*B*	*SE*	*T*	*Si.*	*B*	*SE*	*T*	*Sig*
AB																				
L1	-.009	.01	-.87	.39	-.006	.01	-.52	.61	-.01	.01	-.83	.41	-.004	.02	-.2	.83	-.007	.008	-.88	.39
L2	-.009	.01	-.87	.39	-.006	.01	-.52	.61	-.01	.01	-.83	.41	-.004	.02	-.2	.83	-.007	.008	-.88	.39
L3	-.009	.01	-.87	.39	-.006	.01	-.52	.61	-.01	.01	-.83	.41	-.004	.02	-.2	.83	-.007	.008	-.88	.39
L4	-.009	.01	-.87	.39	-.006	.01	-.52	.61	-.01	.01	-.83	.41	-.004	.02	-.2	.83	-.007	.008	-.88	.39
L5	-.009	.01	-.87	.39	-.006	.01	-.52	.61	-.01	.01	-.83	.41	-.004	.02	-.2	.83	-.007	.008	-.88	.39
PPI																				
30	-.004	.007	-.57	.57	-.004	.008	-.49	.63	-.002	.009	-.19	.85	.006	.01	.64	.53	.27	.18	1.49	.15
60	-.005	.007	-.72	.48	-.004	.008	-.51	.61	-.003	.009	-.33	.75	.005	.01	.55	.59	.27	.18	1.48	.15
120	-.005	.007	-.75	.46	-.004	.008	-.51	.62	-.003	.009	-.38	.71	.006	.01	.59	.56	.26	.18	1.41	.17

Var = Variable

Table 7

Parameter Estimates, Standard Errors for Pre-treatment AB and PPI Predicting Psychopathology, Functioning, from Pre to Follow-up, Covarying for Age

	Pre-treatment to Follow Up																			
Var	PTSD				Depression				Trait Anxiety				Dissociation				General Functioning			
	B	*SE*	*T*	*Sig*	*B*	*SE*	*T*	*Sig*	*B*	*SE*	*T*	*Sig.*	*B*	*SE*	*T*	*Sig*	*B*	*SE*	*T*	*Sig*
AB																				
L1	-.006	.009	-.64	.53	-.01	.01	-1.03	.31	-.008	.01	-.62	.54	-.003	.01	-.22	.83	-.007	.008	-.87	.39
L2	-.006	.009	-.64	.53	-.01	.01	-1.03	.31	-.008	.01	-.62	.54	-.003	.01	-.22	.83	-.007	.008	-.87	.39
L3	-.006	.009	-.64	.53	-.01	.01	-1.03	.31	-.008	.01	-.62	.54	-.003	.01	-.22	.83	-.007	.008	-.87	.39
L4	-.006	.009	-.64	.53	-.01	.01	-1.03	.31	-.008	.01	-.62	.54	-.003	.01	-.22	.83	-.007	.008	-.87	.39
L5	-.006	.009	-.64	.53	-.01	.01	-1.03	.31	-.008	.01	-.62	.54	-.003	.01	-.22	.83	-.007	.008	-.87	.39
PPI																				
30	-.006	.006	-1.14	.27	-.005	.007	-.72	.48	-.006	.009	-.71	.48	-.02	.008	-2.5	.02	.001	.005	.25	.8
60	-.005	.006	-.96	.35	-.003	.007	-.44	.66	-.005	.009	-.6	.55	-.02	.008	-2.57	.02	.002	.005	.44	.67
120	-.006	.006	-1.05	.3	-.005	.007	-.65	.52	-.007	.009	-.83	.42	-.02	.008	-2.55	.02	.001	.005	.29	.77

Var = Variable

Table 8

Correlations Between Age, Gender, Education and Change in Inhibition from Pre to Post-treatment

Variable	Age	Gender	Education
AB (% Accuracy)			
Lag 4	.01	-.06	.02
Lag 5	.01	-.06	-.01
PPI (% Inhibition)			
30 ms	-.27	.00	.27
60 ms	.01	.18	.32

Table 9

Parameter Estimates, Standard Errors for Age, Gender, and Education Predicting Changes in AB and PPI

	AB								PPI							
	Lag 4				Lag 5				30 ms				60 ms			
Variable	*B*	*SE B*	*T*	*Sig.*	*B*	*SE B*	*T*	*Sig.*	*B*	*SE B*	*T*	*Sig.*	*B*	*SE B*	*T*	*Sig.*
Age	.002	.001	2.22	.03*	-.004	0	-.1	.89	-.3	.93	-.3	.75	.04	.96	-.1	.96
Gender	-.03	.03	-.9	.38	.03	.04	.64	.53	-20.9	26.1	-.8	.43	10.09	26.6	.38	.71
Education	0	.004	-.8	.43	-.002	.01	-.5	.63	8.29	2.72	3.05	.5	3.78	3.25	1.16	.26

* $p = .05$

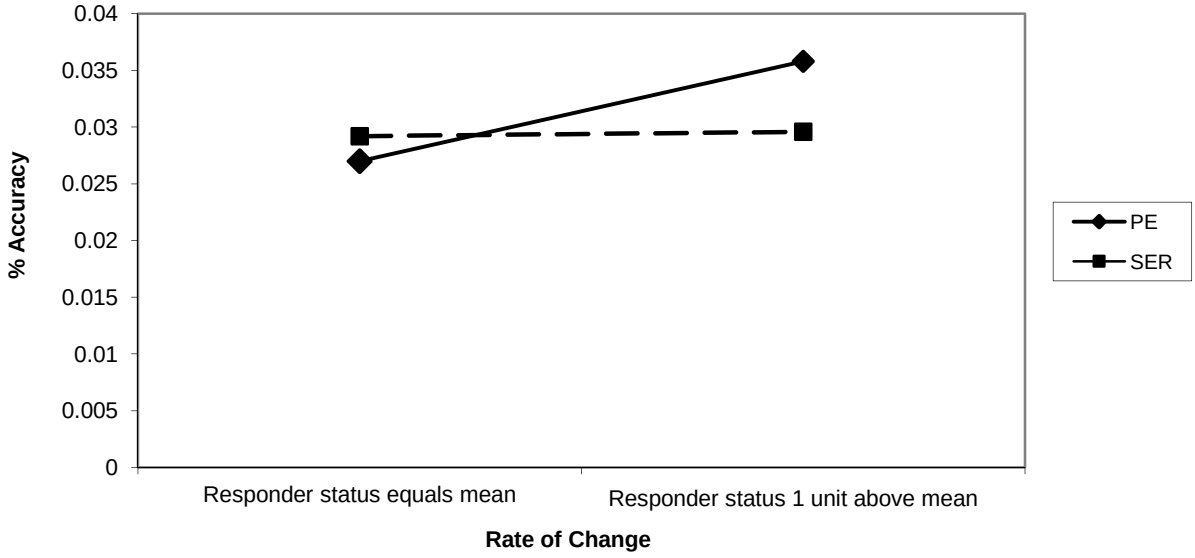

Figure 1. Treatment response, treatment, and time for Lag 3 of AB