COGNITIVE INFLUENCES ON THE SENSORIMOTOR GATING OF THE ACOUSTIC STARTLE REFLEX

By

RUTH M. GLASS

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Alexander W. Kusnecov

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ABSTRACT OF THE THESIS

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By RUTH MINDY GLASS

Thesis Director:

Alexander W. Kusnecov

Prepulse inhibition (PPI) is viewed as a measure of sensorimotor gating in which the startle response to a sudden intense stimulus (pulse) is attenuated by a weaker stimulus (prepulse) that immediately precedes the pulse. Similarly, in the cognitive domain, individuals can filter out unnecessary thoughts and impulses, essentially "cognitive gating." There are many neuroanatomical overlaps between the sensorimotor gating and cognitive gating domains, as well as the coupling of deficiencies of both in certain mental disorders. Using a novel paradigm, the current study investigated whether changes in sensorimotor gating can be linked to cognitive gating. One hundred and two healthy volunteers were divided into groups and underwent two acoustic startle PPI sessions, before and after a specific task. Depending on the group, the task consisted of either a passive activity or one of three cognitive tasks, varying in cognitive gating demands. Passive activity between PPI sessions had differential effects on percent inhibition changes compared to an intervening cognitively demanding task. That is, cognitive gating tasks, but not attentional tasks, interfered with PPI magnitude, with systematic variations occurring between male and female subjects. Overall, the results imply a strong relationship between sensorimotor and cognitive gating domains, providing an

opportunity to broaden our understanding of potential mechanisms underlying each of these processes.

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Table of Contents

LIST OF TABLES

List of Illustrations

INTRODUCTION

Prepulse inhibition (PPI) is a psychophysiological measure of sensorimotor gating in which a physiological response to a sudden intense stimulus (the 'pulse') is attenuated by an immediately preceding weaker stimulus. As a measure of sensorimotor gating, PPI likely reflects a mechanism by which excess or unimportant sensory influences are filtered (or "gated") out in order to focus on and process the most significant aspects of the environment (Braff and Geyer, 1990; Braff, Geyer & Swerdlow, 2001). A common demonstration of this phenomenon is the auditory startle paradigm, in which a weaker acoustic 'prepulse' stimulus reduces the effect of the subsequent louder noise (the pulse) on the eye blink reflex. That is, the initial weaker acoustic stimulus temporarily engages the auditory system, and gates out any response to additional louder acoustic stimuli. Furthermore, PPI appears to involve a dedicated neural circuitry, although full consensus on the precise nature of the circuit schemata has not been achieved (Koch, 1990; Fendt & Yeomans, 2001; Swerdlow, Geyer & Braff, 2001). Most of the proposed networks emphasize the role of the inferior and superior colliculus, the pedunculopontine tegmental nucleus, the ventral tegmental area and the caudal pontine reticular nucleus in either mediating or modulating the PPI response.

As in the sensorimotor domain, cognitive processes likely involve gating operations that filter out unnecessary or superfluous thoughts and impulses in order to maximize responses to the environment. In the healthy human brain, this allows for inhibition of the effects of certain sensory information in order to influence a meaningful cognitive-behavioral response. This process is considered part of the class of "central inhibitory gating mechanisms"—which include sensorimotor gating—and can be referred

to as “cognitive gating” (Swerdlow, Fillion, Geyer, & Braff, 1995). One example of cognitive gating is the well-known Stroop effect, in which the natural tendency to perform one cognitive act (eg., read the name of a color) must be inhibited in order to perform a different cognitive act (eg., identify the color in which the word is printed) (Stroop, 1935; MacLeod, 1991). In essence, the task relies on a cognitive gating mechanism, in which an initial behavioral impulse needs to be filtered out in order to allow for another, more accurate response to be executed. Other examples include the Go/No-Go tests of impulsivity, such as the Go-Stop task (Dougherty, Mathias, Marsh, & Jagar, 2005).

The connection between cognitive and sensorimotor gating has been made through identification of PPI deficiencies in specific clinical groups (Braff et al., 2001). Most of the disorders exhibiting reduced PPI also show abnormalities in impulse control, or, cognitive gating. Disorders such as Tourette syndrome, obsessive-compulsive disorder, Huntington’s disease, autism, and attention deficit hyperactivity disorder are all associated with reduced PPI and gating in general (Braff et al., 2001). The most extensively studied of the disorders with decreased PPI is that of schizophrenia. Since reduced sensorimotor gating is such a robust finding in this population and can reliably be seen in family members of schizophrenia patients, abnormal sensorimotor gating may be an endophenotype of the disease (Braff & Freedman, 2002; Braff, Freedman, Schork, & Gotteseman, 2007). This information can be very useful when diagnosing and treating individuals with schizophrenia because the presence of this deficit may provide insight into behavioral, psychophysiological and even genetic and neurobiological abnormalities in the schizophrenic brain.

To date there has been little information investigating the effects of cognitive gating tasks on modulation of PPI. Therefore, the current work tests the hypothesis that a relationship exists between sensorimotor and cognitive behavioral domains, such that engaging gating mechanisms in one domain, will affect gating efficiency in the other. Specifically, we posit that if engagement in cognitive gating is "overloaded" or taxed, the sensorimotor gating machinery, and particularly PPI, will be affected. Consequently, demanding tasks like the Stroop or Go/No-Go tasks would be expected to cause a reduction in PPI. Not only would a result like this indicate that there may be a general gating mechanism in the brain that overlaps between the psychophysiological and the cognitive domains, but it would also be a helpful and practical finding for understanding and treating disorders such as schizophrenia. If sensorimotor gating is linked to cognitive gating, then one can presume that the presence of one increases the probability of the other being present.

To test the above hypothesis, the current paper used a novel paradigm that relied on behavioral changes across two consecutive PPI sessions. Prepulse inhibition, and sensorimotor gating in general, is typically measured in a single session, and percent inhibition this session is typically correlated with other measures like scores on neuropsychiatric tests or clinical diagnoses. In the current study, most participants underwent two succeeding PPI sessions, interspersed by differing resting conditions or cognitive tasks (**Fig 1**). In this way, changes in PPI over short periods of time and in response to tasks could be identified. To our knowledge, there has only been one other study that has analyzed differences in PPI after neurocognitive tasks (Swerdlow, Sprock, Light, Cadenhead, Calkins, Dobie et al., 2007), yet, the analysis was a small side point

that received little discussion. The experimental design used in the present study provides a new approach with which to look at sensorimotor gating – namely, changes over time and the effects of cognitive engagement. This allows for the formation of a new conceptual model of the phenomenon, integrating it with higher-order, top-down cognitive processes.

Figure 1 illustrates the general design and goals of the study. Prepulse inhibition is measured before and after specific tasks, with a slideshow of neutral images being used as a control condition. It was hypothesized that percent inhibition will significantly decrease in the second PPI session after performing the Stroop and GoStop tasks, which are known to engage a number of brain areas, including the prefrontal cortex, a primary mediator of cognitive gating (Aron et al., 2004; Chikazoe et al., 2007; Murphey et al., 2007). We posit that performing the Stroop will overload this system to the point that it will be reflected in the sensorimotor domain, thus, reducing PPI. This would suggest that fatigue in prefrontal neural areas may impact basic psychophysiological demonstrations of sensorimotor gating.

METHOD

Participants: One hundred and two males and females (mean age: 19.78 years [SD=2.87]) were recruited from the Rutgers University undergraduate pool. All participants reported English as a first language, had normal to corrected vision, and were not colorblind. Table 1 provides the demographic breakdown of the participants. Each participant was randomly assigned an experimental condition and all gave signed consent before participating. The study was approved by the Rutgers Human IRB.

Stimulus and apparatus: Acoustic stimuli were delivered and psychophysiological measures were collected using a Coulbourn Instruments (Lehigh Valley, PA) LabLincV series system. Electromyography and ECG responses were band-pass filtered (13–1000Hz and 1–40Hz, respectively) and 60Hz notch filtered, digitized and recorded (1kHz sampling frequency) using the LabLinc V Human Startle software package coupled with a Dell desktop computer.

General Procedure: Participants were seated in a large comfortable armchair in an enclosed room that consisted of the chair, a table and a computer monitor. There were five treatment conditions (or groups) that each comprised three consecutive stages (**Fig 1a-b**). These stages were the first PPI session, an intervening task, and a second PPI session. Cortisol samples and heart rate measures were collected throughout. Cortisol was collected by having participants chew on small salivettes (SciMart, Inc.), baseline heart rate was measured for five minutes and and again for two minutes immediately before and after the task. In contrast to the four treatment groups, a fifth group was included that

received only a single PPI session, after first being given the neutral slideshow followed by the Stroop task, after which they received the first and only PPI session.Therefore, this group was used to determine whether Stroop engagement affected PPI when it was given for the first time;, the data from this group was compared to the first PPI session of the previous four groups. For all groups, the entire study lasted 90 minutes per participant.

Electrode placement: All electrophysiological equipment, including electrodes and conducting gel, was purchased from BIOPAC Systems (Goleta, CA). Prior to electrode attachment, the participant's skin was lightly scraped with an emery board and cleaned with rubbing alcohol. Each electrode was filled with conductive gel before being placed on the skin. Three ECG electrodes were placed on the participant: one electrode on each inner wrist and one electrode two inches above the right ankle to serve as a ground. For EMG recording, three disposable electrodes were placed on the participant's forehead (viz., ground electrode), while the remaining two electrodes were placed over the inferior portion of the orbicularis oculi of the right eye to measure the eye blink response. Noise was delivered through headphones connected to the LabLinc V hardware, which was hidden behind a floor to ceiling partition six feet to the rear of the subject.

The PPI Session: Each PPI session consisted of 42 randomized trials made up of either an acoustic pulse alone, a pre-startle pulse (prepulse) alone or a prepulse+pulse trial. The startle pulse was a 50ms 95dB burst of white noise. The prepulse was a 65dB noise burst that lasted 50ms and occurred before the pulse in one of three intervals: 100ms, 120ms or 240ms. The breakdown of the trials was as follows: sixteen of the trials were pulse alone,

three of the trials were prepulse alone, three of the trials were prepulse+pulse with a 100ms interval, ten of the trials were prepulse+pulse with a 120ms interval, and ten of the trials were prepulse+pulse with a 240ms interval. Intertrial intervals ranged between 10 and 32 seconds and were randomized. The total time for a PPI session was twenty minutes. Inclusion of variable prepulse-pulse intervals was to identify the optimal interval for observing PPI, which is typically the 120 msec interval (Braff et al., 2001). This was confirmed in the current study, and the data based on this interval was used for all analyses.

Slideshow Control Condition: This treatment condition was used as a control group, in which participants did nothing physically or cognitively active between the two PPI sessions. It was used a means to simply pass the time without imposing any cognitive demands and/or decisions. The slideshow was made up of 20 neutral images from the International Affective Picture System (IAPS). Each image was displayed on the screen for fifteen seconds, and the slideshow automatically repeated itself three times for a total of fifteen minutes. Examples of images: umbrellas, cups and leaves. Participants were told to do nothing but to watch the images on the screen.

The Stroop Task: The Stroop task was taken from the Psychology Experiment Building Language (PEBL) database and can be found online with an in-depth description at http://pebl.sourceforge.net/ (Mueller, & Piper, 2014; Mueller, 2014). The task lasted about 15 minutes. Table 3 provides the twelve different trial types in the Stroop

procedure and the ones used to calculate reaction time and error rate during color conflict (cognitive gating) trials. See figure 2 for examples of what trials looked like.

The GoStop Impulsivity Paradigm: The software used for this task was developed by the Neurobehavioral Research Laboratory and Clinic (San Antonio, TX) and has been empirically tested as an efficient measure of impulsivity (Dougherty et al., 2005). An in-depth description of the task has been discussed in previous literatutre (Dougherty et al., 2005). In brief, participants are required to respond to matching successive numbers flashed on a screen, but must withhold that response if the second number turns red within 350ms of it appearing. The task lasted about fourteen minutes.

The Simple Stroop: This task was created using Microsoft PowerPoint and followed a very similar layout and appearace to that of the Stroop task above. However, in this task, all of the trials were congruent, so that the name of the color always matched the font color. The task lasted fifteen minutes.

Cortisol Assay. Saliva samples were collected in Salivette^{R} tubes (Sarstedt, Germany). Immediately following the test session, saliva samples were frozen at -80°C. A commercial radioimmunoassay (RIA) kit (ICN Biomedicals Inc., Irvine, CA) was used to determine, in duplicate, salivary cortisol levels. The intra- variability was less than 8%, and all samples were analyzed in a single run thus precluding inter-assay variability. Cortisol data is expressed as mg/dL.

Data Analysis:

Percent prepulse inhibition was measured using the mean EMG reading 1-sec before an acoustic stimulus trial and the peak EMG reading during the 200ms following the trial. Each trial consisted either of a pulse alone or prepulse+pulse. Percent inhibition was calculated using the following formula: $100 * \frac{(Pulse\ alone)-(Prepulse+Pulse)}{(Pulse\ alone)}$. Only prepulse+pulse trials with a 120ms latency were used, since this was the optimal condition for all subjects to show PPI. Furthermore, the series of five pulse-alone trials that began each PPI session was not included in the analysis, as these are normally considered habituation trials (Braff et al., 2001).

IBM SPSS Statistics Version 20 (2011) software was used to analyze all of the data. To analyze the data from the Stroop task, composite scores for reaction time and error rates for conflict trials were computed for each participant. The GoStop data was latency (measured in seconds) to respond for matching trials and latency to respond during stop trials. For either task, participants who had scores two standard deviations from the mean for a particular measure were excluded from the data analysis.

RESULTS

First PPI Session: Startle Reactivity and Percent Inhibition for Groups I-IV

Percent inhibition in the first PPI session for Groups I–IV revealed no significant differences between any of the groups ($F(3, 80) = 0.953$, $p = 0.419$. Similarly, the mean startle reactions in the pulse alone trials did not show a main effect of condition ($F(3, 78) = 0.387$, $p = 0.763$. Analysis of sex differences showed no significant difference in PPI nor startle reactivity to pulse-alone between males and females [$t(82) = -0.557$, $p = 0.570$; $t(82) = -0.051$, $p = 0.959$.

These results indicate that subjects randomly allocated to each condition were evenly distributed as to baseline PPI and startle reactivity. Non-parametric, Spearman's rho correlations were performed for first session PPI and age, handedness and ethnicity, but no significant correlations were found.

Effect of the Stroop Test on the First Session PPI and Startle Reactivity

Participants in Group V received their first and only PPI session after being subjected to the Stroop task (see **Fig 1**). The percent inhibition for Group V was compared to the percent inhibition in the first PPI session for all other groups. . The results showed that percent inhibition in Group V did not differ significantly from Groups I-IV. ($F(4, 97) = 0.739$, $p = 0.568$). Moreover, there were no differences in startle reactivity the pulse alone ($F(4, 96) = 0.813$, $p = 0.502$) between any of the groups. There was, however, a significant difference between the percent inhibition in Group V (M=39.82, SD=37.54) and percent inhibition in a second session PPI after Stroop in Group II (M=27.50, SD=34.86), such that first session PPI was significantly greater, $t(38) = -1.07$, $p = 0.293$.

Taken together, these results imply that Stroop does not significantly affect a first session PPI, but that it does influence sensorimotor gating differently during a second PPI session (see below).

Changes in PPI After a Control Resting Condition

One purpose of this study was to examine changes in PPI across two succeeding sessions, and this was established in the Group I (control condition). In this group, the two PPI sessions were separated by presentation of a slideshow containing neutral images. This was necessary, since preliminary testing showed that participants became drowsy if asked to sit without attending to any stimuli. The use of neutral images involved no physical or cognitive action and was a means to simply pass the time without any mental interference. The results showed that for all participants percent inhibition in the PPI trials significantly increased for the second PPI session when compared to the first session (M before=31.37, SD=30.33, M after=50.45, SD=31.42; $t(23)=-2.73$, $p=.012$; **Fig 3a**). However, additional analysis comparing males with females (**Fig 3b, 4**), revealed that this increased percent inhibition was significant only in females (M before=26.67, SD=26.45, M after=53.13, SD=29.18; $t(13)=-2.38$, $p=.033$), but not males (M before=37.96, SD=35.47, M after=46.70, SD=35.57; $t(9)=-1.63$, $p=.137$).

Changes in PPI After Deliberate Cognitive Task Engagement

In comparison to the control condition involving an intervening slideshow (Group I) between two PPI sessions, three different cognitive tasks – the Stroop, the GoStop and the Simple Stroop – were administered in between two PPI sessions. These experimental

groups corresponded to Groups II-IV (see Table 1). Two of these tasks (Stroop and GoStop) were deliberately difficult and challenging. Since these cognitive tasks were impacting the second PPI session, the percent inhibition data were examined in terms of change from the first PPI session. The results showed significant differences in PPI change after the three different tasks, when compared to the neutral slideshow [$F\ (3, 80) = 7.904$, $p<0.01$] (see **Fig 3a**). Using Bonferroni corrections, changes in PPI after the slideshow (M=19.08, SD=34.19) were significantly different to changes after Stroop performance (M=-20.77, SD=31.86; $p<0.01$) and after the GoStop task (M=-15.00, SD=21.26; $p<0.01$; **Fig 3a**). That is, PPI increased after the slideshow, but decreased after Stroop and GoStop. In addition, changes in PPI were affected differentially after the Stroop and Simple Stroop tasks (M=7.68, SD=38.23; $p=.045$), where PPI decreased after the challenging Stroop task, but remained unchanged after the Simple Stroop.

These data were examined more closely for sex differences in PPI change after the specific individual cognitive tasks (**Fig 3b; Fig 4**)**.** As stated earlier, for females, PPI significantly increased after observing the neutral slideshow. However, after performing the GoStop task, PPI for females was reduced relative to the first PPI session (M before=47.86, SD=30.22, M after=35.03, SD=38.39; $t(12)=2.26$, $p=.043$), and did not change relative to the first PPI session after performance of the Stroop or Simple Stroop tasks. Therefore, for females, the Stroop and Simple Stroop tasks prevented the normal increase in PPI that is observed during a quiescent period of neutral image exposure in the control condition. Moreover, the GoStop task not only prevented an increase, but actually reduced the percent inhibition in the second PPI session.

For males, there was no significant change in PPI after the slideshow nor after the Simple Stroop. However, PPI significantly decreased after Stroop (M before=55.02, SD=47.76, M after=23.49, SD=48.37; $p<0.01$) and after the GoStop task (M before=35.71, SD=20.13, M after=17.61, SD=32.61; $p=0.048$). Therefore, as for the females, there was a failure to show greater percent inhibition in the second PPI session (when compared to the first PPI session), if this was preceded by an engaging cognitive task, the Stroop or GoStop.

Finally, non-parametric, Spearman's rho correlations were performed for differences in PPI and age, handedness and ethnicity. No significant correlations were found.

Changes in Cortisol and Heart Rate after Task Performance

Cortisol and heart rate measures were taken at three points during the experiment: once prior to the first PPI session, to establish a baseline measure; once before a given cognitive or control task; and a final sample after the task (see **Fig 1**). The results showed no significant differences in baseline salivary cortisol concentration nor heart rate for any of the treatment groups [$F(4, 53)= 0.702$, $p= 0.593$; $F(4, 55) = 0.377$, $p=0.824$]. An ANOVA was conducted on changes in cortisol and heart rate from the pre-task measure (Cortisol #2) to the post-task measure (Cortisol #3). The results showed no significant changes in cortisol ($F(4, 53)= 2.37$, $p=0.064$) or heart rate ($F(4, 55) = 0.436$, $p = 0.782$) between any of the groups.

Changes in Startle Reactivity after Task Performance

The startle reactivity to pulse alone trials was analyzed and was not found to be different between any of the groups for the first PPI session ($F(4, 96) = 0.813$, $p = 0.520$). This was also the case after task performance, during the second PPI session ($F(3, 79) = 0.959$, $p = 0.416$). In addition, there was no main effect of task type on changes in startle reactivity between PPI sessions 1 and 2 ($F(3,79) = 0.031$, $p = 0.993$).

These results suggest that changes in PPI reported above were not related to changes in startle reactivity *per se*.

Stroop Performance and PPI

Stroop data was analyzed on only fifteen participants (M=7, F=8), since *a priori* decisions to examine the link between Stroop performance and modulation of PPI were not made until midway through the course of running participants. Therefore, Stroop performance data were collected in Group II and Group V, with analyses being conducted on composite reaction time (RT) and composite error rates during conflict trials in which participants identify the color of the word. Since these conflict trials involve the most cognitive gating – the filtering out of an automatic response in favor of the correct response – RT and error during that time provided the best measures of cognitive gating ability.

There were no differences in conflict RT or error rate between males and females in either group that performed the Stroop task. Second session PPI for Group II did not correlate significantly with Stroop performance in either RT or error rate for males or females. However, for the first session PPI, there was a positive correlation for conflict RT, but only for females in Group V ($r(4)=.908$, $p<0.01$;**Fig 5a**). This suggests that

Stroop performance may influence the nature of a first PPI session. There were no other significant correlations between first session PPI and Stroop performance.

When considering changes in PPI (from session 1 to session 2 – that is, for participants in Group II) as a function of intervening Stroop exposure, males showed strong positive and negative correlations with both conflict RT and error rate, respectively ($r(5)=0.865$, $p=.012$; $r(5)= -0.847$, $p=.016$) (**Fig 5b-c**). This correctly suggested that for males, error rate and RT were negatively correlated ($r(5)= -0.930$, $p<.01$) (**Fig 5d**). These significant correlations were not observed for female participants in this group.

GoStop and PPI

The data analyzed were (i) composite scores for percent correct response inhibition during stop trials, (ii) composite latency to respond during go trials, and (iii) composite latency to incorrectly respond during stop trials. There were no significant differences between males and females in any of the three measures. Percent inhibition, latency and stop latency were all not correlated with first session PPI, second session PPI or PPI difference between tasks. They were also not correlated with one another. In short, GoStop performance did not show any significant correlations or relationships.

DISCUSSION

The current study revealed a complex and novel set of relationships between a number of variables related to cognitive and sensorimotor gating. Moreover, these relationships varied between males and females, suggesting that sex differences may underlie how cognitive activity modulates sensorimotor gating, as measured using the noise-induced eye-blink reflex PPI paradigm. The current study used a design in which two PPI sessions were presented to participants, the intent being to determine whether (i) changes in PPI occur across multiple testing sessions, and (ii) if such changes are modified by intervening cognitive demands.

Sensorimotor Gating Improves in Women with a Passive Activity in between Sessions

In Group I, when women passively observed a slideshow of neutral images (a cognitively passive state) between two PPI sessions, their PPI increased significantly (i.e. percent inhibition was greater) in the second session; for men, however, the percent inhibition in the second PPI session did not change relative to the first session. This suggests that females are more likely to show better sensorimotor gating ability when retested, while for males sensorimotor gating remains stable. This data showed that there was no degrading or loss of sensorimotor gating ability across PPI sessions. This provided the opportunity to determine whether states of greater cognitive engagement would alter repeated testing for sensorimotor gating (see discussion further below).

To our knowledge, sensorimotor gating has never been studied in multiple sessions, and hence, the result of improved sensorimotor gating after multiple successions appears to

be novel. Although sensory systems can habituate to stimuli over time (Picton, Hillyard, & Galambos, 1976; Pfleiderer, Ostermann, Michael, & Heindel, 2002), startle responsiveness to pulse alone did not significantly change before and after the task. Therefore, our results were confined to reductions in startle responsiveness during prepulse+pulse trials, thereby implicating sensorimotor gating *per se* as being uniquely altered. In other words, women were getting better at sensorimotor gating with practice. Many different drugs improve sensorimotor gating in humans and mice with deficits in PPI (Quednow, Wagner, Westheide, Beckman, Bliesener, Maier et al., 2006; Duncan, Bollini, Lewinson, Keyes, Jovanovic, Gaytan et al., 2006; Acheson, Stein, Paulus, Geyer, & Risbrough, 2012), but there has been no evidence to date that sensorimotor gating can improve in the absence of medication. Practicing of cognitive and motor tasks has been shown to cause behavioral, neurobiological and neurophysiological changes (Kramer, Schneider, Fisk, & Donchin, 1986; Iacoboni, Woods, & Mazziotta, 1996; Petersen, van Mier, Fiez‖, & Raichle, 1998), such that performance is enhanced and greater recruitment of different areas of the brain occurs when performing a practiced task, when compared to a novel task (Iacoboni et al., 1996). Though PPI is considered a reflex, it is modulated by top-down processes (Li, Du, Li, Wu, & Wu, 2009) that may alter and change with practice to improve automatic responses to sensory stimuli. The first PPI session may be considered a "practice session" that prepares or sensitizes the brain, perhaps through some form of neuroplasticity, for the next encounter with similar sensory stimuli – in the present case, the second PPI session. The slideshow, although an engaging sensory experience, involves no demanding cognitive action and allows the brain to maintain the neuroplastic changes made from the first PPI session, improving sensorimotor gating the

second time around. However, for men, this was not the case and PPI remained the same between sessions. Although not demonstrated significantly in our study, men tend to have higher levels of PPI than women (Swerdlow, Auerbach, Monroe, Hartston, Geyer, & Braff, 1993; Braff et al., 2001) and we suggest that perhaps as a consequence, their sensorimotor gating resists time-dependent or practice-dependent change. One caveat to this notion, however, is that in the present study, we did not find that PPI overall for males was statistically significant from females. Therefore, the difference appears to reside in change upon repeated sensorimotor demands.

Whether the effects of practice on women's PPI are long-term and persist across days, remains to be tested; nonetheless, this could be the first step in an important finding. Many mental disorders display deficits in sensorimotor gating (Braff et al., 2001), the consequence of which can "cause cognitive fragmentation" in individuals who suffer with the disease (Swerdlow et al., 1995). Problems with filtering out incoming sensory information can cause a flooding of the brain with sensory stimulation, severely impairing physical, cognitive and emotional functions. If there were a way to improve sensory gating without medication or drugs, alternative forms of therapy could be devised and negative side effects of gating deficits could be abated.

In sum, the passive watching of a slideshow seems to allow women the opportunity to improve their sensorimotor gating capabilities based on a previous experience with a PPI session. Although men do not show this increase, multiple exposures to PPI experiences might help to improve overall sensorimotor gating.

Cognitive Gating Tasks Interrupt and/or Corrupt Sensorimotor Gating Improvement

Relative to the Group I participants, whose data were discussed above, the remaining participants were randomly allocated to conditions that involved intervening cognitive tasks between the two PPI sessions. These tasks involved progressively greater demands on cognitive gating, and included the Simple Stroop, which lacked conflict, but required attentional demand, the traditional (or complex) Stroop, and the GoStop impulsivity task. These tasks affected the magnitude of PPI during the second session, when compared to the first session. Overall, the GoStop task caused PPI to significantly decrease for females, while the Stroop and Simple Stroop caused an inhibition of the PPI increase observed in the second PPI session in Group I. For men, the Simple Stroop had the same effect as the slideshow and did not affect PPI; however, both the Stroop and GoStop tasks decreased PPI. Cortisol, heart rate and startle reactivity measures did not significantly change as a result of the tasks, suggesting that it is unlikely stress or modifications of startle reactions played a role in the changes in PPI.

Based on the data of Group I, the normal PPI for the second session was for males to remain stable, while females showed greater PPI. However, once a significant cognitive demand was imposed, such as the (complex) Stroop task, females failed to show the improved PPI, while males showed less PPI. In both cases, it may be said that PPI was impaired or degraded. This same degradation was observed for both males and females after the GoStop task, in that PPI was significantly reduced in the second PPI session. This decline may signal a corruption of sensorimotor gating abilities, in that the cognitive tasks between sessions negatively affect the stability of sensorimotor gating in males. Alternatively, for females, the stability of PPI after the Stroop represents an

interruption of the practice effect discussed above, whereas the decline after GoStop signifies an interruption and/or corruption of sensorimotor gating abilities.

These effects of more demanding cognitive tasks on prepulse inhibition suggest a strong overlap between two seemingly distinct domains. Neuroanatomically, sensorimotor gating and inhibitory control have been shown to share common structures that support their functions. The frontal lobe (Drewe, 1975; Knight et al., 1999; Weisser et al., 2001; Aron et al., 2004), and specifically the PFC (Hazelett et al., 1998; Judd et al., 1992; Knight et al., 1999; Nee et al., 2007) have been indicated as crucial areas for proper functioning of both sensorimotor gating and cognitive inhibitory control. The inferior frontal gyrus also is a mutually important region for both PPI and cognitive gating functions (Kumari et al., 2005; Chikazoe et al., 2007), as is the frontostriatal circuitry (McAlonan et al., 2002; Murphey et al., 2007). As most of these areas are involved in executive function, filtering incoming information and motor behavior, it seems logical that both sensorimotor gating and cognitive gating would require input from these areas; however, it might also be the case that these overlaps are also driving a division of resources between sensorimotor and cognitive gating. Indeed, it has recently been shown in studies of attention that working memory and sensory gating share a common pool of resources, such that central mechanisms modulate sensory gating (Sörqvist, Stenfelt, & Rönnberg, 2012). As working memory requires increased amounts of resources from this shared pool, the ability to filter out sensory information decreases due to a diminished share of the resources needed to devote to sensory gating. This may be due to limitations of the PFC to allocate attention to multiple sources, thus modulating early perceptual representation (Gazzaley & Nobre, 2012). The shared brain regions and networks – and

specifically the PFC – that are involved in both sensorimotor and cognitive gating could also be acting as a shared resource pool for the two domains, with central processing of inhibitory control modulating the sensory gating. When the resources are exhausted due to intense cognitive gating - here brought about by the Stroop and GoStop - the modulation involved in sensory gating is no longer optimal and PPI is altered. For males, the tasks overwhelm the common circuitry so that it can no longer filter out sensory information as effectively, thereby producing a significant decline in PPI. For females, the task-induced exhaustion of shared resources resulted in the corruption of the tendency to improve PPI across sessions (as occurred for Group I and discussed above), and also decreased PPI, suggesting impaired the ability to filter out unnecessary sensory information.

Performance on the cognitive tasks also appeared to relate to sensorimotor gating. Even though women performed just as well as men on both the GoStop and the Stroop task, the tasks had differential effects on women's sensorimotor gating. Though the current study did not see sex differences in task performance, it has been reported that women generally perform quicker than men on the Stroop (Mekarski, Cutmore, & Suboski, 1996), but not on Stop-signal tasks such as the GoStop (Thakkar, Congdon, Poldrack, Sabb, London, Cannon et al., 2013). Shorter reaction times on the Stroop may signify a greater ease of processing during the task, requiring less demand on the shared circuitry. Because of the smaller demand, the Stroop did not corrupt sensorimotor gating by making it worse, it just did not allow for the improvement displayed after the slideshow. The GoStop demanded more resources, thus sensorimotor gating declined afterwards.

Seemingly opposed to the hypothesis of shared resources, Stroop results after a PPI session (Group II) were comparable to Stroop results after a passively observed neutral slideshow (Group V), possibly indicating that auditory-evoked sensorimotor gating demands do not influence cognitive gating performance. We have three varying explanations for this. Firstly, the previously proposed top-down modulation occurs by central processing onto sensory gating, and not the other way around (Gazzaley & Nobre, 2012); therefore, demanding cognitive gating tasks can affect the functioning of sensory gating, but sensory gating does not impact cognitive gating. Alternatively, this could be due to the fact that the PPI sessions were not continuous trials like the Stroop and GoStop trials, but rather had inter-trial intervals that allowed for short rest periods between trials. These inter-trial rest periods may have alleviated the demands on the shared resources, so that cognitive performance remained intact. Lastly, just as PPI was only affected following a previous PPI session, perhaps cognitive gating would follow a similar pattern. Future studies should test Stroop performance in a succession very much like the current study used for PPI, wherein a first Stroop session is followed by a PPI session which is then followed by a second Stroop session. Perhaps, then, one may find an influence of sensorimotor gating on cognitive gating.

In sum, we propose that the neuroanatomical and cognitive overlaps between the sensorimotor gating domain and the cognitive gating domain form a shared network of resources dedicated to executing proper functioning, making it possible for the actions of one domain to impact the other.

Cognitive Gating Performance is Related to Sensorimotor Gating Performance

Though different patterns emerged for men and women, performance on the Stroop task was heavily correlated with sensorimotor gating performance, as measured by PPI. These results support previous research that found a trending level of significance between PPI and Stroop performance scores (Bitsios & Giakoumaki, 2003). For women, percent inhibition in first session PPI given *after* Stroop (Group V) was positively correlated with RT on the Stroop. This suggests, that delaying a response during a conflict trial is associated with more efficient sensorimotor gating. Similarly, for men, both RT and error rate during Stroop strongly correlated with the changes in PPI between tasks (Group II). In this case, it is suggested that the longer participants were able to withhold a response during a conflict trial, error rate was reduced, and PPI decline was less likely.

If RT and error rate reflect the ability to inhibit automatic and initial thoughts and behaviors, then they can also be thought of as measures of effective cognitive gating. The longer RTs of both males and females suggest more efficient cognitive gating, as evidenced by the lower error rate, and the increased PPI and/or reduced decline of PPI suggest enhanced sensorimotor gating. Therefore, the strong correlations between Stroop performance and PPI suggest an overlap between the two domains. Individuals who have robust cognitive gating abilities also display efficient sensorimotor gating abilities and vice versa. These results lend support to the hypothesis proposed above that cognitive and sensorimotor gating domains may share similar neurological mechanisms and may be more closely related than previously thought.

There were no significant correlations between any of the GoStop performance measures and PPI. This may be due to the performance measures used to analyze the data. Inhibition in the GoStop task is measured by taking the amount of correct responses

(i.e. no response) to stop trials and dividing by the total number of stop trials. Latency and stop latency are the amounts of time a participant takes to respond once the number appears and when the stop signal appears, respectively. Cognitive gating is needed in order to withhold responding in case the number turns red, the stop signal (see instructions for this task in the methods section). However, the gating involved in the GoStop task is different to the Stroop because whereas in the Stroop one must decide to respond with a particular answer choice, in the GoStop, the choice is between responding and not responding. In other words, one can decide to wait to respond until the matching number flashes off the screen and only then decide whether to respond or not. Because the program counts late responses as responses, and even though participants were told to respond while the number is still on the screen, this strategy helps participants keep their inhibition rates high during stop trials and their inhibition rates low during go trials. Looking closer at the data, it appears that many participants did employ this strategy for some of the trials, thus skewing their inhibition rates and latencies. However, no participant received a perfect score, nor near a perfect score, on the task, implying that they did perform the task in the correct manner on many of the trials. The cognitive gating involved in those trials is most probably what is driving the decline in PPI during the second session.

Changes in PPI are Not Due To Stress, Attentional Mechanisms or Changes in Startle Reactivity

There was always the possibility that the changes in PPI were due to factors other than cognitive gating, such as stress or arousal. There have been multiple studies that show

that both cortisol (Kunz-Ebrecht, Mohamed-Ali, Feldmana, Kirschbaum, & Steptoe, 2003) and heart rate (Tulen, Moleman, van Steenis, Boomsma, 1989; Caudell, & Galucci, 1995) can increase in response to physiological and psychological stress induced by the Stroop task, however in the current study, both cortisol and heart rate did not significantly change in response to the task. Anecdotally, when participants were asked how stressful they found the task, they mostly responded that they felt very little stress when performing the task. Though some did profess feeling stressed during the task, there was no correlation found between cortisol or heart rate elevations and changes in PPI.

Another factor that could have been affecting PPI changes was that of the attentional mechanisms required in both the Stroop and GoStop task. It has been proposed that both PPI and the Stroop task are mediated by attentional processes rather than inhibitory control (Scholes, & Martin-Iverson, 2009), and therefore it might be the attentional overlap between the two domains that is causing the effect. If the tasks are overwhelming the attention center of the brain that is also needed to effectively execute PPI, then perhaps that might be why there is a decrease in sensorimotor gating after the tasks. However, our creation of the “Simple Stroop” task was designed so that all the attentional mechanisms that were required in the Stroop were also needed in the Simple Stroop. The only difference between the two tasks was that the Stroop required cognitively gating out colors from words while the Simple Stroop did not. Prepulse inhibition did not change significantly, for either males or females, after performing the Simple Stroop. We posit that while the attentional mechanisms did interrupt the improvement of PPI in females, it was not sufficient to corrupt it, as occurred after the GoStop task. Though females did not significantly decrease in PPI after the Stroop, their

change after Stroop was significantly decreased compared to their change after the Simple Stroop. In males, the Simple Stroop had no effect on sensorimotor gating, being no different to the neutral slideshow condition.

Though habituation and sensitization to startle has been shown to occur in both short-term and long-term settings (Ornitz & Guthrie, 1989), this did not occur in the current study. There were no significant changes in eye blink response to pulse trials after performance of any of the tasks, and no task caused any more changes in startle reactivity than another. Participants were startled just as much during the second PPI session as they were during the first, regardless of what task they performed. Therefore, it seems that habituation or sensitization to startle between the two sessions is not an underlying cause of changes in PPI before and after a task.

In sum, neither increased levels of stress nor the attentional demands of the tasks nor changes in startle reactivity caused a change in PPI in either males or females. The only factor that had a significant effect on sensorimotor gating was that of the cognitive gating requirements of the Stroop and GoStop tasks.

Limitations and Future Studies

Further studies are needed to reveal the relationship between sensorimotor gating and cognitive gating. Though the current study did find a correlation between Stroop performance and PPI in males, other studies have not (Swerdlow et al., 1995). In addition, while our results support previous findings that there are no sex differences in Stroop performance (MacLeod, 1991), there have been reports of slower reaction times in

men during the Stroop (Mekarski et al., 1996). In addition, future studies should provide more incentive for participants to execute the GoStop task without strategies. The biggest limitation of the current study was the number of participants per group. The decision to collect Stroop and GoStop performance data was made half-way through the study, and thus, the number of participants in those groups were small, and require replication with more participants. Lastly, since the experimental design used in this study is new to the literature, additional studies using this design are needed to corroborate the findings reported here.

CONCLUDING REMARKS

The current study provides strong evidence for a relationship between sensorimotor gating and cognitive gating in humans. By using a novel paradigm, we believe we were able to show that overwhelming shared gating mechanisms by demanding cognitive tasks affects the functional execution of prepulse inhibition. This study also demonstrated that PPI could improve over time with previous exposure to occurrences involving sensorimotor gating. Both of these novel findings could have major impacts on the study and treatment of disorders that are characterized by sensorimotor gating deficits. Understanding the way in which the system adapts over time as well as how it relates to other psychophysiological and cognitive domains could prove invaluable to research as it moves forward in understanding the role sensorimotor gating and cognition play in the diseased brain.

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TABLES

Table 1. Demographic Summary of Study Participants (N=102)

Condition	**Participants** n	**Male** n	**Female** n	**Age** M (SD)
Slideshow	24	10	14	19.5 (2.7)
Stroop	22	11	11	19.8 (3.0)
Go Stop	22	9	13	20.4 (4.2)
Simple Stroop	16	7	9	19.4 (1.5)
Slideshow-Stroop	18	8	10	19.7 (1.8)

	Ethnicity				
Condition	**White** %	**African American** %	**Hispanic/Latino** %	**Asian/Pacific Islander** %	**Other** %
Slideshow	54	13	8	21	4
Stroop	45	14	5	36	0
Go Stop	41	14	9	27	9
Simple Stroop	38	6	6	44	6
Slideshow-Stroop	33	6	6	49	6

	Dominant Hand	
Condition	**R** n	**L** n
Slideshow	20	4
Stroop	21	1
Go Stop	21	1
Simple Stroop	13	3
Slideshow-Stroop	17	1

Table 2: Summary of Treatment Groups. Groups I, II, III and IV received two PPI sessions with an intervening cognitive task before the second session. Group I served as the control group for cognitive engagement, being asked to passively watch a slideshow of neutral images. Group V only had one PPI session that followed a slideshow and then a Stroop task.

Group	Study Design
I	PPI Session 1 → **Slideshow** → PPI Session 2
II	PPI Session 1 → **Stroop** → PPI Session 2
III	PPI Session 1 → **GoStop** → PPI Session 2
IV	PPI Session 1 → **Simple Stroop** → PPI Session 2
V	Slideshow → **Slideshow** → PPI Session 1

Table 3. Stroop Trial Types. There were twelve different trials types involved in the Stroop task. Participants were told to either identify the target word itself or the color in which the word was printed. If a trial was a non-conflict, then the word and the color it was printed in were matching (e.g. the word "red" was printed in a red color), and if a trial was a conflict trial then the word and the color font did not match (e.g. the word "red" printed in a green color). Participants indicated their response by either choosing names of colors printed in a black color, in their matching colors or as a colored patch. The three starred trials were the ones used in the composite scores for RT and error rate during conflict trials, as these trials involve the greatest amounts of cognitive gating.

Trial Type	**Identify**	**Conflict/Non-conflict**	**Answer Choice**
1	Word	Non-conflict	Black words
2	Word	Conflict	Black words
3	Color	Non-conflict	Black words
4	Color	Conflict	Black words
5	Word	Non-conflict	Colored words
6	Word	Conflict	Colored words
7	Color	Non-conflict	Colored words
8	Color	Conflict	Colored words
9	Word	Non-conflict	Colored Patches
10	Word	Conflict	Colored Patches
11	Color	Non-conflict	Colored Patches
12	Color	Conflict	Colored Patches

FIGURES

Figure 1. Experimental Design. Male and female participants were randomly allocated into one of five different treatment groups. Groups I-IV had exactly the same sequence of treatment, being given two PPI sessions, and an intervening task; however, the nature of the cognitive task differed between each of these groups. Group V received only a single PPI session, with participants first being given a slideshow, followed by the Stroop task, and then a PPI session. Cortisol samples and heart rate measures were taken immediately before and after the first PPI session and after each designated task. For each participant, the duration of experimentation was 90 minutes.

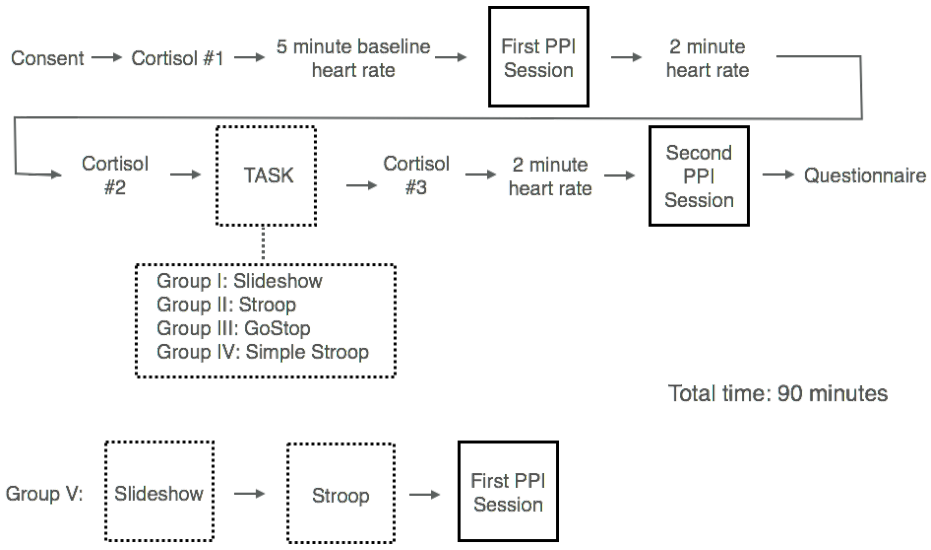
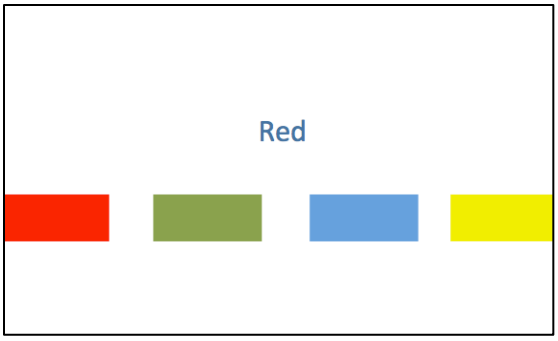


Figure 2a–c. Sample Stroop Trials. The first image is what the screen would look like during a conflict trial with black word answer choices. If the participants were asked to identify the word, then the correct answer would be red; if the participants were asked to identify the color, then the correct answer would be blue. The second image is a non-conflict trial with color word answer choices. Both the correct identification of word and color are red. The third image is a conflict trial with color patch answer choices. If the participants were asked to identify the word, then the correct answer would be red; if the participants were asked to identify the color, then the correct answer would be blue.

a

b



c

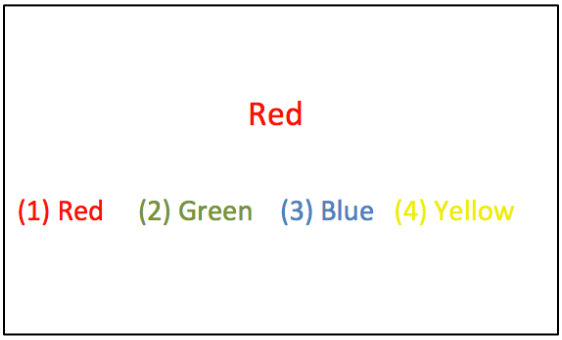


Fig 3a. Different Tasks Differentially Affected Overall PPI. Prepulse inhibition was measured before and after different cognitive tasks. The data shows the relative change in PPI from that measured in the first PPI session. A positive value indicates that percent inhibition in the second session was greater than for the first session. Compared to the neutral slideshow condition used as a control, change in PPI was significantly different in both the Stroop and GoStop tasks. No effect on PPI was observed after the Simple Stroop task. Bars represent mean ± SE of groups with 16-24 participants.

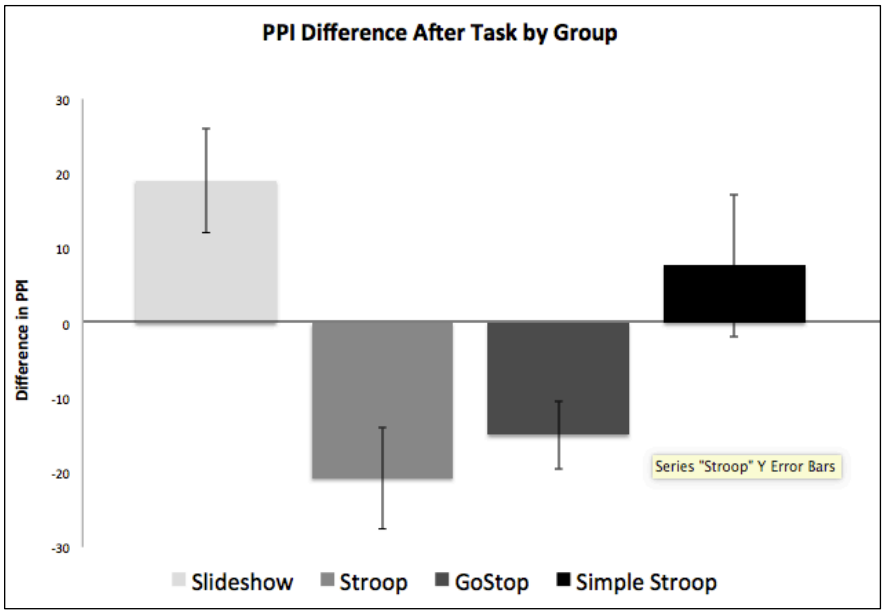


Fig 3b. Different Tasks Differentially Affected PPI for Each Sex. The data in Figure 2a was split according to the sex of the participant. Changes in PPI were different for males and females in the control slideshow condition. However, the Stroop and GoStop tasks affected PPI change equally in males and females. Bars represent mean ± SE of groups with 7–14 participants.

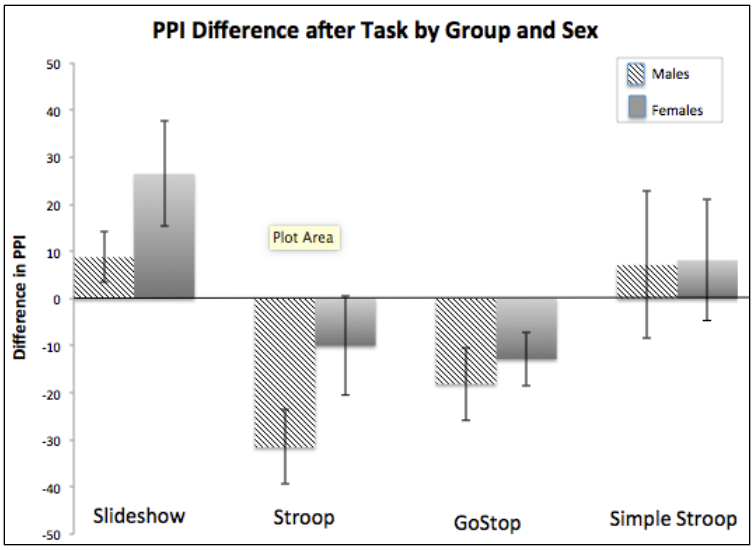


Fig 4. Prepulse Inhibition Changes Depending on the Task Type. The percent inhibition in the first and second PPI sessions is shown for each sex and according to the cognitive task that preceded the second PPI session. For females in the control slideshow condition, percent inhibition increased from PPI session 1(before) to PPI session 2 (after), whereas male percent inhibition remained stable across sessions. The imposition of cognitive demands reduced percent inhibition in both males and females. Bars represent mean ± SE of groups with 7-14 participants.

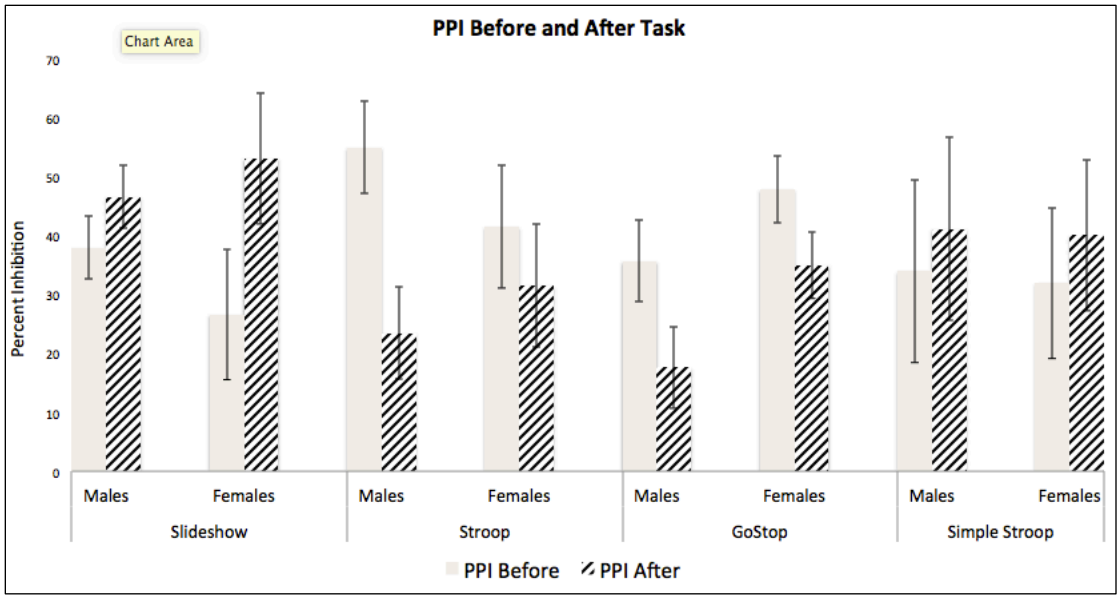
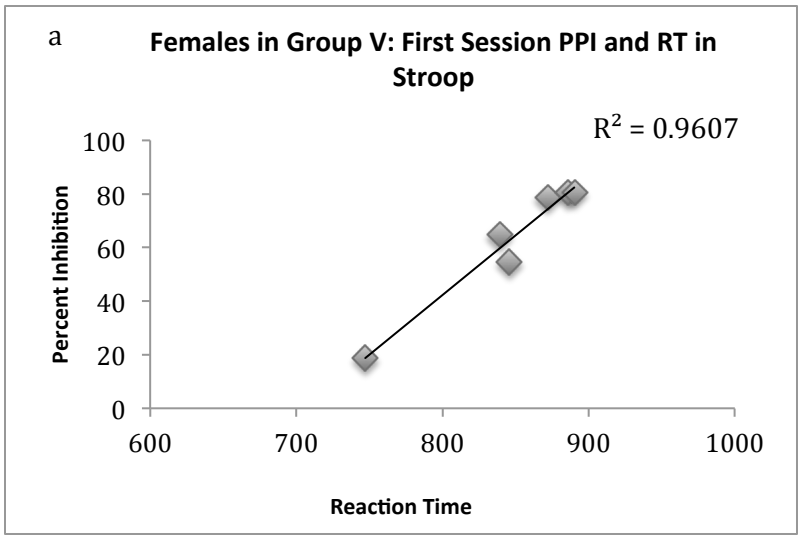
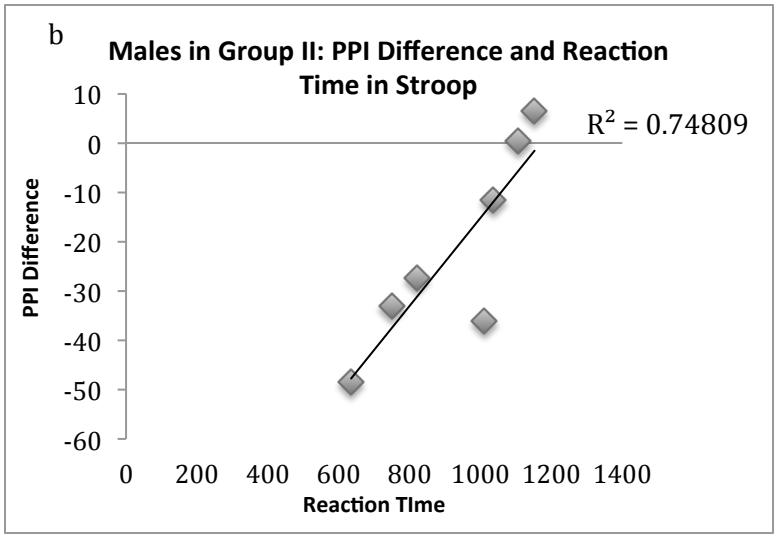


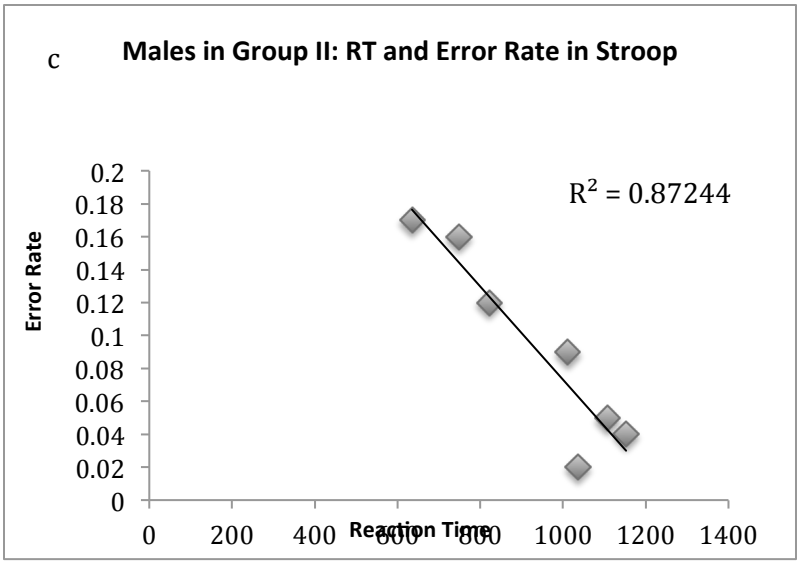
Fig5a-d: Correlations of Reaction Time, Error Rate and PPI Difference in Stroop tasks. Reaction time (RT) and error rates during the Stroop task were correlated with first session PPI after the Stroop task (Group V) and with changes in PPI across the two sessions that contained an intervening Stroop task (Group II). **(a)** Females in Group V (N=6) had a significant positive correlation between Stroop RT and first session PPI. This indicates that increased latency to respond during the Stroop task predicts greater percent inhibition during the PPI Session. **(b)** Males in Group II (N=7) had a significant positive correlation between Stroop RT and magnitude change in PPI across the two sessions in which they were tested. This indicates that the longer one took to respond during the Stroop task, the less likely that PPI decreased across sessions. **(c)** Males in Group II had a significant *negative* correlation between changes (across sessions) in percent PPI and error rate during Stroop performance. This indicates that the more errors participants made during the Stroop task, the more likely that percent inhibition decreased in the second PPI session. **(d**) Males in Group II had a significant negative correlation between RT and error rate during Stroop performance. This indicates that increased latency to respond was associated with fewer errors.



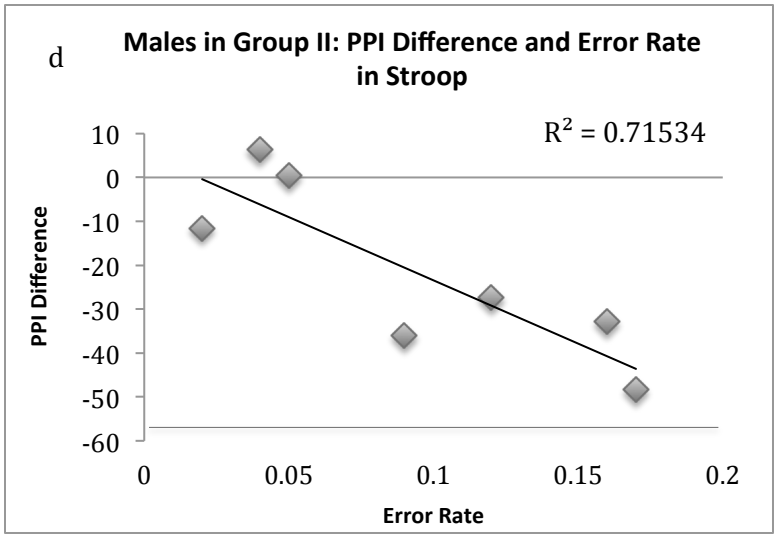
b


Males in Group II: PPI Difference and Reaction Time in Stroop
R² = 0.74809
PPI Difference
10
0
-10
-20
-30
-40
-50
-60
0
200
400
600
800
1000
1200
1400
Reaction TIme

c


Males in Group II: RT and Error Rate in Stroop
R² = 0.87244
Error Rate
0.2
0.18
0.16
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
0
200
400
600
800
1000
1200
1400
Reaction Time

d


Males in Group II: PPI Difference and Error Rate in Stroop
R² = 0.71534
PPI Difference
10
0
-10
-20
-30
-40
-50
-60
0
0.05
0.1
0.15
0.2
Error Rate