THE EFFECTS OF BARORECEPTOR STIMULATION ON SHORT-TERM VERBAL MEMORY

by

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Individuals remember arousing, emotional stimuli better than neutral. Vagus nerve stimulation (VNS) has been associated with changes in such 'affective memory' in clinical samples. The current study utilized carotid baroreceptor stimulation (CBS), an indirect method of vagus nerve stimulation, to investigate this association further in normal, college-aged participants. Results showed that CBS marginally enhanced verbal memory for negative words and slowed heart rate, but these effects were not robust. Our findings indicate that physiological manipulations may contribute to differential rates of memory for arousing, emotional stimuli, suggesting that preferential memory for such stimuli might be attributed, in part, to individual differences in physiology. These findings are discussed within both the context of the Laceys' (1974) hypothesis that baro-afferent signaling may be associated with concomitant changes in heart rate and cognitive function and from the perspective that stimulation may affect brain regions involved in emotion and memory processing.

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PREFACE

I would like to thank my committee members for their advisement on this project. I would also like to thank Michael Eddy for his technological assistance and David Mendelson, Diksha Mishra, and Matthew Robinson for serving as my research assistants.

1.0 INTRODUCTION

Arousing, emotional stimuli are often remembered over neutral stimuli (Kensinger & Corkin, 2003). Electrical stimulation of the vagus nerve (vagus nerve stimulation; VNS), a nerve integral to the neuro-cardiac baroreflex, has been shown to selectively modulate this ‘affective memory’ (Critchley et al., 2007). Yet, the physiological pathway responsible for the association is unknown; VNS may affect memory by altering baroreceptor firing and heart rate, two factors linked to cognitive processing by the Laceys’ intake-rejection hypothesis (Buchanan, Etzel, Adolphs, & Tranel, 2006; Jennings, 1986; B. C. Lacey & J. I. Lacey, 1974; W. L. Libby, Lacey, & Lacey, 1973). VNS may also increase neurological activity in brain regions central to emotion and memory. Studies of VNS and memory are limited as stimulators are only implanted in epileptic or severely depressed individuals. However, the effects of VNS can also be achieved via external suction of the carotid sinus (carotid baroreceptor stimulation; CBS), a non-invasive, under-researched procedure. As such, this study assessed the effects of CBS on affective memory and cardiac control. We will present our hypotheses following a review of the affective memory literature, presentation of VNS and memory research, and a discussion of neurophysiological pathways by which VNS and CBS may facilitate affective memory.

1.1 AFFECTIVE MEMORY

1.1.1 BACKGROUND

Memory is influenced by a variety of factors ranging from the order in which stimuli are encountered (e.g. the serial position effect) to whether stimuli are presented repeatedly or only once (e.g. distributed practice) (Reisberg & Heuer, 1995). Most relevant to the current study is research indicating that memory for a stimulus is influenced by its intrinsic arousing, emotional qualities. Arousing, emotional material is often, but not always, better remembered than neutral (Kern, Libkumam, Otani, & Holmes, 2005). Emotional stimuli are typically characterized across two dimensions: 1) arousal, how stimulating or calming they are and 2) valence, how negative or positive they are (Kensinger, 2004). While studies have tried to parse out the unique contributions of arousal and valence to memory, the literature provides inconclusive findings; thus, the dimensions are typically combined (Doerksen & Shimamura, 2001; Dolcos, LaBar, & Cabeza, 2004; Hamann, Ely, Grafton, & Kilts, 1999; Kensinger, 2004; Kensinger & Corkin, 2003; Kensinger & Schacter, 2006; LaBar & Cabeza, 2006). Some studies regarding valence (independent or dependent of arousal) suggest that positive stimuli alone or negative stimuli alone are best remembered (most often, the latter is reported). But, many studies indicate that positively *and* negatively valenced stimuli are remembered at higher rates than neutral, stimuli when testing both recall and recognition memory, (Baumeister, Bratslavsky, Finkenauer, & Vohs, 2001; Doerksen & Shimamura, 2001; Dolcos et al., 2004; Hamann et al., 1999; Kensinger & Corkin, 2003; Kensinger & Schacter, 2006; Lewis, Critchley, Smith, & Dolan, 2005).

1.1.2 THEORIES

Many theories address affective memory, drawing from both the cognitive and neurochemical literatures. We review the cognitive theories and only note the neurochemical ones as our study does not assess neurochemical variables. The cognitive theories propose that arousing, positively and negatively valenced, emotional stimuli are more memorable than neutral because they lend themselves to greater organizational clustering, mental elaboration, and rehearsal. Specifically, emotional, arousing qualities of the stimuli serve as a cognitive organizing principle that thematically clusters the stimuli, facilitating encoding (Kensinger & Corkin, 2003; Talmi, Schimmack, Paterson, & Moscovitch, 2007). Individuals also appear more likely to mentally elaborate upon and rehearse, particularly in a personally-relevant manner, emotive stimuli, enhancing memory (Heuer & Reisberg, 1990; Kensinger, 2004; Kensinger & Corkin, 2003; Kensinger & Corkin, 2004). Moreover, arousing, emotional stimuli are often more distinctive and/or have greater survival value than neutral stimuli which may render them more likely to capture attention and further processing (Christianson, 1992; Dolan, 2002; Kensinger & Corkin, 2003). To this end, evidence suggests that arousing, emotional stimuli selectively command more attentional resources than neutral stimuli, enhancing initial encoding (Dolan, 2002; Heuer & Reisberg, 1990; Kensinger, 2004; Talmi et al., 2007). Research also indicates that emotional information may be perceived and retained automatically by a so-called ‘pre-attentive mechanism’, a sub-conscious evaluative process that later triggers conscious attention (Christianson, 1992; Ferre, 2003). In sum, the cognitive literature provides a variety of potential explanations for affective memory.

Another literature suggests that either positive or negative material may have a distinct mnemonic advantage as opposed to equivalent effects. Positive words may be particularly memorable because of the so-called ‘pollyanna effect’ which suggests that individuals are inherently, evolutionarily biased towards more positive stimuli because they increase mood, offering a self-protective, self-enhancing effect (Baumeister et al., 2001). Moreover, the positivity bias may aid emotion regulation by permitting individuals to focus on finding happiness in the present moment instead of focusing on negative, apprehensive thoughts about the future (Kapucu, Rotello, Ready, & Seidl, 2008; Murphy & Isaacowitz, 2008).

Despite these arguments, more empirical research supports negativity bias (Baumeister et al., 2001). Negative information is viewed as evolutionarily significant, with greater survival value than positive information (Baumeister et al., 2001; Ito, Larsen, Smith, & Cacioppo, 1998; Ohira, Winton, & Oyama, 1998; Rozin & Royzman, 2001). Survival may require particular memory of negative information since the cost of forgetting it is potentially more critical than the cost associated with positive information (Baumeister et al., 2001). Evidence suggests that attentional mechanisms, noted earlier as a rationale for the general remembrance of arousing, emotional items, may mediate enhanced memory of negative items. Both pre-attention and subsequent attentional processes have been implicated in the superior memory for negative items (Kern et al., 2005; Ohira et al., 1998; Rozin & Royzman, 2001).

The negativity bias varies between individuals and seems particularly acute in depressed individuals. Depressed individuals often exhibit an exaggerated, mood congruent ‘negativity bias’, preferentially attending to and remembering negative material more so than non-depressed individuals. Following reduction of their symptoms, patients’ bias is often reduced and comparable to that seen in non-depressed individuals (Critchley et al., 2007; Shook, Fazio, & Vasey, 2007). In sum, while theoretical bases exist for both the positivity and negativity biases, somewhat more evidence supports the negativity bias, particularly in depressed individuals.

1.2 VAGUS NERVE STIMULATION, CAROTID BARORECEPTOR STIMULATION, & AFFECTIVE MEMORY

1.2.1 VAGUS NERVE STIMULATION & MEMORY: ANIMAL & HUMAN MODELS

As previously stated, research indicates that VNS may influence memory in general and also affective memory. Support comes from both the animal and human literatures; no studies have investigated the effect of CBS on memory. In animal models, VNS consistently enhances memory (Clark, Krahl, & Jensen, 1995; Clark et al., 1998; Miyashita & Williams, 2006; Roosevelt, Smith, Clough, Jensen, & Browning, 2006). Clark, Krahl, Smith, and Jensen (1995) reported that the efficacy of post-training VNS takes on an inverted-U shaped function with rats who received a moderate level of stimulation showing better memory task performance than those who received low or high levels of stimulation.

There are only three published studies investigating the effects of VNS on memory in humans; two studies of epileptic patients examined the effects of VNS on memory for neutral stimuli whereas one investigated its effects on affective memory in a severely depressed patient. The Food and Drug Administration only approves VNS for use in epileptic or severely depressed individuals. VNS was originally developed to treat epilepsy and is associated with decreased seizure activity and more normal electroencephalogram findings in that population (Krapohl, Deutinger, & Komurcu, 2007). The procedure has been used to treat depression since it was associated with increased mood in epileptics (Krapohl et al., 2007).

In the first study of VNS and memory for neutral stimuli, participants demonstrated enhanced performance on a word-recognition task following stimulation that was administered two minutes after word presentation (Clark, Naritoku, Smith, Browning, & Jensen, 1999). Similarly, another group administered the Hopkins Verbal Learning Task (a serial neutral word memory task) to participants, immediately stimulated them, then had them write down all the words could freely recall (Ghacibeh, Shenker, Shenal, Uthman, & Heilman, 2006). The authors also stimulated the participants before a delayed recall task and then again before a delayed recognition task. Researchers only found effects of VNS on memory when the number of words recalled during the delayed recall condition was divided by the highest number of words recalled in the immediate recall conditions, suggesting that VNS may selectively influence memory retention or consolidation. VNS did not affect memory as measured by participants' performance on the immediate or delayed free recall tasks alone or on the delayed recognition task alone.

The only investigation of VNS and affective memory was a case study of a patient receiving VNS for treatment-resistant depression. The participant showed decreased recognition memory for negative, arousing words shown during the active phase of the stimulation cycle in comparison to memory performance for negative, arousing words that were shown during the non-active phase of the cycle. Memory for arousing positive and neutral words was comparable for both phases of the stimulation cycle (Critchley et al., 2007). Since depressed individuals often exhibit an exaggerated negativity bias, these results may reflect the antidepressant properties of VNS, either acutely or chronically (since the patient had received VNS for 7 months prior to participating in the study and reported less severe depression at study exit than entrance). Since a control group was not included, it is uncertain whether these results are depression-dependent. Thus, solid conclusions regarding the relationship between VNS and affective memory in a healthy, larger sample cannot be drawn. Overall, although the mechanism by which VNS affects memory remains unknown, a very small literature suggests that VNS is associated with an enhancement of memory that may be modulated by the affective qualities of the to-be-remembered stimuli.

1.2.2 PATHWAYS LINKING VAGUS NERVE STIMULATION & CAROTID BARORECETOR STIMULATION TO AFFECTIVE MEMORY

1.2.2.1 COGNITIVE PROCESSING & CARDIAC FUNCTION

A link between the cognitive theories of affective memory and the role of VNS in memory enhancement may be found by reviewing evidence suggesting that brief changes in heart rate are associated with particular cognitive states. Specifically, cardiac deceleration occurs during states of environmental intake such as attention, the orienting response, and anticipation whereas cardiac acceleration occurs during states marked by an internal focus or environmental rejection and disengagement like mental work and mental elaboration (Andreassi, 2007; Jennings, 1974, 1986; B. C. Lacey & J. I. Lacey, 1974). As applied to memory, cardiac deceleration has been associated with the input portion of a memory task while acceleration has been associated with the retention portion (Jennings & Hall, 1980). Furthermore, deceleration during the input phase is correlated with better memory performance on recall and recognition tasks. Taken together, cardiac deceleration may foster an externally-focused cognitive state conducive to sensory and environmental intake like learning during the memory task input period. Conversely, cardiac acceleration may support a cognitive state conducive to an internal focus and mental work like retaining information during the memory task retention period. All studies have measured heart rate on a second by second basis or averaged over time periods ranging from a few seconds to 2 minutes (Jennings, 1974; B. C. Lacey & J. I. Lacey, 1974; Lacey & Lacey, 1978; W. L. Libby et al., 1973). Overall, research suggests that shifts in cognitive state may be accompanied by changes in heart rate and this relationship appears capable of enhancing memory.

The above research begs the question of why heart rate should be associated with cognition. While no definitive physiological pathway has been identified, it is thought that neuro-cardiac communication may be regulated in common by the central nervous system in service of adaptive cognitive and behavioral states. More specifically, research suggests that bodily baroreceptors, mechanoreceptors that regulate heart rate and blood pressure by sending afferent signals to the brain in a circuit termed the ‘baroreflex pathway’ (see the next section for more information), may mediate this relationship. When heart rate and blood pressure are elevated, the baroreceptors propagate the release of action potentials, potentially inhibiting cortical and subcortical activity involved in sensory intake. This facilitates an internal focus and environmental disengagement (Lacey & Lacey, 1970, 1978, 1979). Inversely, when heart rate and blood pressure are lower, there may be less signaling along this reflexive pathway, allowing neural activity involved in sensory intake. This relationship between cardiac function and neuro-cognitive processing has been termed the ‘intake-rejection hypothesis’ (B. C. Lacey & J. I. Lacey, 1974). As such, changes in heart rate may alternately support cognitive states of internal or external focus, promoting adaptive behaviors such as the previously-presented optimal memory performance. Moreover, the ‘intake’ portion of the Laceys’ hypothesis complements the attention theory of affective memory which contends that individuals selectively attend to emotive stimuli because they have survival value. It is possible that cardiac deceleration naturally accompanies this selective attention, improving intake of and memory for emotive stimuli. Limited research partially supports this proposition (Buchanan et al., 2006). Since this attentional bias is thought to be evolutionarily salient, it follows that a neurophysiological mechanism, such as that described by the Laceys, is in place to support it. Taken as a whole, concomitant changes in heart rate and cognitive state may underlie memory in general and affective memory specifically.

1.2.2.2 VAGUS NERVE & CAROTID BARORECEPTOR ANATOMY & PHYSIOLOGY

Both VNS and CBS are involved in the baroreflex pathway central to the intake-rejection hypothesis; as such, these procedures may be uniquely positioned to alter neuro-cognitive processing and memory. We will describe the cardiovascular effects of VNS and CBS followed by a discussion of possible pathways by which VNS and CBS may influence memory. To begin, the efferent vagus nerve, a component of the parasympathetic nervous system, exerts a tonic, negative chronotropic influence over the heart via the release of acetylcholine at the cardiac sinoatrial node (Solomon, Berg, & Martin, 2006). As such, in conjunction with sympathetic influences, the efferent vagus plays an important role in the regulation of heart rate. Two strategies for activating the efferent vagus nerve are to electrically stimulate the afferent vagus (at the neck) or to stimulate the afferent carotid artery baroreceptors (at the carotid sinus) (Eckberg & Sleight, 1992; Porges, 2003). The vagal and carotid afferents terminate in the dorsal, medial, and ventral portions of the nucleus of the tractus solitarius (NTS), a center of neurovisceral integration in the medulla (Eckberg & Sleight, 1992; Seller, 1991). When negative pressure is applied to the carotid sinus, the baroreceptors become distended as they would due to an internal increase in blood pressure. Action potentials are transmitted to the NTS where increased firing is interpreted as increased blood pressure, leading to the stimulation of the efferent fibers of the dorsal motor nucleus of the vagus nerve and their subsequent activation of the parasympathetic response to decrease heart rate and blood pressure (Andreassi, 2007; Scher, O'Leary, & Sheriff, 1991). This baroreflex pathway can also be activated by direct electrical stimulation of the vagal afferents. Thus, both VNS and CBS should elicit cardiac deceleration.

1.2.2.3 CARDIOVASCULAR EFFECTS OF VAGUS NERVE STIMULATION

The literature linking VNS and cardiac deceleration is somewhat inconsistent. In animal studies, electrical stimulation of vagal afferents slows heart rate via increased acetylcholine secretion (Kawada et al., 2007; Mizuno et al., 2007). Few studies have investigated the cardiovascular effects of VNS in humans and those that do provide conflicting results; all involved epileptic patients. While some authors report that stimulation has no transient or aggregate effects on heart rate and heart rate variability (Barone et al., 2008; Setty, Vaughn, Quint, Robertson, & Messenheimer, 1998), others have found that stimulation may influence both parasympathetic and sympathetic indices of cardiovascular function (Galli et al., 2003; Kamath, Upton, Talalla, & Fallen, 1992; Stemper, Devinsky, Haendl, Welsch, & Hilz, 2008). Most studies of transient VNS show non-significant trends toward cardiac deceleration during stimulation whereas studies of aggregate VNS measured via longer term monitoring (e.g. 24-hour ambulatory Holter monitoring) show no such effect. This raises the possibility that chronic stimulation results in habituation of the cardiac response. Moreover, stimulation parameters (intensity and cycle time) varied across studies and most studies had fewer than 10 participants. Finally, limited experimental control in the form of participant selection and data collection, particularly in the ambulatory studies, may also account for discrepant findings.

1.2.2.4 CARDIOVASCULAR EFFECTS OF CAROTID BARORECEPTOR STIMULATION

Research indicates that transient CBS reliably produces cardiac deceleration. CBS is typically administered via devices applying pressure ranging from 40 to -65 mmHg (Eckberg & Sleight, 1992). Varying pressure typically results in almost linear increases or reductions in carotid artery diameter accompanied by cardiac acceleration or deceleration. The duration of pressure applications ranges from 1 to 5 seconds (Eckberg & Sleight, 1992). Research in Dr. J. Richard Jennings' lab has also employed a laboratory-built carotid baroreceptor stimulator. In a recent experiment, the device administered –37 mmHg suction for .5 seconds. In comparison to controls receiving suction to the backs of their necks, those who received CBS showed cardiac deceleration during exhalation with stimulation initiated on the r-wave of the electrocardiogram (Figures 1 and 2) (Jennings, Eddy, Shapiro, & van der Molen, 2006). This indicates that CBS is effective under appropriate physiological conditions. Taken as a whole, CBS is a reliable method for inducing cardiac change. While it might appear more reliable than VNS, it is likely that the limited experimental control, small sample sizes, and varied stimulation parameters employed by VNS researchers may account for the inconsistent effects of VNS on cardiac function. Moreover, the majority of CBS studies apply stimulation transiently whereas most VNS studies examine stimulation's aggregate effects. Thus, the VNS studies are more likely to be affected by habituation of the cardiac response.

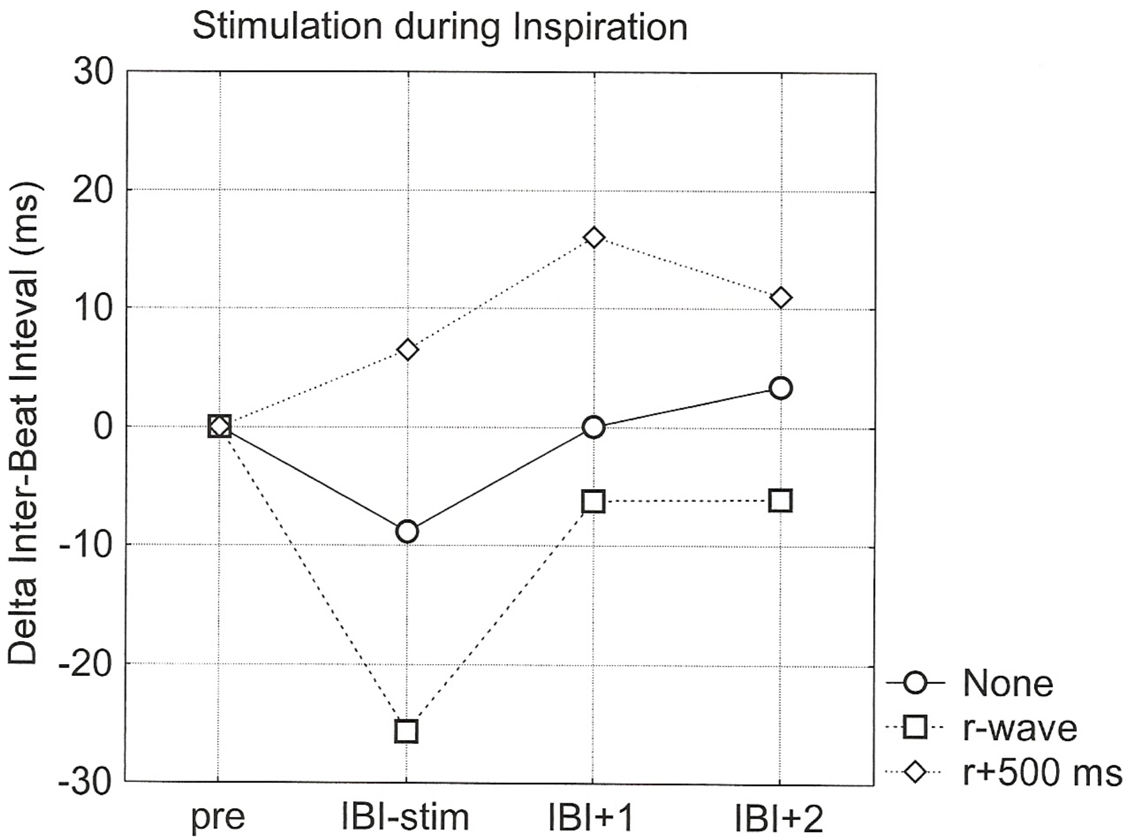

Figure 1. Interbeat Interval Unchanged by Stimulation Applied During Inspiration

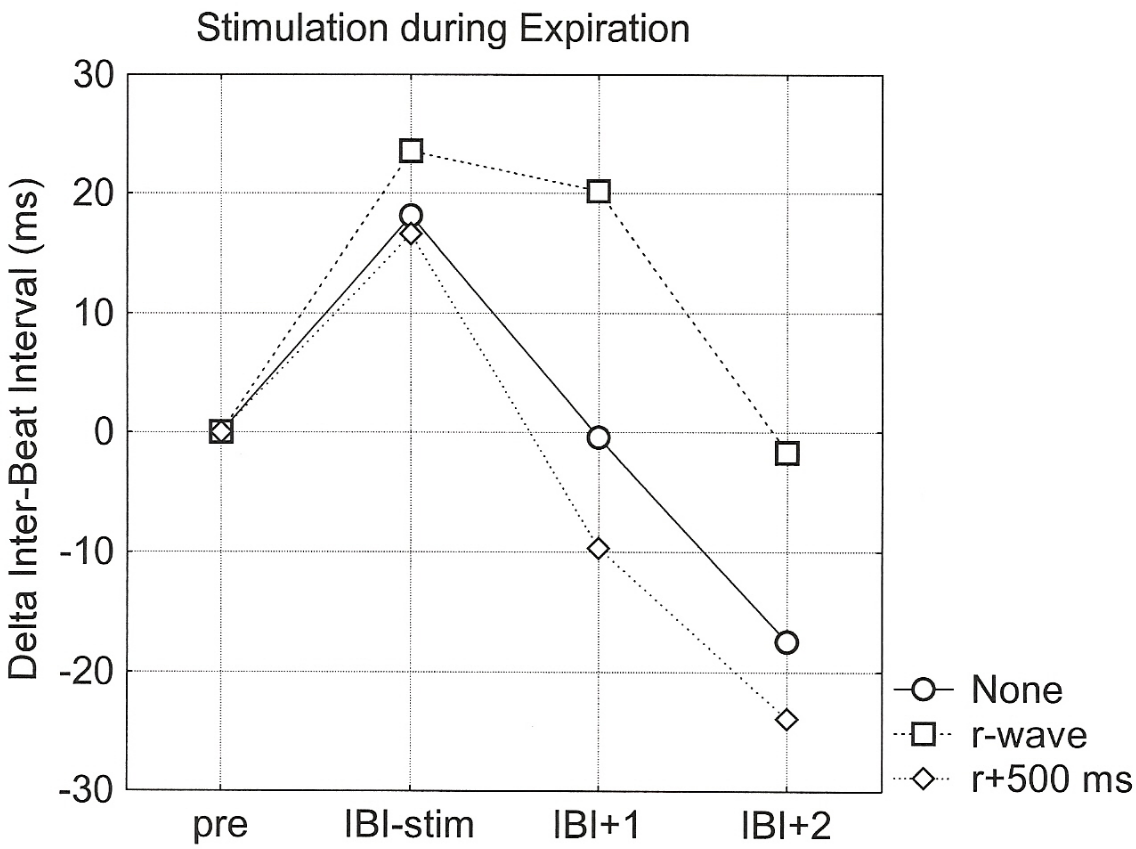

Figure 2. Interbeat Interval Lengthened by Stimulation Applied During Expiration

1.2.2.5 CARDIOVASCULAR PATHWAYS CONNECTING STIMULATION TO AFFECTIVE MEMORY

As presented, VNS and CBS modulate the baroreflex pathway and induce cardiac deceleration, enabling them to potentially influence neuro-cognitive processing and memory. Regarding the baroreflex, the Laceys' suggest that increased afferent baroreceptor activity, such as that provided by VNS and CBS, is associated with increased environmental rejection, an internallyfocused cognitive state, and mental work and elaboration. As such, VNS and CBS may particularly enhance memory if applied when the to-be-remembered stimuli are being rehearsed and consolidated, transferred from short to longer-term memory. Regarding cardiac deceleration, heart rate slowing is associated with sensory and environmental intake and externally-focused cognitive states like attention. Thus, VNS and CBS may be particularly effective if applied when the to-be-remembered stimuli are initially presented and learned. Moreover, since arousing, emotional stimuli may be most memorable because they command more attention than neutral stimuli, this ‘intake’ portion of the intake-rejection hypothesis may be particularly relevant to affective memory. Specifically, cardiac deceleration elicited by stimulation may selectively enhance intake, attention for, and processing of emotive stimuli because such stimuli are already naturally commandeering those neural resources. Overall, VNS and CBS may exert differential influences on memory via the baroreflex pathway and cardiac deceleration.

1.2.2.6 NEURAL PATHWAYS CONNECTING STIMULATION TO AFFECTIVE MEMORY

In addition to their roles in the baroreflex pathway, VNS and CBS may activate memory and emotion-relevant brain structures via their connections with the NTS. Specifically, the dorsal NTS shares indirect connections with the ventral hippocampus (via the basolateral and basomedial amygdala, medial PFC, and hypothalamus) and directly projects to the medial and lateral prefrontal cortex (PFC) and the central nucleus of the amygdala (Figure 3) (Castle, Comoli, & Loewy, 2005; Chiba, 2000; Ishikawa & Nakamura, 2006; Ricardo & Koh, 1978; Rogers & Fryman, 1998; van der Kooy, Koda, McGinty, Gerfen, & Bloom, 1988). The hippocampus regulates emotional responses including anxiety and fear and is also involved in short-term working memory (Bannerman et al., 2004; Seamans, Floresco, & Phillips, 1998; Trivedi & Coover, 2004) while the medial PFC is thought to be involved in the emotional processing component of decision-making and in memory processing (Simpson, Snyder, Gusnard, & Raichle, 2001; Vertes, Hoover, Szigeti-Buck, & Leranth, 2007). The amygdala is implicated in both basic emotion processing and in memory for emotive stimuli (Cahill et al., 1996; Canli, Zhao, Desmond, Glover, & Gabrieli, 1999; Kilpatrick & Cahill, 2003). Moreover, the hippocampus, amygdala, and PFC are inter-connected. These structures, along with the thalamus and hypothalamus (brain regions also affected by VNS and CBS) are all components of the limbic system. The limbic system is a neural circuit associated with emotion and motivation (Figure 3) (Chiba, 2000; Ishikawa & Nakamura, 2006). Since VNS and CBS should increase afferent traffic to the NTS and its projection areas, including these limbic structures, it is plausible that the emotional salience of the experimental tasks will be enhanced rendering all stimuli, regardless of their own intrinsic emotive qualities, more easily remembered. Alternatively, it is possible that emotive stimuli may naturally activate these neural circuits and become dually memorable following stimulation. It is important to note that the cardiovascular and neural pathways linking VNS and CBS to affective memory are speculative and may or may not be mutual exclusive.

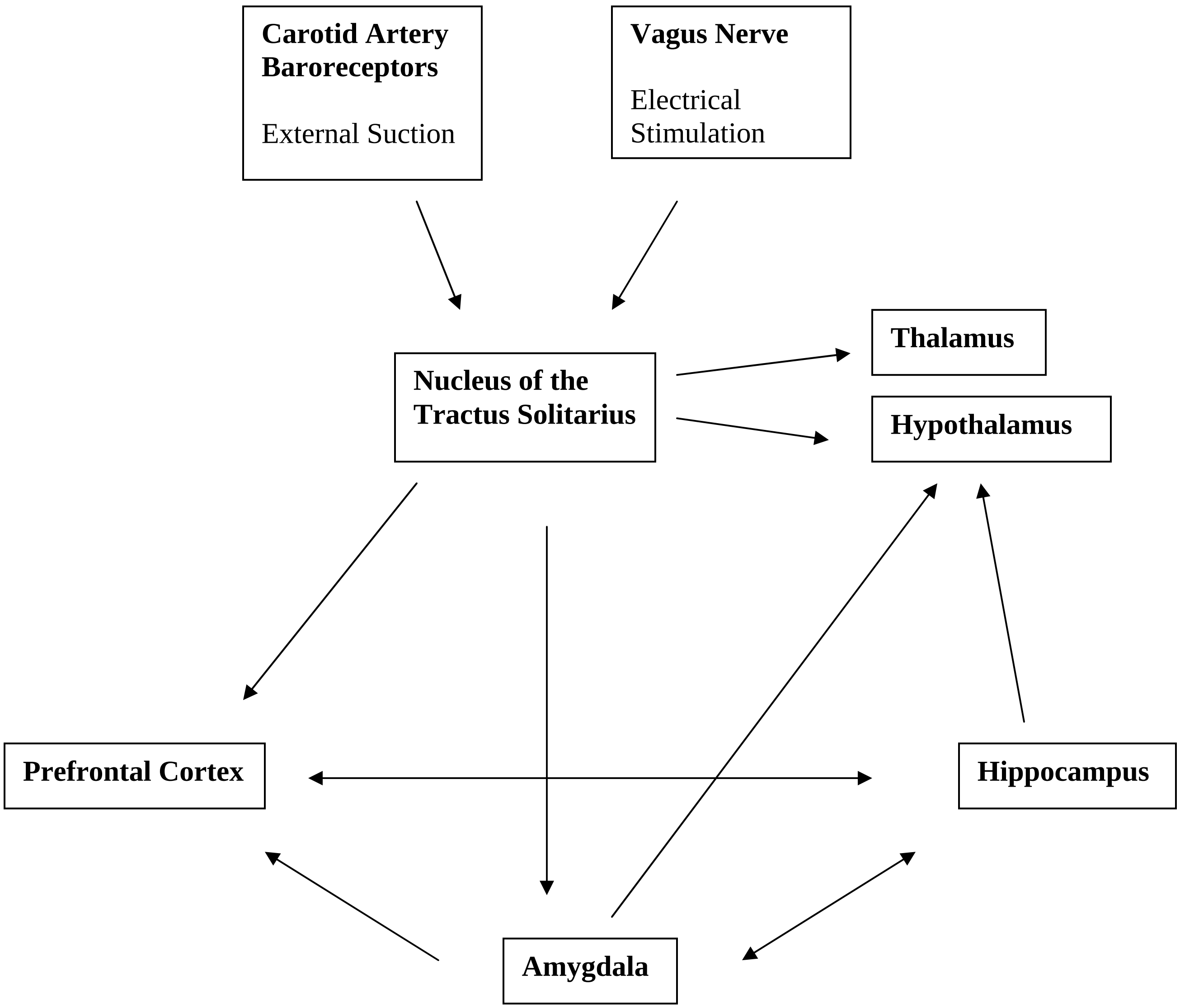

Figure 3. Pathway Affecting Memory Following Carotid Baroreceptor and Vagus Nerve Stimulation

1.3 STATEMENT OF PURPOSE

The current study assessed the effects of CBS on affective memory for verbal stimuli and on heart rate. Thus, our protocol was most similar to that of Critchley and colleagues (2007). Arousing positive and negative words and less arousing neutral words were the to-be-remembered stimuli. Since researchers often combine the valence and arousal dimensions of emotion, as did the Critchley group, our stimuli incorporated both. Participants were exposed to 3 randomized conditions during which they completed computerized memory tasks. In one condition, they completed the tasks without suction, in another suction was administered simultaneously during word presentation (suction at learning condition), and in another suction was delivered after word presentation (suction at retention condition). Suction was delivered this way as the prior VNS studies showed differential memory effects indicating that the timing of stimulation may influence its efficacy. The cycle time of CBS was based on that of prior VNS studies while the degree of suction was based on prior CBS work. Moreover, since previous VNS and memory studies found differential effects of VNS on recognition and recall memory, we assessed both. Finally, our study featured double-blinded random assignment to CBS or a control group. Taken as a whole, our protocol borrows many elements from the VNS and memory literature in order to examine the effect of CBS on affective memory.

1.4 HYPOTHESES

1. Demonstrate that participants who receive CBS performed better on memory tests following suction than controls.

a. Explore whether CBS is differentially effective when applied at learning or for a 6-minute period beginning immediately after word presentation is completed (retention).

b. Explore whether CBS is differentially effective in word-recall or word-recognition conditions.

2. Determine whether a) all participants will remember arousing positive and negative words at a higher level than neutral words in all conditions and b) the CBS group will remember arousing positive and negative words at an increased level over controls in the suction conditions. It is hypothesized that both will be the case.

3. Validate that the external baroreceptor stimulator is capable of indirectly activating the vagus nerve; CBS participants' heart rate should decrease during stimulation.

2.0 METHOD

2.1 STUDY DESIGN

Participants were randomly assigned to the CBS group or to the control group in a double-blinded protocol following their provision of informed consent. The CBS group received –50 mmHg of suction provided by a laboratory-built device to the baroreceptors in the carotid arteries of the neck. The control group received the same treatment, but to the backs of their necks. Following 5-minute baseline assessments of heart rate, participants in both groups were randomly exposed to three conditions: a non-suction condition during which arousing, positively and negatively valenced words and neutral words were presented in a computerized format, a condition in which suction was applied during word presentation (suction at learning condition), and a condition in which suction was applied after presentation of the word set (suction at retention condition). Cardiac monitoring occurred throughout. After each condition, participants completed a computerized recognition test and a paper and pencil recall test. They filled out a questionnaire at the end of the session and were debriefed. See Figures 4 and 5 for flow charts. Experimental sessions took place between 12-6 pm. Experimental procedures were approved by the University of Pittsburgh Institutional Review Board.

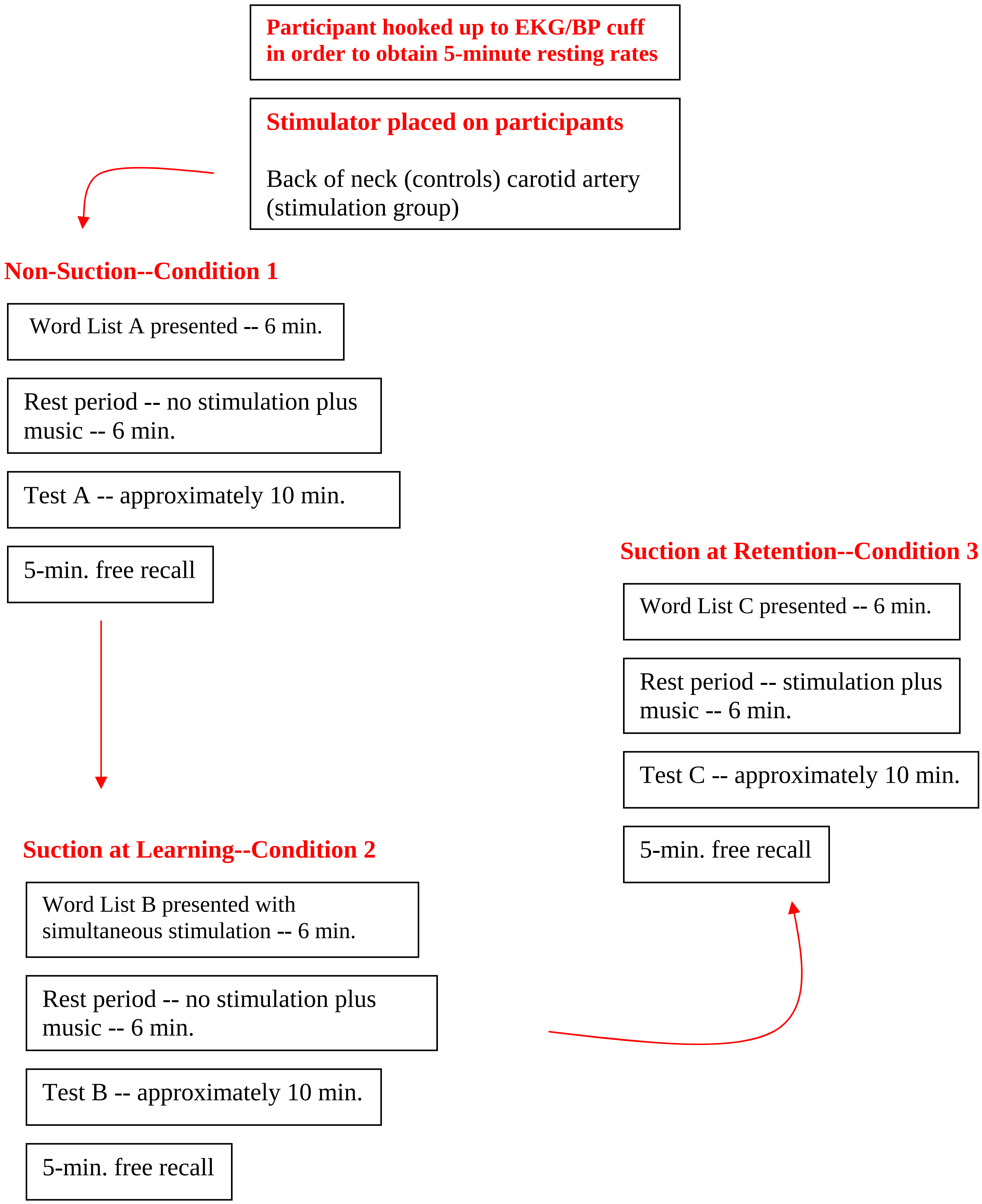

Figure 4. Experimental Flowchart (Suction Conditions Were Randomized)

Experimental Protocol

There are 2 groups, those who will receive authentic baroreceptor stimulation and those who will receive stimulation on the backs of their necks. Both groups are exposed to the 3 conditions.

Participant hooked up to EKG/BP cuff in order to obtain 5-minute resting rates. EKG/BP cuff remain on participant for rest of session.

Condition 1 Stimulator placed on back of neck or carotids for duration of the experiment.

1. Word List A presented (90 words, 1 second on/3 seconds between, 6 minutes total, fully randomized for each participant).
2. Immediately followed by 6 minutes of no stimulation rest period. Music will play during this time.
3. Test A presented. (Computerized, 180 words, show a word w/ "was this a word you saw in the most recent list? Yes or no?". Once they respond, the screen changes to "how confident are you in your response on a scale of 0-5, 0 meaning 'not confident' to 5 meaning 'very confident'". Screen changes when they respond. For each word, a countdown is included that shows which word they are on out of the total (eg. 45/180). Word order is fully randomized for each participant).
4. 5-minute free recall test.

Condition 2

1. Word List B presented (90 words, 1 second on/3 seconds between, 6 minutes total, fully randomized for each participant). Stimulation will be provided simultaneously with word presentation in a 30 seconds on/30 seconds off cycle.
2. Immediately followed by a 6 minute rest period with music playing.
3. Test B presented. (Computerized, 180 words, show a word w/ "was this a word you saw in the most recent list? Yes or no?". Once they respond, the screen changes to "how confident are you in your response on a scale of 0-5, 0 meaning 'not confident' to 5 meaning 'very confident'". Screen changes when they respond. For each word, a countdown is included that shows which word they are on out of the total (eg. 45/180). Word order is fully randomized for each participant).
4. 5-minute free recall test.

Condition 3

1. Word List C presented (90 words, 1 second on/3 seconds between, 6 minutes total, fully randomized for each participant).
2. Immediately followed by stimulation in a 30 seconds on/30 seconds off cycle lasting 6 minutes total accompanied by music.
3. Test C presented. (Computerized, 180 words, show a word w/ "was this a word you saw in the most recent list? Yes or no?". Once they respond, the screen changes to "how confident are you in your response on a scale of 0-5, 0 meaning 'not confident' to 5 meaning 'very confident'". Screen changes when they respond. For each word, a countdown is included that shows which word they are on out of the total (eg. 45/180). Word order is fully randomized for each participant).
4. 5-minute free recall test.

To counterbalance, the word lists and their respective tests' order will be randomized across participants. For example, participant 1 may get List A/Test A in condition 1, List C/Test C in condition 2, and List B/Test B in condition 3 while participant 2 may get List C/Test C in condition 1, List A/Test A in condition 2, and List B/Test B in condition 3. Suction conditions will also be randomized across participants.

Figure 5.

2.2 PARTICIPANTS

Participants were college students recruited from the University of Pittsburgh subject pool. Inclusion criteria stipulated that all participants spoke English as their first language and were between the ages of 18-30, to preserve homogeneity of the sample. They also could not take medications for depression, anxiety disorders, epilepsy, or heart conditions, and they must not have a personal or biological family history of heart disease (such as heart attacks, strokes, blood clots, or other problems with the heart or blood vessels) detected before 45 years of age. Pregnant females were excluded. All participants abstained from drinking alcohol and drug use for 24 hours prior to their participation and from nicotine and caffeine consumption for 4 hours prior.

2.3 MATERIALS

2.3.1 WORDS

Words presented to participants were selected from the Affective Norms for English Words (ANEW) database (Bradley & Lang, 1999). They are rated along the valence dimension on a scale ranging from 1, very unpleasant, to 9, very pleasant and along the arousal dimension from 0, not arousing, to 9, very arousing; word frequency is also reported. Words rated as neutral along the valence dimension have lower arousal ratings than positive or negative words. As previous studies using the ANEW have done, words with a valence rating >7, such as aroused and delight, were selected as positive words and words with a valence rating <3, such as suicide and ugly, were chosen as negative words (Critchley et al., 2007; Kensinger & Schacter, 2006; Lewis et al., 2005). Neutrally valenced words with ratings ranging from 7 to 3, such as trumpet and salute, were also included. All words were matched for frequency. Since researchers using the ANEW have used between 88 and 180 words per trial, the current study presented participants with 90 words (30 of each valence) per stimulation condition.

2.3.2 WORD PRESENTATION PROCEDURE

All words were presented for 1 second with a 3 second inter-stimulus interval. Participants were presented three lists containing 90 words, one during the non-suction condition, another during the suction at learning condition, and another just prior to the suction at retention condition. Although there were three basic lists, the list and word order was randomized for each participant. Word presentation in each condition was followed by a 6-minute period, music was played during this time in the non-suction and suction at learning conditions while stimulation plus music occurred in the suction at retention condition. This break before the recognition and recall tests was based, in part, on the procedures utilized by other VNS and memory researchers who waited, on average, less than 20 minutes between word presentation, stimulation, and recognition and recall testing (Clark et al., 1999; Critchley et al., 2007; Ghacibeh et al., 2006). See Figures 5 and 6 for flowchart.

2.3.3 MEMORY TESTS

For the recognition memory test, participants were presented with a computerized list of 180 words, 90 of which were the previously presented words and 90 of were the foils of comparable valence, arousal, and frequency to the studied stimuli. The order of word presentation was randomized for each participant. Following each recognition test, participants were asked to freely recall all originally presented words that they could within a 5-minute time period. Recall data was somewhat confounded by the prior recognition testing, however the recognition tests were intended to be the primary measures. The recognition tests were scored to assess the proportion of correct responses and using the hits (correct responses on recognition tests) versus false alarms (instances where participants responded that a word was a target when it was actually a foil) signal detection method described by Grier (1971). This adjusts for biases in answer selection. Grier's method produces 2 measures, A' (a measure of sensitivity during recognition; how hard or easy it is to detect the target words from the foils) and B' (a measure of response bias during recognition; an index of one's willingness to reply that they believe a word presented during the recognition tests is a target word). A' scores range from 1 to 0 with higher scores indicating increased sensitivity. B' scores range from 1 to –1 with lower scores indicating decreased bias. Recall tests were scored to analyze the proportion of correct responses and number of errors.

2.3.4 DEBRIEFING QUESTIONNAIRE

Participants filled out a survey upon completion of the experiment. They were asked whether or not they believed they received true CBS, if they were distracted by the neck suction, and if it affected their performance. They were also asked whether or not they experienced changes in their mood, level of awareness/consciousness, experienced changes in mental imagery, and whether they used any particular strategies during the different conditions see Appendix B for copy of questionnaire. Following the survey, participants were orally debriefed by the experimenter and received a written summary of the experiment.

2.3.5 BARORECEPTOR STIMULATOR

Following piloting procedures described in Appendix A, CBS participants received –50 mmHg suction (30 seconds on, 30 seconds off cycle) to the carotid barorecetors located in the carotid sinus via a laboratory-built device. The carotid sinus was identified by manual palpation of the carotid horns (boney protrusions within the carotid triangle of the neck) (Eckberg, 1977a). The area was marked to ensure proper placement of the suction device. Similarly, the lateral portions of the back of the neck were marked prior to placement of the device on controls.

2.3.6 CARDIAC MEASURES

Electrocardiogam (ECG) measurements were collected during baseline and all word presentation and break periods. A modified lead II electrode placement using 3 silver-silver chloride electrodes (Conmed; Andover Medical, Haverhill, MA) was used. The ECG signal was digitized (12 bit), sampled (at 1000Hz), and stored for offline processing using Mindware acquisition software (Mindware, version 2.16; Mindware Technologies Ltd., Columbus, OH). R wave markers in the ECG signal were assessed for artifacts by visual inspection and by an automatic artifact detection algorithm available in a customized software package (Mindware Heart Rate Scoring Module, version 2.16; Mindware Technologies Ltd., Columbus, OH). The time between beats (interbeat interval; IBI) was used calculated using the r-wave of the electrocardiogram and measured to the nearest millisecond.

2.4 STATISTICAL PLAN

The general design was a mixed model repeated measures ANOVA with one between and two within-groups variables. The between-groups independent variable was assignment to the control group or to the CBS group. The first within-group variable was word valence (3 levels: positive, negative, and neutral). The second within-group variable was the type of suction given (3 levels: no-suction, suction at learning, and suction at retention). During each condition, the dependent variables heart rate and recognition and recall test performance were recorded. Specific dependent variables used to assess memory for the recognition tests were: the proportion of correct responses to the recognition test, A', and B'. Specific dependent variables used to assess memory for the recall tests were: the proportion of correct responses to the recall test and number of errors made during recall (the number of words written that were not among the target words). From this point forward, whenever recognition and recall analyses are mentioned, all of the above dependent variables are being referenced, unless otherwise specified. Also, select hypotheses required us to include additional dependent variables. We analyzed the proportions of hits (correct responses on the recognition tests) and misses (incorrect responses reflecting when participants failed to identify a target word as such on recognition tests) for the words that were presented during the discrete 30-second suction pulses (suction "on" words) as versus hits and misses for the words that were presented during the 30-second non-suction periods (suction "off" words) in the suction at learning condition.

All analyses including heart rate were initially run incorporating data from the baseline, non-suction, suction at learning, and suction at retention conditions in the same model and all analyses including memory performance were initially run incorporating data from all conditions but baseline. However, the results reported here are based on analyses that only included particular conditions of interest (e.g. baseline versus suction at learning) in separate models. This was done for two reasons. First, including so many conditions in which suction was not provided (baseline, non-suction condition) in analyses with conditions in which suction was administered could mask the effects of suction, particularly since suction was expected to produce small to moderate effects. Secondly, as described more fully in the Participants section of the Results, certain participants had missing data for particular conditions. Analyses that included all of the conditions removed all of these participants whereas analyses of specific conditions of interest only removed those participants who were missing data for those particular conditions, effectively increasing our sample size and power.

Finally, all memory analyses were run two ways 1) with the full sample (except those with partial, missing data, where appropriate) 2) with only those participants from the CBS group who showed heart rate deceleration for the suction at learning and retention conditions and all controls (excluding those with partial, missing, data where appropriate). Information regarding individuals with missing data can be found in the Participants section of the Results and information regarding CBS participants' cardiac response to suction can be found in the Manipulation Check section of the Results. In cases where the results of these analyses were comparable, only those for the whole sample were reported (since the sample size and power were greater); when there were discrepancies between results, both were reported.

2.4.1 HYPOTHESIS 1

We first tested the hypothesis that CBS participants performed better on memory tests following suction than controls. Specific conditions compared included the non-suction and the suction at learning conditions, the non-suction and the suction at retention conditions, and the suction at learning and the suction at retention conditions. The group (CBS group or control group) by suction condition (non-suction, suction at learning, suction at retention) interaction for participants' overall (total scores not broken down by valence) recognition test scores and recall test scores was the effect of interest. Contrasts were used to analyze whether CBS was differentially effective when applied at learning or retention. We also analyzed whether, in the suction at learning condition, memory was particularly enhanced for the words that were presented during the discrete 30-second suction pulses (suction "on" words) as versus memory for the words that were presented during the 30-second non-suction periods (suction “off” words). Accordingly, the group by suction phase (on, off) by suction condition interactions for the numbers of hits and misses were analyzed in models comparing participants’ memory performance between the following conditions: suction at learning condition alone (suction “on” and “off” words), suction at learning condition (suction “on” and “off” words) versus non-suction, suction at learning condition (suction “on” and “off” words) versus suction at retention condition.

2.4.2 HYPOTHESIS 2

The second hypothesis was that A) participants remembered arousing positive and negative words at a higher rate than neutral words in both the control and CBS groups and that B) CBS participants remembered arousing positive and negative words at an increased level over controls during the suction conditions. Specific conditions compared included the non-suction and the suction at learning conditions, the non-suction and the suction at retention conditions, and the suction at learning and the suction at retention conditions. Part A was tested by the main effect of valence and part B was tested by examining the 3-way group by suction condition by word valence interaction for recognition and recall test performance. Pre-planned comparisons were run to compare the rates of memory based on word valence for the sample overall and between the two groups. Regarding part B, we also analyzed whether, in the suction at learning condition, memory was particularly enhanced for the words that were presented during the discrete 30-second suction pulses as versus memory for the words that were presented during the 30-second non-suction periods; this was done using the same analyses as described in Hypothesis 1 section of the Statistical Plan.

2.4.3 HYPOTHESIS 3

Finally, to test the third hypothesis that the baroreceptor stimulator was capable of indirectly activating the vagus nerve, the group by suction condition interaction for the mean IBI was examined in analyses comparing baseline and suction at learning condition values and baseline and suction at retention condition values. Analyses also compared IBI values from the word presentation period of the non-suction condition to values from the suction at learning condition and values from the break period of the non-suction condition were compared to their values from the suction at retention condition. Moreover, we conducted analyses to look at the IBI during the total time suction was “on” versus the IBI during the total time suction was “off” in the suction at learning and suction at retention conditions, respectively. These analyses compared the mean IBI from baseline to that of the suction at learning condition, the mean IBI from baseline to that of the stimulation at retention condition, the mean IBI from the word presentation period of the non-suction condition to that of the suction at learning condition, and the mean IBI from the break period of the non-suction condition to that of the suction at retention condition. The effect of interest was the 3-way group by suction phase (on, off) by suction condition interaction. In all models, pre-planned comparisons were used to show that the IBI increased in the active suction conditions versus the baseline and non-suction conditions in the CBS group and that people in the CBS had higher IBIs than controls during the learning and retention suction conditions.

Statistical procedures followed those developed by Keppel and Wickens (2004).

2.4.4 COVARIATES

All analyses included gender as a covariate since physiological responses are known to often vary between genders (Abdel-Rahman, Merrill, & Wooles, 1994; Shoemaker, Hogeman, Khan, Kimmerly, & Sinoway, 2001); analyses without gender were conducted and similar results were obtained. Gender was included to remove gender-specific variance from the error term, but, as only 5 males were randomly assigned to the CBS group, the sample size did not permit the interpretation of interactions with gender. We attempted to include ethnicity as a covariate (we grouped the 2 biracial participants with African Americans, the participant who identified as “other” with Asians (based on information that she was Indian), and the individual who identified as Hispanic with Caucasians) (see Table 1). However, in many instances, this resulted in incomplete designs. Thus, ethnicity was not included as a covariate in the final analyses.

Table 1 Participant Demographics

Characteristic	Mean	SE	Mean	SE
	Experimental Group		Control Group	
Age (years)	18.31	0.09	18.55	0.18
Years of college finished	1.16	0.07	1.34	0.11
Basal Interbeat Interval	859.37	21.89	849.48	22.99
Basal Systolic BP	122.70	1.65	122.09	1.74
Basal Diastolic BP	70.88	1.22	68.40	1.29
Characteristic	**Count**		**Count**	
	Experimental Group		Control Group	
Gender				
Male	5		13	
Female	27		16	
Ethnicity				
Caucasian	24		21	
African American	3		3	
Asian	3		3	
Biracial	1		1	
Hispanic	0		1	
Other	1		0	

Note. Standard error abbreviated ‘SE’, blood pressure abbreviated ‘BP’.

3.0 Results

The distributions and descriptive statistics for all variables were examined for outliers and normalcy prior to analyses. The only variable requiring transformation due to the presence of outliers was the number of errors made during recall for each condition. This variable was transformed using the square root function. All analyses incorporating this variable used the transformation.

3.1 PARTICIPANTS

Sixty-one participants were recruited. Their demographic characteristics are listed in Table 1. Thirty-two participants were in the CBS group and 29 in the control group. One female participant from each group had incomplete data for the suction at learning condition while 2 female participants from the CBS group and 1 female from the control group had incomplete data for the suction at retention condition. Incomplete data resulted from suction device malfunctions during the conditions listed. Thus, 29 CBS (5 males, 24 females) and 27 (13 males, 14 females) control participants had complete data. Individuals with partial data were included in all analyses for which they had full data.

3.2 MANIPULATION CHECKS

Of the 31 CBS participants with full data for the suction at learning condition, 20 showed heart rate deceleration upon suction (defined as a decrease in IBI from non-suction condition levels);

of the 30 people in the CBS group who had full data for the suction at retention condition, 24 showed heart rate deceleration upon suction (defined as a decrease in IBI from non-suction condition levels). There was not a significant difference between the number of participants who showed cardiac deceleration in the suction at learning and retention conditions (p=.20 Test of Difference Between Proportions, Statistica).

Participants were asked whether they believed that they received true CBS or a sham treatment. Among the CBS group, 23 individuals reported that they received CBS while 9 contended they received sham stimulation. Among controls, 19 reported that they received CBS while 10 contended they received sham stimulation. Between group differences were not significant (p=.48 Test of Difference Between Proportions, Statistica). All who thought that they received sham stimulation reported that they did not think that the level of stimulation applied was strong enough to affect their physiology or noted that, since they did not feel their heart rate slowing, they thought they received sham stimulation. Also, there were no significant differences between groups for participants' responses to any of the questions on the Debriefing Questionnaire (see Appendix B) (p values ranged from .38 to .85 Test of Difference Between Proportions, Statistica).

3.3 HYPOTHESIS 1

We tested the hypothesis that CBS participants performed better on memory tests following suction, as indicated by their total scores across all valences, than controls. Analyses were conducted as planned and none provided significant group by suction condition interactions. The highest F value obtained was 2.16 and no analysis approached statistical significance.

3.4 HYPOTHESIS 2

The second hypothesis was that A) participants remembered arousing positive and negative words at a higher rate than neutral words in both the control and CBS groups and that B) CBS participants remembered arousing positive and negative words at an increased level over controls during the suction conditions. Regarding part A, the hypothesis was partially supported; across all comparisons of conditions, the proportion of correct responses to the recall tests was better for arousing, emotional words as versus neutral. Specifically, the ‘word valence’ main effect was significant in separate models comparing non-suction and suction at learning conditions ($F(1, 55)=4.51$, $p<.05$), non-suction and suction at retention conditions ($F(1, 54)=6.35$, $p<.01$), and suction at learning and the suction at retention conditions ($F(1, 52)=11.69$, $p<.01$) for the dependent variable proportion of correct responses to the recall test. Pre-planned comparisons showed that participants’ memory for positive words was better than their memory for negative and neutral words. In turn, memory was also better for negative as versus neutral words (see Table 2 for significant comparisons).

Table 2 Means that Correspond to the Main Effect of Word Valence for the Proportion of Correct Responses to the Recall Tests and B’

Conditions in Model	Mean Proportion Correct Recall (SE)		
	Positive	Negative	Neutral
Non-suction and Suction at Learning	0.24 (0.02)	0.21 (0.01)	0.20 (0.02)
Non-suction and Suction at Retention	0.23 (0.02)	0.21 (0.02)	0.19 (0.01)
Suction at Learning and at Retention	0.25 (0.02)	0.22 (0.02)	0.18 (0.01)
Conditions in Model	**Mean B’ (SE)**		
	Positive	Negative	Neutral
Non-suction and Suction at Learning	0.0004 (0.05)	-0.03 (0.06)	0.16 (0.06)
Non-suction and Suction at Retention	-0.02 (0.05)	-0.06 (0.07)	0.10 (0.07)
Suction at Learning and at Retention	-0.02 (0.05)	-0.04 (0.06)	0.14 (0.05)

Note. Standard error abbreviated ‘SE’. For the proportion of correct responses to the recall tests, in the first set of conditions, comparisons between Positive and Negative and Positive and Neutral are significant ($p<.05$ and $p<.01$, respectively). In the second set of conditions, the comparison between Positive and Neutral is significant ($p<.01$). In the third set of conditions, comparisons between Positive and Negative and Negative and Neutral are significant ($p<.05$) and the comparison between Positive and Neutral is significant ($p<.01$). For B’, comparisons between Positive and Neutral and Negative and Neutral were significant ($p<.01$) for each model.

Across all comparisons of conditions, it appeared that B', or response bias, was greatest for neutral words. Specifically, the main effect 'word valence' was significant in separate models comparing non-suction and suction at learning conditions ($F(1, 54)=14.88$, $p<.01$), non-suction and suction at retention conditions ($F(1, 55)=11.03$, $p<.01$), and the suction at learning and the suction at retention conditions ($F(1, 52)=12.28$, $p<.01$) for the dependent variable B' (response bias). Pre-planned comparisons showed that participants' B' was about the same for positive and negative words, but that each was significantly less than for neutral words (see Table 2 for significant comparisons). Though the main effect 'word valence' was not significant in models incorporating the proportion of correct responses to the recognition tests and A' as dependent variables, means from these analyses are listed in Table 3. They do not reveal a trend toward arousing, emotional words being associated with better memory.

Table 3 Means that Correspond to the Main Effect of Word Valence for the Proportion of Correct Responses to the Recognition Tests and A’

Conditions in Model	Mean Proportion Correct Recognition (SE)		
	Positive	Negative	Neutral
Non-suction and Suction at Learning	0.76 (0.01)	0.76 (0.01)	0.77 (0.0)
Non-suction and Suction at Retention	0.75 (0.01)	0.76 (0.01)	0.77 (0.01)
Suction at Learning and at Retention	0.76 (0.01)	0.77 (0.01)	0.76 (0.01)
Conditions in Model	**Mean A’ (SE)**		
	Positive	Negative	Neutral
Non-suction and Suction at Learning	0.83 (0.01)	0.84 (0.01)	0.84 (0.01)
Non-suction and Suction at Retention	0.84 (0.01)	0.84 (0.01)	0.84 (0.01)
Suction at Learning and at Retention	0.83 (0.01)	0.85 (0.01)	0.84 (0.01)

Note. Standard error abbreviated ‘SE’. None of the comparisons described above resulted in a significant F test.

Regarding part B, our hypothesis was partially supported. Analyses were conducted as planned and revealed significant and trend-level interactions at both the within and between subjects levels. More specifically, in analyses comparing the non-suction and suction at retention conditions, the 3-way group by suction condition by word valence interaction was significant with the dependent variables proportion of correct responses to the recognition test ($F(1, 54)=4.81$, $p<.01$) and A' ($F(1, 54)=3.33$, $p<.05$). Regarding within- subjects effects for both models, it appears that CBS was associated with improved memory for negative words, slightly decreased memory for positive words, and minimal effects on neutral words. Comparisons between these within-subject means were not significant. Thus, these within-CBS-group trends partially supported our hypothesis.

Regarding between-subjects effects when the proportion of correct recognition responses and A' were the dependent variables, the CBS group appeared to have better memory than controls for positive and neutral words in the non-suction condition and for negative and neutral words in the suction at retention condition. Pre-planned comparisons showed that the CBS group's scores were significantly greater than controls' for positive words in the non-suction condition (for proportion correct: CBS group mean score=0.79, control group mean score=0.73, $F(1, 54)=4.86$, $p<.05$. For A': CBS group mean score=0.86, control group mean score=0.81, $F(1, 54)=3.61$, $p=.06$) and for neutral words in the suction at retention condition (for proportion correct: CBS group mean score=0.79, control group mean score=0.73, $F(1, 54)=4.03$, $p<.05$. For A': CBS group mean score=0.86, control group mean score=0.81, $F(1, 54)=3.91$, $p=.053$) (see Figures 6 and 7). However, this same interaction term was not significant, though it was trend-level, in a duplicate analysis using A' as the dependent variable that included only those participants from the CBS group who showed heart rate deceleration for the suction at learning and retention conditions and all controls (F(1, 48)=3.04, p=.052); the pattern of the means remained similar. These between-groups effects were unexpected. The former may represent a pre-existing group difference while the latter appears to be driven by decreased memory for neutral words within the control group. These effects do not appear to be associated with CBS.

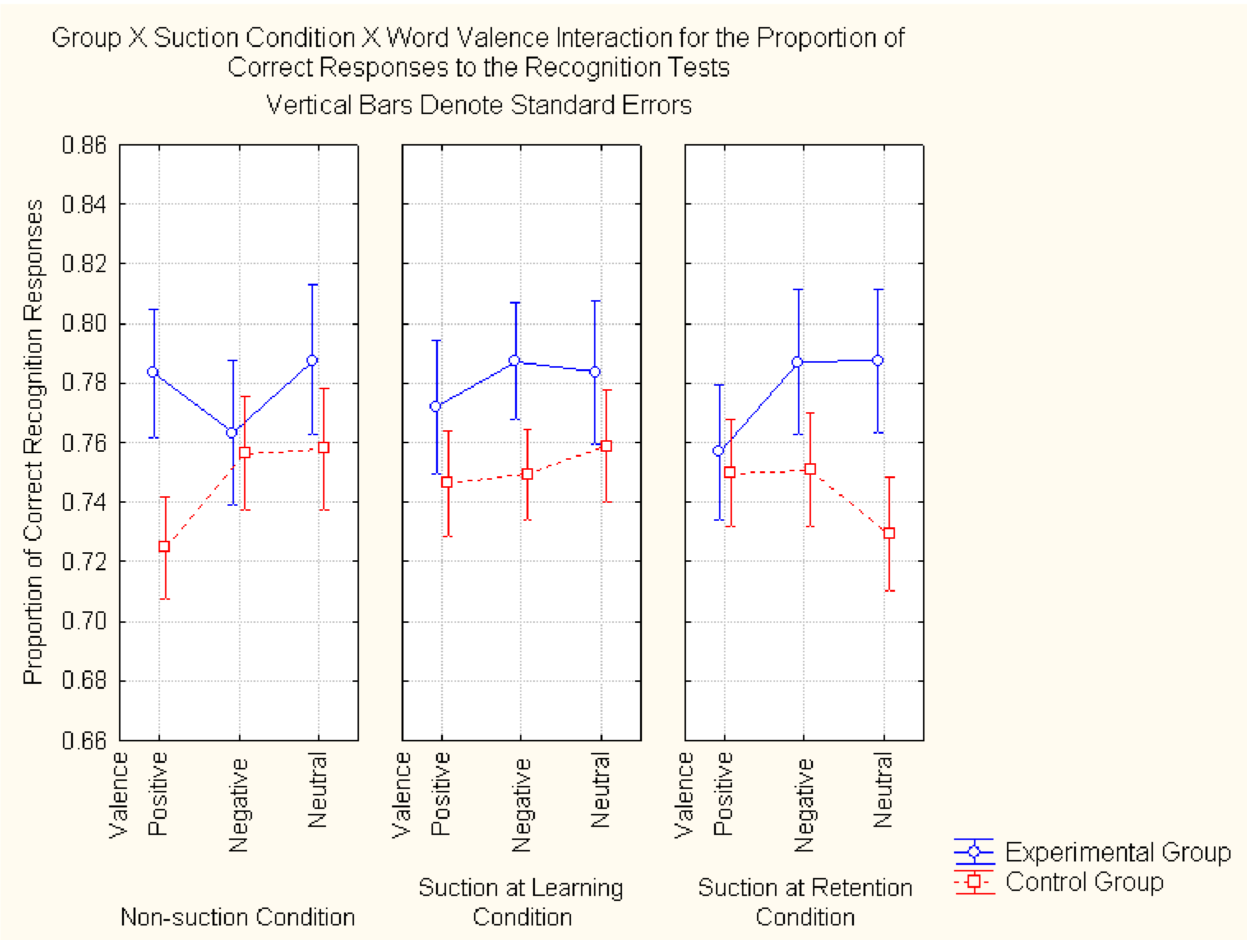

Figure 6.

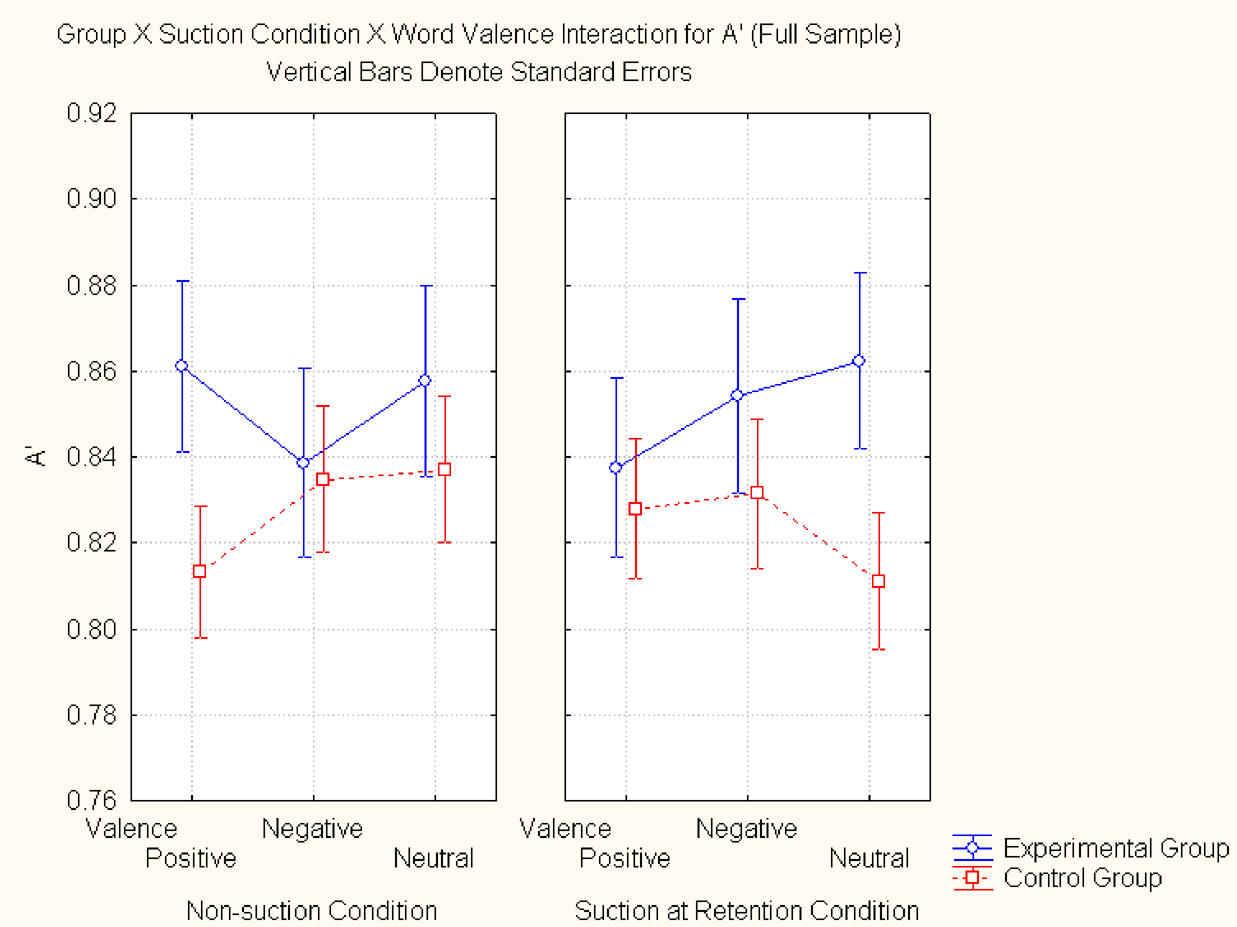

Figure 7.

Since higher A' scores indicate increased sensitivity to detecting the target words and since the pattern of means was similar for both A' and the proportion of correct responses to the recognition tests, it is possible that CBS was associated with improved memory for negative words within the CBS group because it increased participants' sensitivity to them. It is important to note that B', response bias, cannot explain this effect as it did not show a significant 3-way group by suction condition by word valence interaction and since the pattern of means associated with that interaction term did not reveal systematic changes in bias (see Figure 8).

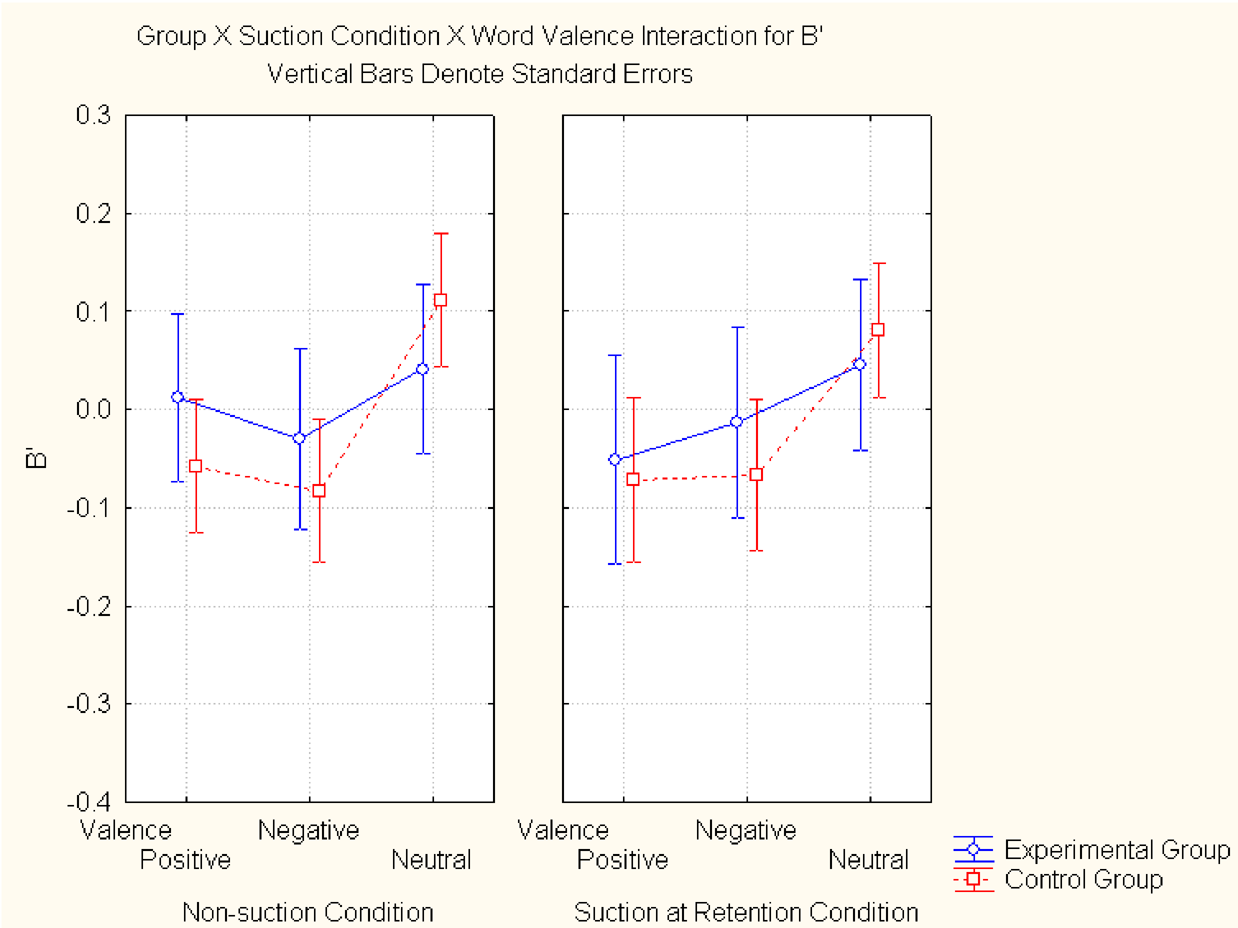

Figure 8.

Analyses incorporating all 3 conditions in the same model supported the above findings. The group by suction condition by word valence interaction for the proportion of correct recognition responses was significant ($F(1, 52)=2.95$, $p<.05$; see Figure 6) while the same term was trend-level significant for A' ($F(1, 52)=2.26$, $p=.064$). Both models shared similar patterns of means and no pre-planned comparisons were significant. Though we stated that we would not report analyses including data from all 3 conditions in the same model (see the Statistical Plan section of the Methods section), we report these analyses as they were the only models incorporating all 3 conditions and covarying for gender that approached significance.

3.5 HYPOTHESIS 3

The third hypothesis was that the baroreceptor stimulator was capable of indirectly activating the vagus nerve. Our results partially supported this hypothesis. When comparing the non-suction to either the suction at learning or the suction at retention conditions, CBS participants had a significantly greater mean IBIs while suction was delivered in the suction at learning and suction at retention conditions in relation to their mean IBIs from comparable time periods in the non-suction condition. Moreover, the CBS group's mean IBIs while suction was applied in the suction at learning and suction at retention conditions were significantly greater than they were while suction was not applied in those conditions. While these results support our hypothesis, similar effects were seen in controls when comparing the non-suction and suction at retention conditions. Also, the CBS group seemed to have higher mean IBIs regardless of condition or phase of suction.

More specifically, results showed that the 3-way group by suction phase (on, off) by suction condition interaction was significant in an analysis comparing the mean IBI between the non-suction and suction at learning conditions ($F(1, 55)=4.08$, $p<.05$; see Figure 9). The pattern of means showed that the CBS group had higher mean IBIs than controls in both conditions regardless of whether suction was on or off. Pre-planned comparisons showed that the CBS group's mean IBI while suction was on in the suction at learning condition was significantly higher than their mean IBI during a comparable time period from the non-suction condition ($F(1, 55)=4.19$, $p<.05$) and that the CBS group's mean IBI while suction was on was higher than it was while suction was off (F(1, 55)=2.48, p=.12) in the suction at learning condition. While pre-planned comparisons were conducted to analyze all between-group differences, none produced significant, or trend level, effects. This suggests that, though ‘group’ was in the significant interaction term, between-group differences were weak.

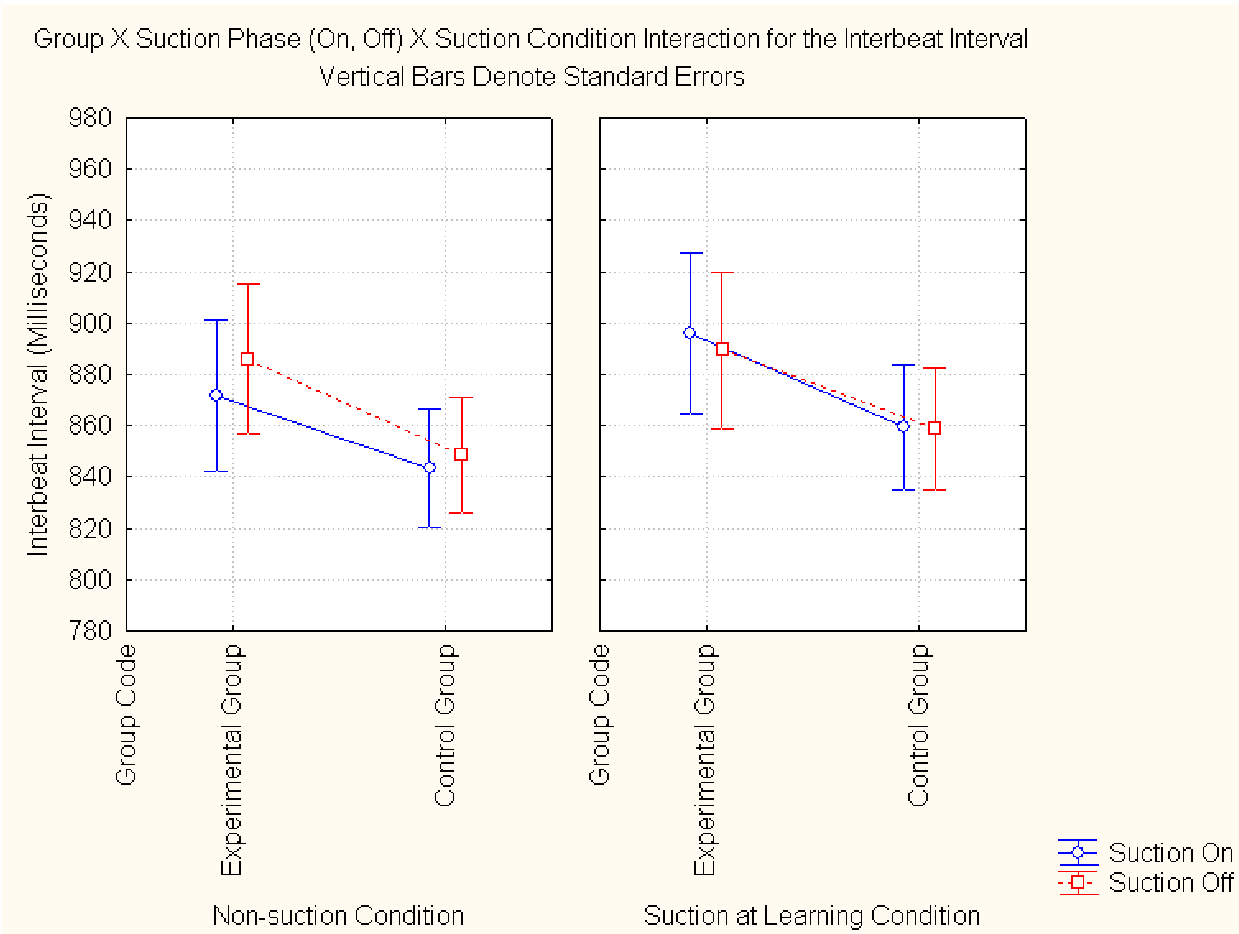

Figure 9.

Results for the 3-way group by suction phase (on, off) by suction condition interaction for the model comparing the mean IBI between the non-suction and suction at retention conditions (F(1, 54)=6.78, p<.05; see Figure 10) were similar to those listed above. The pattern of means demonstrated that the CBS group had higher mean IBIs than controls in both conditions regardless of whether suction was on or off. Among the CBS group, pre-planned comparisons showed that their mean IBI while suction was on in the suction at retention condition was higher than their mean IBI during a comparable time period from the non-suction condition ($F(1, 54)=10.62$, $p<.01$) and that their mean IBI was significantly higher while suction was on than when it was off in the suction at retention condition ($F(1,54)=14.36$, $p<.01$). However, among the control group, pre-planned comparisons also showed that their IBI while suction was on in the suction at retention condition was significantly higher than their mean IBI during a comparable time period from the non-suction condition ($F(1, 54)=4.98$, $p<.05$) and that their IBI was significantly higher while suction was on than when it was off in the suction at retention condition ($F(1, 54)=4.74$, $p<.05$) Again, although pre-planned comparisons were conducted to analyze all between-group differences, none produced significant, or trend level, effects, suggesting that between-group differences were weak.

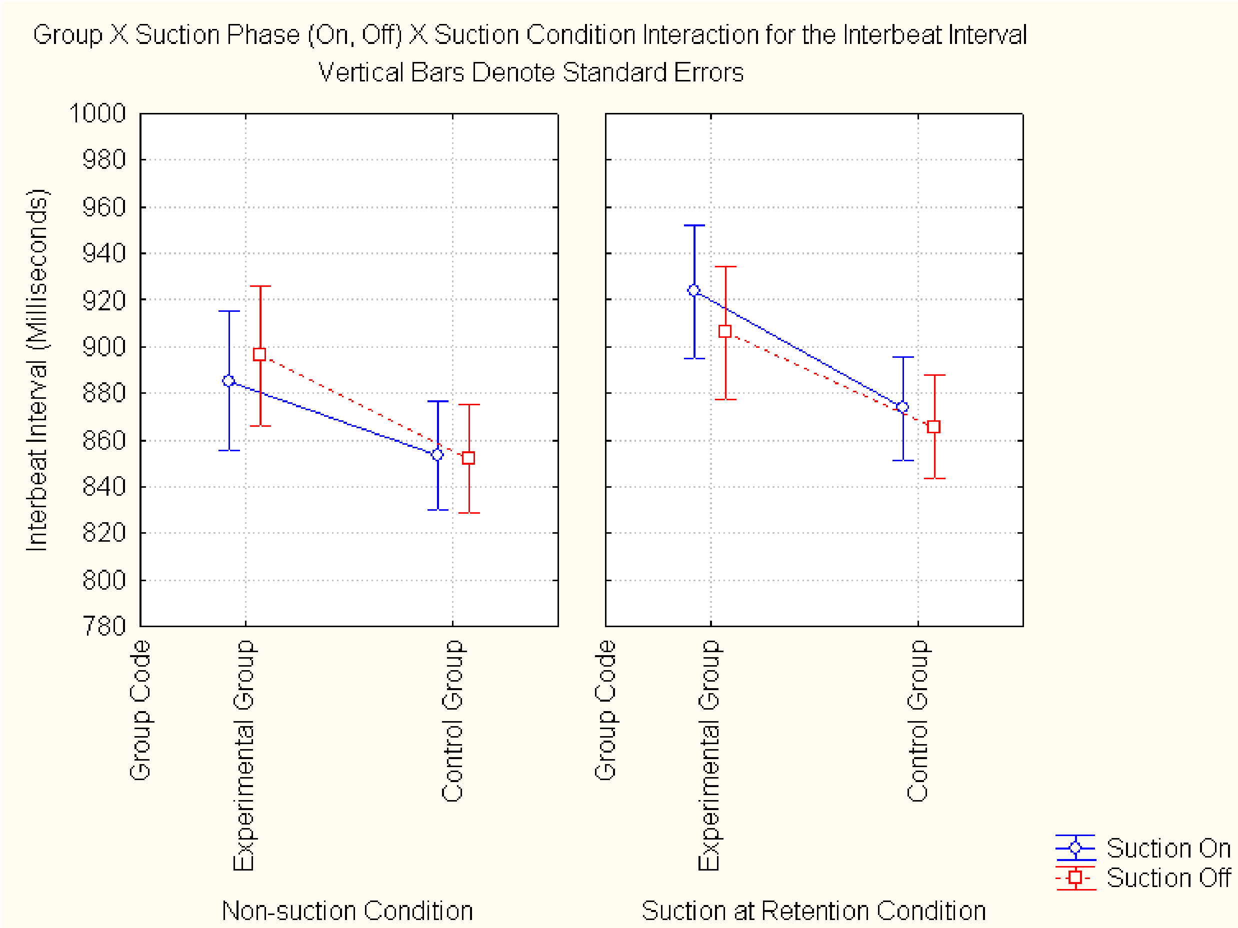

Figure 10.

Finally, via graphing and visual inspection of IBI values we found that the cardiac response to suction did not have a clear phasic pattern for any participant. Thus, it is likely that our existing analyses adequately captured any temporal effects of suction.

3.6 EXPLORATORY ANALYSES

Exploratory analyses of blood pressure and participants' confidence in their recognition test responses were also collected and analyzed. Our findings can be found in Appendices C and D.

4.0 DISCUSSION

Overall, we found that, while CBS did not influence memory as measured by participants' total scores on the recognition and recall tests, it marginally enhanced memory for negative words, partially supporting our hypotheses. Moreover, it produced the expected cardiac deceleration. Though these effects were not robust, they are intriguing new findings in an under-researched field and will be discussed in more detail.

4.1 RESULTS IN THE CONTEXT OF THE HYPOTHESES

Regarding hypothesis 1, we did not find evidence that CBS participants performed better overall on the memory tests, rather we found that memory for negative words was selectively, marginally improved (partially supporting the second hypothesis, described in more detail below). This was not entirely unexpected because CBS and VNS are likely to selectively influence affective memory as versus overall memory as we indicated in our Cardiovascular and Neural Pathways linking VNS and CBS to Memory sections in the introduction. More specifically, affective stimuli are often paid more attention than neutral stimuli while cardiac deceleration is associated with increased sensory intake and attention. Thus, the cardiac deceleration elicited by CBS may have selectively enhanced intake, attention for, and processing of affective stimuli because such stimuli were already naturally commandeering those neural resources. Furthermore, since the carotid and vagus nerves terminate in the NTS, a brain region heavily connected to both memory and emotion-relevant areas, it is possible that the effects of suction may be more emotion-specific than general. Expressly, the NTS shares indirect connections with the hippocampus and directly projects to the PFC and the amygdala, structures that are traditionally viewed as being part of the limbic system and central to memory and emotion processing and motivation (Castle et al., 2005; Chiba, 2000; Ishikawa & Nakamura, 2006; van der Kooy et al., 1988).

Regarding the first part of Hypothesis 2, our results supported our expectations showing that arousing, valenced words were remembered better than neutral words in the sample as a whole across all conditions. In particular, the proportion of correct responses to the recall tests was greater, in turn, for positive, negative, and neutral words. Also, B', response bias or an index of participants' willingness to respond affirmatively that a word presented during recognition tests was a target word, was greatest for neutral words across all comparisons of conditions. This suggests that the specificity of their memory for these words was not as accurate as for the emotive words. Overall, these results parallel prior literature indicating that enhanced memory performance may be associated with arousing, emotional material relative to neutral (Doerksen & Shimamura, 2001; Dolcos et al., 2004; Hamann et al., 1999; Kensinger, 2004; Kensinger & Schacter, 2006; LaBar & Cabeza, 2006; Lewis et al., 2005). The former finding also complements a subset of the affective memory literature. While the majority of this literature finds that positive and negative, arousing words are comparably memorable, some studies have found that either positive stimuli only or negative only are better remembered, though more often the latter is reported (Doerksen & Shimamura, 2001; Dolcos et al., 2004; Hamann et al., 1999; Kensinger & Schacter, 2006; Lewis et al., 2005). Positive words may be particularly memorable because of the so-called ‘pollyanna effect’ and the positivity bias may also be an index of emotion regulation capacity (Baumeister et al., 2001; Kapucu et al., 2008; Murphy & Isaacowitz, 2008). While, these theories are supported by limited empirical research, it is possible that such intrinsic biases were operating in our participants. Finally, it is important to note that, while our findings did not extend to the proportion of correct responses to the recognition tests or A’, the affective memory literature provides conflicting reports as well. Some studies cite affective memory effects in both recall and recognition paradigms, whereas others do not (Kensinger, 2004; Kensinger & Corkin, 2003; Kensinger & Corkin, 2004; Kensinger & Schacter, 2006; Kern et al., 2005). Moreover, these discrepant main effects are particularly difficult to interpret as they averaged across the various conditions of our CBS and control manipulations.

Regarding the second part of Hypothesis 2, we found that CBS had minimal, if any, effects on memory. Results showed that, for the proportion of correct responses to the recognition tests and A’, the CBS group performed better than controls across almost all valences during the two suction conditions (though the CBS group’s performance was slightly higher, both groups had comparable scores for positive words in the suction at retention condition). However, marginal effects within the CBS group only showed that performance for positive words was somewhat lower than performance for negative and neutral ones in conditions in which suction was applied. Moreover, while their performance for negative words markedly improved between the non-suction and suction conditions, the CBS group’s memory for positive words declined between the non-suction and suction conditions; performance for neutral words remained stable across conditions. Similar results were found with A’. Overall, our results suggest that CBS may marginally enhance recognition memory for negative words, may have little effect for positive words, and may not influence memory for neutral words. These findings must be interpreted with the caveat that, given what appears to be the CBS group's relatively superior memory performance (mainly for positive and neutral words) to control's in the non-suction condition, they may be influenced by a pre-existing group difference. Finally, it is important to note that the proportion of correct responses to the recall tests was not influenced by CBS. Since most prior VNS and memory studies used recognition tasks, we did not necessarily expect significant findings in models incorporating it. While there was a main effect of word valence for the proportion of correct recall responses, it is possible that, since participants' mean recall across all conditions was low (22% (SD=0.1)), we may have encountered a floor effect in our analyses between groups and conditions.

It must be stated that our study was not designed to replicate the existing VNS and memory literature, but rather to incorporate components of it (i.e. the focus on both recognition and recall memory, suction at learning and retention) in order to test the effects of CBS on affective memory. As such, it is difficult to compare our findings directly to those reported in prior research. Compared to the only study that examined VNS and affective memory, our findings are particularly intriguing. In that study, a patient receiving VNS for treatment-resistant depression showed decreased recognition memory for negative, arousing words shown while VNS was applied during the active phase of the stimulation cycle in comparison to memory performance for negative, arousing words that were shown during the non-active phase of the cycle; memory for arousing positive and neutral words was comparable with or without VNS (Critchley et al., 2007). While both our study and that conducted by Critchley and colleagues show that stimulation may not influence recognition memory for neutral words and may slightly decrease memory for positive words, we both report that stimulation may selectively alter memory for negative words.

There are many possible explanations for our discrepant finding regarding the direction of stimulation's effects on memory for negative words. Chief among these is the fact that the Critchley project was a case study of a severely depressed man, rendering the 'direct' comparison between Critchley's results and ours obtained from a sample of college students impossible. Such depressed individuals often exhibit an exaggerated, mood congruent 'negativity bias', preferentially attending to and remembering negative material more so than non-depressed individuals; following reduction of their depressive symptoms, patients' bias is often reduced and comparable to that seen in non-depressed individuals (Critchley et al., 2007; Shook et al., 2007). This clinically meaningful cognitive bias and its potential manipulation by the acute and/or chronic anti-depressant effects of VNS complicate comparisons to our results. In sum, while explicit comparisons between studies are precluded, it is intriguing that both CBS and VNS may selectively alter memory for negative words, a phenomenon to be discussed in greater detail in the next section.

Prior to discussing hypothesis 3, it is important to note that more CBS participants experienced cardiac deceleration during the suction at retention condition (80%) than during the suction at learning condition (65%). This discrepancy may point to interference posed by the word presentation occurring concurrently with CBS in the suction at learning condition; it is possible that the task induced sympathetic activation, masking the parasympathetic effects of suction. However, we cannot completely explain this finding as we did not administer CBS outside of the memory tasks. Also, we did not find a clear phasic pattern of cardiac deceleration for any CBS participants during the periods in which they received suction. It is possible that the effect of suction was not distinctively phasic because we did not control for the phases of the cardiac or respiratory cycles at which suction was administered, masking cyclical effects on both the within and between-subjects levels.

Our data partially supported the third hypothesis that the baroreceptor stimulator was capable of indirectly activating the vagus nerve. Results showed that the CBS group's heart rate while suction was on in the suction at learning condition was significantly lower than their heart rate during a comparable time period from the non-suction condition. Also, the CBS group's heart rate while suction was on was lower than it was while suction was off in the suction at learning condition. However, similar effects were seen in both the CBS and control groups when comparing the non-suction and suction at retention conditions. Thus, while CBS was associated with cardiac deceleration among CBS participants during the appropriate time periods, sham stimulation was also associated with cardiac deceleration during those same time periods. While this may indicate that CBS was not effective, it could also be driven by unintentional sampling bias since it appears that CBS participants had lower heart rates than controls regardless of the phase of suction and at baseline (though not significantly so). Thus, while our results largely supported our hypothesis, the presence of pre-existing group differences remains a concern particularly since between-group comparisons were not significant.

Putting our cardiac-vagal results into the context of prior literature, we found that CBS was associated with modest cardiac deceleration, complementing prior CBS studies (Baskerville, Eckberg, & Thompson, 1979; Jennings et al., 2006). Regarding the VNS literature, authors report that VNS has limited transient and no aggregate effects on measures of heart rate (Barone et al., 2008; Setty et al., 1998). It is possible that CBS has been shown to slow heart rate while VNS has not because of differences in stimulation parameters (intensity and cycle time) or because of some as-yet-unknown subtlety differentiating CBS and VNS mechanisms of action.

In particular, many of the VNS studies examined heart rate collected over 24-hour periods; since the heart may habituate to repeated, long-term stimulation like this, these studies may have missed VNS' more acute cardiac effects. Moreover, studies of VNS are based on small samples of depressed or epileptic patients, often without excluding individuals suffering from cardiac conditions such as hypertension or individuals taking medications with cardiac side effects such as phenytoin. Since these populations are the only ones VNS implantation is approved for by the Food and Drug Administration, further research of VNS in carefully-selected sub-sets of the depressed and epileptic populations is warranted. As such, it is possible that future VNS studies manipulating stimulation parameters and enrolling participants with minimal cardiac anomalies will find differences in heart rate as well.

Lastly, from the heart rate and cognitive function literature, among the control group, we would expect heart rate to slow during the suction at learning condition and the time period comparable to it from the non-suction condition since participants should be attending to and taking in the experimental stimuli at these times (Jennings & Hall, 1980; B. C. Lacey & J. I. Lacey, 1974; Lacey & Lacey, 1978, 1979; W. L. Libby et al., 1973). We also would expect heart rate to speed during the suction at retention condition and the time period comparable to it from the non-suction condition since participants were actively attempting to remember the experimental stimuli and likely engaging in mental elaboration, activities typically associated with cognitive processing and disengagement from the environment. Instead, we found that controls' heart rate during the break period of the non-suction condition was slightly slower than during the word presentation phase and their heart rate during the suction at retention condition was also slightly slower than during the suction at learning condition. Similar effects were seen among the CBS group. There are many reasons why our results diverge from prior findings.

Principally, all previous cardiac function and cognitive processing literature is based on either second-by-second or short-term (e.g. 2-minute) assessments of heart rate, rendering it difficult to make direct comparisons to our 6-minute assessments of heart rate (Jennings, 1974; B. C. Lacey & J. I. Lacey, 1974; W. L. L. Libby, B. C. & Lacey, 1973). Moreover, our word presentation period may not have been a 'pure' attention task; since participants knew that the words were to be memorized, it is possible that this induced both attentional intake and also mental elaboration, processes associated with cardiac deceleration and acceleration, respectively. Accordingly, research shows that, in tasks designed to simultaneously provoke attention and mental elaboration, there are neither the clear cardiac decelerations nor accelerations. Rather, the resulting cardiac rhythm is a summation of these effects showing only small and varying changes in heart rate (B. C. Lacey & J. I. Lacey, 1974; J. I. Lacey & B. C. Lacey, 1974). While these factors may exert competing influences on the relationship between heart rate and cognition, our study added yet another layer of complexity via the authentic and sham CBS manipulations. Though we cannot definitely interpret our results within their context, these competing influences on the relationship between cardiac and cognitive function may help to explain our unexpected findings (i.e. that comparable numbers of CBS participants did not show cardiac deceleration in both suction conditions and that both the CBS and control groups showed similar heart rate changes between the non-suction and suction at retention conditions).

4.2 POTENTIAL PATHWAYS LINKING CAROTID BARORECEPTOR STIMULATION TO ALTERED MEMORY FOR NEGATIVE WORDS

Our central finding is that CBS was associated with minor improvements in recognition memory for negative words, did not alter memory for neutral words, and was associated with slight declines in memory for positive words. These differential effects may be best understood from the perspective of the cognitive processing and cardiac function literature. In the introduction, we speculated that the Laceys' intake-rejection may underlie affective memory. Expressly, the 'intake' portion of the Laceys' hypothesis suggests that cardiac deceleration decreases baro-afferent firing, allowing cortical and subcortical processing to support cognitive states of sensory and environmental intake like attention. It is thought that arousing, emotional stimuli are particularly memorable because they command more attention than neutral stimuli. Thus, cardiac deceleration may naturally accompany this selective attention, improving intake of and memory for emotive stimuli. Going a step farther, research indicates that negative stimuli might be paid the most attention because such stimuli often are critical to survival; then, might cardiac deceleration selectively accompany *negative* stimuli? Research suggests this may be the case, animals presented with threatening stimuli demonstrated vagally-mediated bradycardia, a phenomenon not seen when positive stimuli were presented (Bradley & Lang, 2007). Regarding humans, negative stimuli have been associated with significant cardiac deceleration whereas neutral and positive stimuli have been associated with less cardiac deceleration; positive stimuli were sometimes even accompanied by cardiac acceleration (Bradley & Lang, 2007; Buchanan et al., 2006; Cacioppo, Tassinary, & Berntson, 2007; B. C. Lacey & J. I. Lacey, 1974; W. L. Libby et al., 1973; W. L. L. Libby, B. C. & Lacey, 1973). Moreover, Buchanan and colleagues (2006) found that cardiac deceleration was greatest for negative stimuli and that the rate of deceleration was associated with improved recall for both negative and neutral stimuli. However, they noted that cardiac acceleration was associated with improved recall for taboo stimuli (similar to our positive stimuli). Thus, cardiac deceleration may selectively facilitate memory for negative and, to a lesser extent, neutral stimuli while acceleration may do so for positive stimuli. Finally, it is intriguing to note that Critchley and colleagues (2007) found that, while their VNS-implanted depressed patient encoded negative words that he later recognized correctly, he showed increased activation of the brainstem, right anterior insula, & ventromedial prefrontal cortex (a region identified as being involved in affective memory). This may indicate that neural coupling between autonomic function and emotion processing is selectively enhanced for negative stimuli by VNS. Taken as a whole, cardiac deceleration and the neuro-cognitive sensory, environmental, and attentional intake processes it might support may be particularly relevant for negative stimuli.

Within the context of the current study, it is possible that the cardiac deceleration caused by CBS facilitated a cognitive state of sensory and environmental intake. This relationship was likely most salient for negative words, contributing to their slightly enhanced remembrance. Unfortunately, the work cited above assessed heart rate on a second-by-second level or averaged across brief (2-minute or less) time periods, making it difficult to interpret our results in the context of this literature. Accordingly, future studies of affective memory and CBS or VNS focusing on that time scale might be worthwhile.

4.3 LIMITATIONS

Our study is marked by some limitations. The central limitation of this study was that, as the first study of its kind, we may not have employed the optimal experimental design in terms of CBS parameters and the arrangement of suction conditions. Regarding CBS parameters, although the 30 second on/30 second off cycle delivering –50 mmHG suction was based on prior research showing that these parameters could effectively alter vagal function, these studies did not incorporate memory-related tasks (Baskerville et al., 1979; Jennings et al., 2006). It is possible that different degrees of suction given over longer, or shorter, pulses would have produced greater cardiac and memory effects. Also, our results regarding heart rate slowing are difficult to interpret in light of the fact that we did not include a non-task suction condition. As conducted, our findings show that CBS delivered during word presentation and during the break period does slow heart rate, but it also appears that CBS participants had slower heart rates at baseline and during the non-suction memory condition indicative of a possible pre-existing group difference. Adding a non-task suction condition may help to parse out the effects of suction. Moreover, the addition of a Finapress device may have provided more information regarding subtle changes in baroreceptor sensitivity during suction. Lastly, our participants were all college students who were approximately 18 years old, thus, the generalizability of our findings is somewhat limited.

As a final point, it is important to acknowledge the unequal distribution of male and female participants between groups. To account for any potential effects this may have on our results, all analyses reported here were conducted with female participants only, as they were the larger subset of our sample and provided the necessary statistical power. Results were similar to those reported for the larger sample. We also examined the distributions and descriptive statistics for the variables of interest within the male and female subgroups separately and both groups had comparable values.

4.4 CONCLUSIONS AND DIRECTIONS FOR FUTURE RESEARCH

CBS somewhat enhanced verbal memory for negative words and slowed heart rate but that the effects were not robust. Although we tested and found evidence to support a priori hypotheses, these are only semi-confirmatory findings because of exploratory nature of our study. Moreover, consideration of possible pre-existing, between-groups differences in memory and heart rate is reasonable given our results. Yet, as the first study of its kind, these results lay the groundwork for future CBS research. In order to build on these findings, research is needed to identify the optimal CBS parameters both for effectively influencing the cardiovascular system and for enhancing memory. For this purpose, ECG, Finapress, and blood pressure measurements should be included in future studies. Finally, since no other studies have examined the association between CBS and memory, studies both replicating our results and also modifying our study design (e.g. adding a non-task suction condition, altering the CBS parameters, and testing different forms of memory) are needed. To further explore our hypothesis that CBS may selectively enhance memory for negative stimuli because cardiac deceleration particularly facilitates the intake of negative, possibly survival-threatening material, studies that isolate the relationship between CBS, cardiac function, attention, and emotional stimuli on a second-by-second basis is warranted. Such work would be more directly comparable to the existing literature supporting cardiac deceleration as an index of environmental intake and attention. Moreover, research aimed at discerning the neural pathways that may underlie the association between CBS and VNS and memory would also be informative as it is likely that unique neural-cardiac associations underlie ours and others' findings. To conclude, our results indicate that manipulations of the cardiovascular system likely influence neuro-cognitive processing, potentially contributing to differential rates of memory for positive arousing, negative arousing, and neutral stimuli. Since physiological manipulations appear capable of these effects, affective memory may be attributed, in part, to basal and context-induced individual differences in physiology.

5.0 APPENDIX A

PILOTING

Pilot participants were recruited to assess the memory tests' difficulty and to ensure that the stimulation parameters were safe and effective. Since the current stimulator was based on one designed by Jennings, Eddy, Shapiro, and van der Molen (2006) and those authors only stimulated participants for separate 500 millisecond periods at -37mmHg, we wanted to ensure that stimulation for 30 second pulses over 6 minute periods, as stipulated by the current protocol, was feasible. Moreover, since stimulation up to –65 mmHg has been safely used by others (Baskerville et al., 1979; Ebert et al., 1984; Eckberg, 1976, 1977a, 1977b; Eckberg & Eckberg, 1982; Eckberg & Sleight, 1992; Ludbrook, Mancia, Ferrari, & Zanchetti, 1977; Mancia, Ludbrook, Ferrari, Gregorini, & Zanchetti, 1978), we wanted to compare the degree of cardiac deceleration yielded by different levels of mmHg.

5.1 PARTICIPANTS

Pilot participants were recruited from the community during May through early August 2007. They all received authentic CBS and none were included in the final data analyses. Inclusion criteria stipulated that all participants spoke English as their first language and were between the ages of 18-30, to preserve homogeneity of the sample They also could not take medications for depression, anxiety disorders, epilepsy, or heart conditions, and they must not have a personal or biological family history of heart disease (such as heart attacks, strokes, blood clots, or other problems with the heart or blood vessels) detected before 45 years of age. Pregnant females were excluded. All participants abstained from drinking alcohol and drug use for 24 hours prior to their participation and from nicotine and caffeine consumption for 4 hours prior.

5.2 PROCEDURE

5.2.1 MEMORY TASKS

The same memory task protocol used for the final study was used during piloting.

5.2.2 CAROTID BARORECEPTOR STIMULATION

The same suction protocol used for the final study was used during piloting. However, during initial piloting, the laboratory-built device delivered -37 mmHg of suction to the external carotid baroreceptors for a 30 seconds on and 30 seconds off cycle lasting the entire length of the word presentation in the suction at learning condition, 6 minutes, and lasting 6 minutes in the suction at retention condition. These parameters were chosen based on those used in human VNS and memory studies and in prior CBS studies. In sum, Clark, Naritoku, Smith, Browning, and Jensen (1999) waited until 2 minutes after words-embedded-in-paragraph presentation and then stimulated participants for 30 seconds with no off period (0.50 mAmp-1.50mAmp, 30 Hz, 0.50-ms pulse width), Critchley et al. (2007) stimulated participants for a 30 seconds on 66 seconds off cycle that lasted the entire length of word presentation, approximately 5 minutes, (20 Hz, 500 microsecs, 2.25 mAmp), and Ghacibeh, Shenker, Shenal, Uthman, and Heilman (2006) stimulated participants for an average of 30 seconds on 5 off for an unspecified amount of time immediately after word presentation (1-2.75 mAmp). Neck devices typically apply pressure ranging from 40 to -65 mmHg with no studies reporting complications of the procedure (Eckberg & Sleight, 1992). Baroreceptor suction experiments typically use pressure parameters between -5 and -65 mmHg with a median level of stimulation around -30 mmHg (Baskerville, Eckberg, & Thompson, 1979; Ebert et al., 1984; Eckberg, 1976; Eckberg, 1977; Eckberg &Eckberg, 1982). The duration of neck pressure applications ranges from 1 second to 5 seconds (Eckberg & Sleight, 1992). During the later stages of piloting, CBS was decreased to –50 mmHg as this level of stimulation elicited more reliable cardiac deceleration (for further information see the Pilot Results section)

5.2.3 STATISTICAL PLAN

All pilot participants received authentic CBS. Repeated measures ANOVAs were used to compare participants' heart rate during the periods in which they received suction in the suction at learning and retention conditions to comparable periods from the non-suction condition. Repeated measures ANOVAs were also used to compare heart rate during the total time suction was "on" to heart rate during the total time suction was "off" in the suction at learning and retention conditions, respectively. Finally, repeated measures ANOVAs were used to compare participants' recognition memory performance (proportion of correct responses) across valences and suction conditions; we wanted participants' mean performance to be around 70% correct so that there would not be floor or ceiling effects masking effects of suction.

5.3 RESULTS

Among laboratory assistants who met the inclusion criteria, suction at –37, -40, and –50 mmHg was compared. Titration procedures showed that suction at –50 mmHg most reliably decelerated heart rate and was well-tolerated by all participants. Thus, 14 participants recruited from the community completed various components of the experiment. Nine (5 males, 4 females) individuals completed the entire experiment receiving –50 mmHg suction, 2 (females) completed just the memory portion, 4 (3 females, 1 male, including one person form the memory-only group) completed portions of the suction procedure (-50 mmHg) only.

Repeated measures ANOVA showed that participants' mean IBI during word presentation in the non-suction condition (mean IBI=840.76) was significantly lower than their mean IBI during word presentation in the suction at learning condition (mean IBI=862.55; $F(1, 7)=6.47$, $p<.05$). We also compared the IBI during the total time suction was "on" to the IBI during the total time suction was "off" for the suction at learning and at retention conditions. The IBI for the total time suction was "on" was greater than the IBI during the total time suction was "off" for both conditions (see Table A1; suction at learning: $F(1, 8)=12.32$, $p<.01$; suction at retention: $F(1, 8)=18.99$, $p<.01$). Memory performance ranged from 98% to 53% correct with an average performance of 73% across all conditions. Using repeated measures ANOVA as planned, we did not find significant effects of memory accuracy by suction condition or valence.

Table A1 Differences Between Interbeat Intervals Recorded During Suction On vs. Off Periods in Pilot Participants

Condition	Mean	Standard Error	Mean	Standard Error
	Suction "on"		Suction "off"	
Suction at Learning	853.42	32.48	839.28	33.62
Suction at Retention	791.08	85.52	772.22	83.68

Note. Comparisons between Suction at Learning "on" and "off" and between Suction at Retention "on" and "off" were significant ($p < .01$).

6.0 APPENDIX B

DEBRIEFING QUESTIONNAIRE

Debriefing Questionnaire - Subject Number_______

Do you believe that you received true baroreceptor stimulation or do you think that you were in a control group?

Were you distracted by the neck suction?

Do you think that the neck suction affected your performance on the memory tests?

Did you experience changes in your mood during the session? If yes, please describe.

Did you experience changes in your level of awareness during the session? If yes, please describe.

Did you experience changes in mental imagery during the session? If yes, please describe.

Did you use any strategy to remember the words?

Was your memorization strategy different for different trials?

Was your memorization strategy different for times when you were/were not suctioned?

7.0 APPENDIX C

EXPLORATORY BLOOD PRESSURE ANALYSES

Blood pressure was measured every 2 minutes during the baseline and during the word presentation and break periods of each condition. Average blood pressures were calculated for each period. Participants were seated upright with their feet flat on the floor and the cuff was placed on their non-dominant arm. Blood pressure was measured with an automated device (auscultatory-Korotkoff method: Critikon Dinamap, GE Healthcare).

To test whether blood pressure was affected by CBS, the group by suction condition interaction for systolic and diastolic blood pressure (SBP and DBP) was examined in analyses comparing participants' baseline and suction at learning condition values and their baseline and suction at retention condition values. Analyses were also conducted comparing their values from the word presentation period of the non-suction condition to their values from the suction at learning condition and their values from the break period of the non-suction condition were compared to their values from the suction at retention condition. None of these analyses produced a significant group by suction condition interaction term. For DBP, the highest F value obtained was 2.29 and no analysis approached statistical significance. But, an analysis comparing SBP during baseline and suction at retention produced a trend-level significant group by suction condition term ($F(1, 52)=3.64$, $p=.062$); the pattern of means shows that, while controls' SBP remained stable between conditions, the CBS groups' SBP declined from baseline to suction at retention (see Figure C1).

In conclusion, exploratory blood pressure analyses showed that, while CBS participants' DBP was not affected by suction, their SBP was lower in the suction at retention condition than it was at baseline. Controls' SBP remained stable across these conditions. Although this SBP decrease is an isolated finding, it may indicate that CBS elicited the expected baroreflex response, appropriately lowering the peak contractile pressure of the heart. As this is an isolated finding, it is possible that CBS was not sustained long enough to reasonably activate a compensatory blood pressure response in all conditions. Also, while heart rate is an index that can respond on the order of milliseconds, the blood pressure response is much slower given bodily hemodynamics (Berntson, Quigley, & Lozano, 2007). Since the auscultatory method of blood pressure measurement used in this study is based on detecting Korotkoff sounds, sounds that correspond to the movement of blood in an artery at a given pressure, over the course of many heart beats, such temporal effects of CBS may have been masked. Furthermore, because we took participants' blood pressure every 2 minutes, our measurements may have missed the effects of CBS. Overall, it is likely that a combination of small effects and un-timely measurement contributed to minimal blood pressure findings.

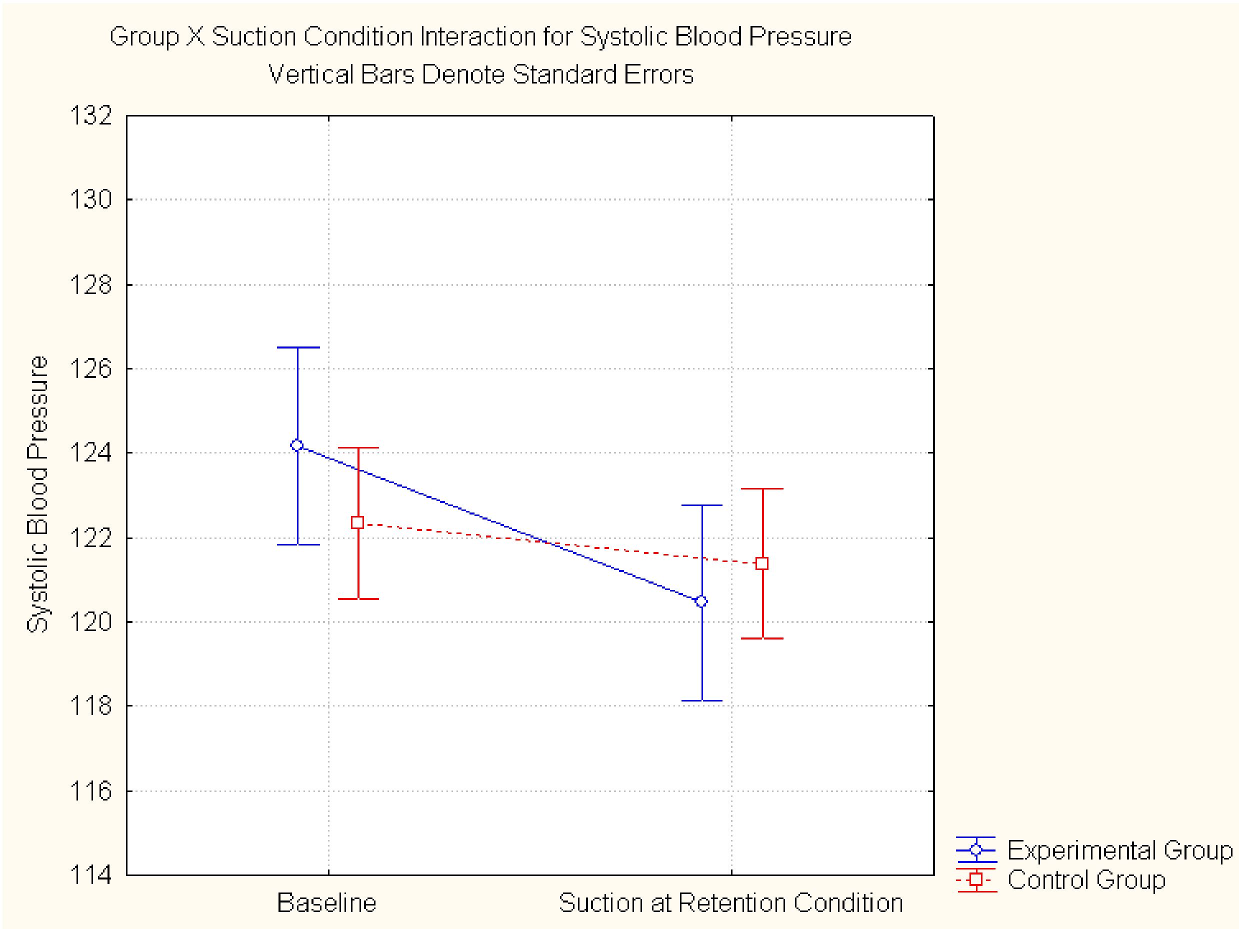
Group X Suction Condition Interaction for Systolic Blood Pressure
Vertical Bars Denote Standard Errors
Systolic Blood Pressure
132
130
128
126
124
122
120
118
116
114
Baseline
Suction at Retention Condition
Experimental Group
Control Group

Figure C1.

8.0 APPENDIX D

EXPLORATORY ANALYSES OF PARTICIPANTS' CONFIDENCE CORRESPONDING TO THEIR RECOGNITION TEST RESPONSES

Upon completing each item on the computerized recognition tests, participants were asked, "was this a word you saw in the most recent list, yes or no?". Once they responded, they were asked "how confident are you in your response on a scale of 1-6, 1 meaning 'not confident' to 6 meaning 'very confident'. Confidence ratings were analyzed and interpreted as detailed in Murdock (1974), producing graphs that plot confidence as a function of hits and false alarms. We attempted to analyze this data using both total confidence within each condition and using confidence associated with each valence within each condition with parametric statistics as well, but all analyses resulted in incomplete designs. The confidence ratings were treated as both continuous (raw data) and categorical variables (raw data grouped intro quartiles; highest quartile represents greatest confidence).

Separate graphs were created for the CBS and control groups (see Figures D1 and D2). Confidence was divided into quartiles and data points representing confidence ratings within each suction condition were produced. In both groups, confidence ratings associated with recognition memory did not vary systematically between conditions. Also, for both groups, the higher 2 quartiles of confidence ratings were associated with relatively greater proportions of hits versus false alarms whereas the lower 2 quartiles were associated with relatively fewer hits and more false alarms. However, CBS participants demonstrated a greater proportion of hits versus false alarms for quartile 4, across all conditions, than controls. An examination of the standard errors associated with the hits and false alarms for quartile 4 confidence among the CBS group showed that the proportion of hits for the suction at learning condition was slightly lower than for the non-suction and suction at retention conditions (see Table D1). The proportion of false alarms for the suction at retention condition was also slightly lower than for the non-suction and suction at learning conditions. Though these between-condition differences existed, they were not significant and it is unlikely that the between-groups difference in the 4th quartile of confidence can be attributed to CBS. Moreover, an examination of the mean number of hits and false alarms associated with quartile 4 confidence did not suggest a condition by valence or a group by condition by valence interaction. Thus, it unlikely that changes in confidence explain our CBS-related recognition affective memory results.

Table D1 Standard Errors Associated with the Proportion of Hits and False Alarms for Quartile 4 Confidence Among the Carotid Baroreceptor Stimulation Group

Proportion of Hits

Condition	Mean	Standard Error
Non-suction	79.6	3.9
Suction at Learning	73.3	3.8
Suction at Retention	78.5	3.9

Proportion of False Alarms

Condition	Mean	Standard Error
Non-Suction	13.9	3.7
Suction at Learning	13.3	3.6
Suction at Retention	10.1	3.1

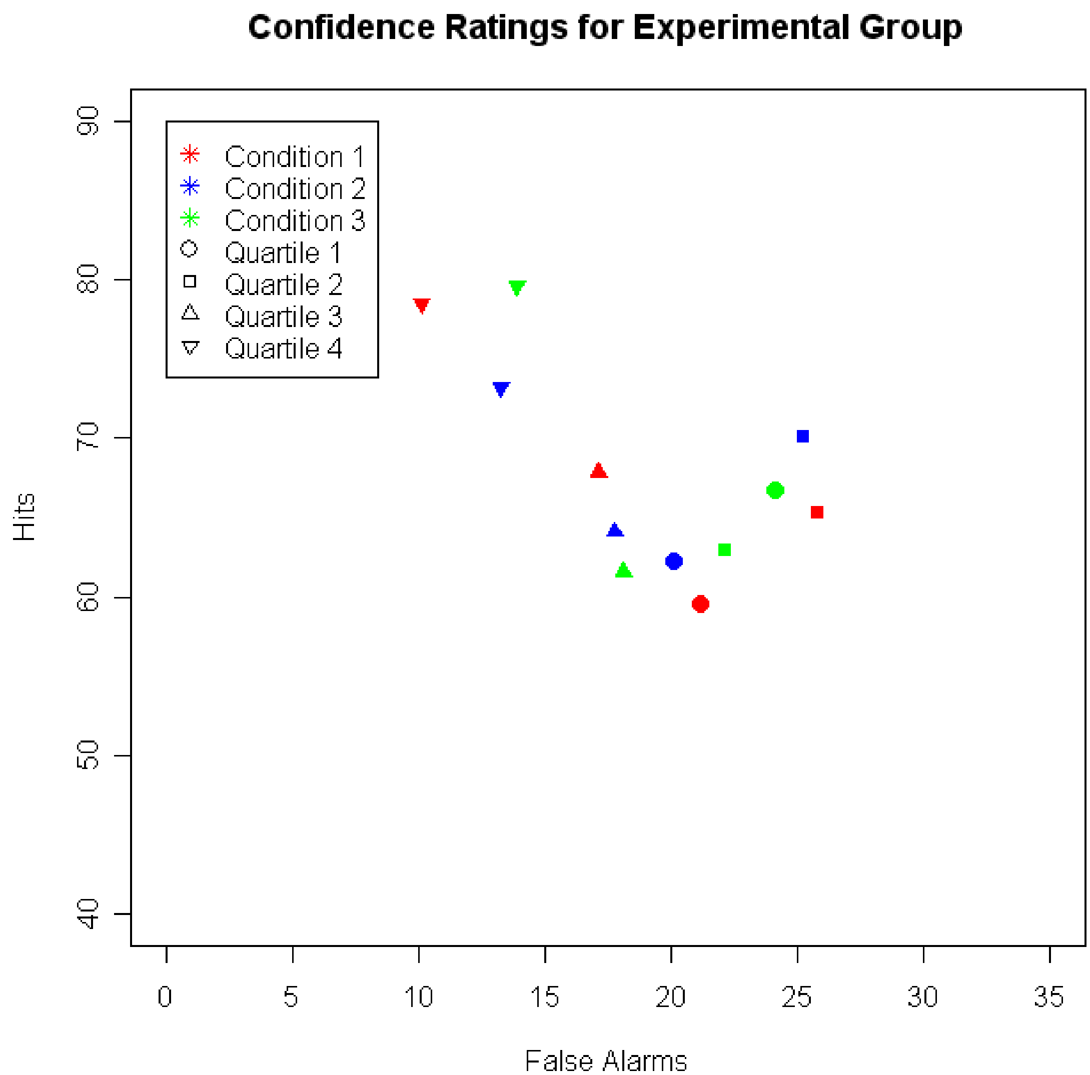

Figure D1.

Note. Condition 1=Non-suction condition, condition 2=suction at learning condition, condition 3=suction at retention condition.

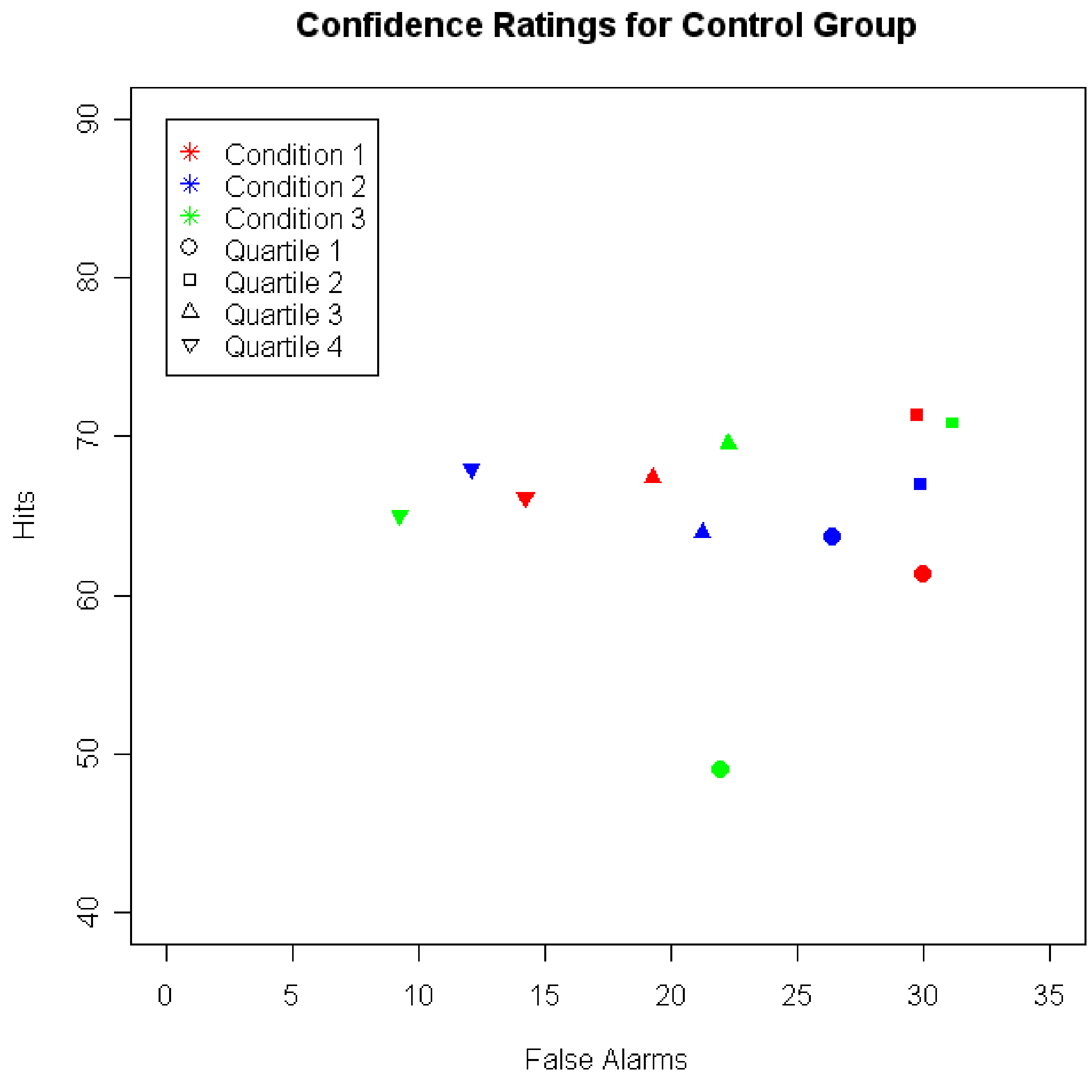

Figure D2.

Note. Condition 1=Non-suction condition, condition 2=suction at learning condition, condition 3=suction at retention condition.

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