INTRODUCTION

The key idea of the somatic marker hypothesis is that decision-making is a process that is influenced by marker signals that arise in bioregulatory processes, including those that express themselves in emotions and feelings. The primary purpose of this study was to provide evidence that supports the notion that physiological changes related to emotion (somatic states), which arise in the body outside the brain, do play a role in influencing decisions.

There are three possible routes by which somatic signals expressed in the body can feedback to the brain and influence cognition. One is through the spinal cord, another is through the vagus nerves, and a third is an endocrine route. Several lines of evidence prompted the testing of the hypothesis that the vagus nerves might be a critical peripheral conduit for somatic signals to influence decision-making. First, subjects with spinal cord injury between the 2nd and 6th cervical vertebra did not show impairments in decision-making as measured by a laboratory instrument known as the gambling task (North and O'Carroll, 2001). This instrument has been shown to be sensitive to real-life deficits in decision-making (Bechara et al., 2000a). Normal decision-making in spinal cord injury subjects has two important implications. One, because sympathetic signals enter and exit the spinal cord at and below the first thoracic level, changes in sympathetic activity are not in-and-of-themselves critical to determining somatic emotional tone. Two, this study suggests that the important afferent pathways are extraspinal, via the cranial nerves (e.g., the vagus) or possibly endocrine routes.

The second line of evidence comes from a preliminary study, in which we have collected data from subjects with idiopathic polyneuropathies affecting primarily small diameter and/or autonomic fibers, and we observed mild impairments in gambling task performance (Bechara et al., 1998a). In this preliminary study, we have collected data from 20 subjects with peripheral neuropathies, mainly of the sensory type. We compared their performance in the gambling task to that of 15 demographically matched controls. We found that the subjects with peripheral neuropathies performed deficiently on the gambling task relative to the controls. However, since peripheral neuropathy does not represent a complete ‘disconnection’ between the body and the brain, it was not surprising to see that the impairment was relatively mild in relation to some of the performances seen in subjects with brain lesions. Since spinal cord lesions did not impair decision-making, but peripheral neuropathies involving autonomic fibers appear to, this provided further indirect support for the hypothesis that the important afferent pathways for somatic state signals are extraspinal, and probably mediated through the vagus nerves.

The third line of support comes from the evidence that stimulation of the vagus nerve improved human memory (Clark et al., 1999), perhaps using the same neural mechanism that is responsible for improved memory of emotionally laden stimuli compared to non-emotional laden stimuli. Fourth, positron emission topography (PET) experiments in humans undergoing left vagus nerve stimulation (VNS) for the treatment of epilepsy have demonstrated a complex
The vagus nerves are among the largest cranial nerves. They are predominantly sensory nerves, with 80% of the fibers afferent, and serve as a neural interface to the enteric plexi, which may also be important in the detection of circulating catecholamine levels, and they may function as an extraganglionic integrator of the autonomic nervous system. The left vagus nerve largely carries afferent signals from the fundus of the stomach, and the right vagus nerve largely carries afferent signals from the atra of the heart, liver and duodenum. Afferent fibers terminate in the nucleus tractus solitarius (NTS) (Grill and Norgren, 1978; Bechara et al., 1993). The caudal portions of NTS receive visceral sensation, whereas the rostral portions receive gustatory information. The NTS also projects with 80% of the fibers afferent, and serve as a neural interface to the enteric plexi, which may also be important in the detection of circulating catecholamine levels, and they may function as an extraganglionic integrator of the autonomic nervous system. The left vagus nerve largely carries afferent signals from the fundus of the stomach, and the right vagus nerve largely carries afferent signals from the atra of the heart, liver and duodenum. Afferent fibers terminate in the nucleus tractus solitarius (NTS) (Grill and Norgren, 1978; Bechara et al., 1993). The caudal portions of NTS receive visceral sensation, whereas the rostral portions receive gustatory information. The NTS also projects to the amygdala, hippocampus, hypothalamus, and parts of the medial reticular formation. However, the most significant projection is to the parabrachial nucleus, with visceral fibers ending predominantly in the lateral regions of the nucleus, whereas gustatory fibers terminate predominantly in the medial regions of the parabrachial nucleus (Grill and Norgren, 1978; Bechara et al., 1993). In turn, the parabrachial nucleus relays signals to the thalamus, which in turn projects to the striatum, orbital frontal cortex, and insula, which all play a significant role in a neural system critical for decision-making (Bechara et al., 2002). If the vagus nerves participate in trafficking visceral sensation key to forming emotional valence at the time of decision-making, might vagus nerve stimulation (VNS) influence decision-making? To address this question, we tested epileptic patients with previously implanted left vagus nerve stimulators with the gambling task. Patients performed two repeat versions of this task. Using a counterbalanced design, low-level vagus nerve stimulation was covertly delivered during one of the two sessions of performing the gambling task. Additionally, the cognitive status of the participants was assessed with a standard battery of neuropsychological tests measuring intellect, memory, language, perception, attention, executive function and mood.

**METHODS**

**Participants:** All protocols were pre-approved by the University of Iowa Human Subjects Committee. Eleven participants were recruited from the University of Iowa Comprehensive Epilepsy Program out of a pool of 24 medically refractory epileptic patients with implanted vagus nerve stimulators (Cyberonics Inc. NeuroCybernetic Prosthesis System, Houston, TX). Thirteen potential participants were excluded from participation for documented mental retardation, severe visual impairments and/or aphasia. Each participant was separately interviewed and tested. Demographic and medical information regarding the participants included in the study are presented in Table I.

**Stimulation Parameters:** After informed consent was obtained, intermittent stimulation was deactivated. To allow external control of the device, it was programmed to respond to a magnetic pulse by delivering 60 seconds of 0.5 mA, bipolar, left vagus nerve stimulation with a frequency of 30 Hz and a pulse width of 500 μsec. When reprogramming was complete, the participant was

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randomized to stimulation-on during either the first or the second trial of the decision-making task.

**Tasks:** We assessed decision-making using the gambling task. Participants were presented with four decks of cards on a computer screen and instructed to draw cards from any of the decks by mouse click in an attempt to win fictitious money. Participants were told: (1) with each card draw, money would be won; (2) sometimes, a card draw would result in both winnings and losses; (3) net winnings would accumulate if they learned to stay away from the worst decks; and (4) at times during the experiment their vagus nerve stimulators would be active. Unknown to the participants was the stimulation schedule and that two of the decks were stacked to deliver large rewards but high losses, making them disadvantageous over time. The other two (winning) decks yielded lower rewards but more minor losses. The task terminated after 100 card draws. Participants performed the task twice with the disadvantageous decks given different labels and repositioned to different screen locations on the second trial. Labels and screen locations remained stable within a trial. To further reduce the practice effect during the second trial, the wins and losses associated with draws were more closely matched, making the disadvantageous decks more difficult to discern. Between trials of the gambling task, participants underwent neuropsychological testing for approximately 2.5 hours. The neuropsychological tests assessed a range of cognitive domains, including attention, intellect, reading, visual spatial, anterograde memory, and executive functioning skills. This testing was performed with the stimulator off. After completion of all testing the participant’s stimulator was restored to their pre-experimental settings.

The computer program used in this experiment to produce the gambling task was based on the program previously used by our laboratory (Bechara et al., 2000a). Modification was necessary to pause the task for 65 seconds after every minute of play. At the onset of play, the program sent a signal to an electromagnet placed over the participant’s stimulator. During one of the two trials this signal resulted in a magnetic pulse to trigger the participant’s stimulator and 60 seconds of vagus nerve stimulation (Figure 1). The loop of playing and pausing was repeated until the participant picked all 100 cards (9 to 11 iterations). Pauses were necessary in the task to avoid exceeding the 50% duty cycle limit recommended by the stimulator’s manufacturer. Proper operation of the electromagnet and the generator was verified by monitoring radio frequency emissions from the stimulator.

**Blinding:** Though not considered requisite for the data analysis, the experimental design sought to blind the participants as to when stimulation occurred. Steps taken to blind the participants
included the following. (1) The research assistant instructing the participants was blind as to which trial VNS occurred. (2) The electromagnet was placed over the stimulator during both trials and produced neither sound nor heat detectable by the participants. (3) Participants were instructed not to speak during either trial because VNS induces transient changes of vocal tones. (4) Participants were not told that all stimulation occurred during one of the trials. (5) While it was necessary for an unblinded experimenter (CM) to be present during the trials, he neither spoke to nor faced the participants during the experiment. At the end of the experiment, participants were asked during which trial more stimulation had occurred. Based on these reports, it was determined that only one participant was able to discern during which trial VNS occurred.

Variables: The independent variables were the stimulation state (on versus off) and the task order (on-first versus off-first). The order of trials was equally counterbalanced across participants. The dependant variable was the performance on the gambling task. These scores were analyzed in terms of net scores (the total number of cards selected from the ‘good’ decks minus total number from the “bad” decks) in 5 consecutive blocks of 20 cards. Dividing the picks into blocks of 20 cards each in the statistical analyses was independent of the number of cards picked by an individual subject during each 60-second play period.

RESULTS

Neuropsychological Testing: The majority of tested participants demonstrated mild to moderate neuropsychological deficiencies (Table II). Most deficiencies were in spheres of verbal memory and visual perception. (As noted earlier, participants who participated in the experiment but showed neuropsychological deficits, as judged by a neuropsychologist who was blind to the experimental conditions, were excluded from further analyses.)

Telemetry Data: Overall, the magnetic triggering signal was successful in triggering the participants’ stimulators 96% of the time. Three of the participants had a single failure of stimulation, which occurred in the last 25 cards because the participants had repositioned themselves away from the electromagnet. One participant was able to feel VNS as a mild cervical tingling. This was the only observed or reported side effect of VNS in this study.

Performance on the Gambling Task: By and large, participants performed disadvantageously on the gambling task. This is not surprising given that the majority of these participants are unable to function in the world without the assistance of their families. Intriguingly, participants showed improved performance (selected more advantageous cards) in the stimulated relative to the un-stimulated condition. Stimulation improved performance regardless of whether stimulation occurred during the first or the second trial. A 3 way (2 × 2 × 5) ANOVA on the net scores from (1) the participants who received the stimulation when the gambling task was performed for the first or second time (a between group comparison) × (2) the conditions under which the vagus nerve stimulation was on or off (a within group comparison) × (3) the 5 blocks of 20 cards from the 100 trials of the gambling task (a within group comparison) revealed a significant interaction of condition and block [F (4, 24) = 3.92; p < .01]. In this analysis, there was no significant main effect of order, of stimulation condition, of blocks, nor any other significant interaction (Figure 2a).

Although Figure 2a shows that participants demonstrated better performance in the stimulation “on”, as opposed to “off”, condition, the ANOVA surprisingly did not reveal a significant main effect

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of stimulation condition. However, a careful reading of the data presented in Figure 2a shows that when the stimulator was active, the participants (on average) started by selecting disproportionately from the disadvantageous decks. In later blocks, the participants performed relatively better, except for the last block. In contrast, with the stimulator off, although participants began selecting more often from the advantageous decks (perhaps this was a chance occurrence), they progressively selected from disadvantageous decks until the last block of 20 cards when the performance was slightly reversed. This initial difference (in block 1) in how participants aggregated towards the disadvantageous or advantageous decks is coincidental, and we cannot attribute it to any aspect of the experimental manipulations conducted in this study. On several occasions, in other studies, we have encountered similar results with various groups of subjects; we have no explanation for this initial performance difference, and we can only attribute it to chance. However, the most critical measure in our study is how do participants perform over time, i.e., over subsequent trials, relative to their initial or baseline performance. For this reason, we reanalyzed our data, taking into account, and adjusting for, this initial baseline difference.

Taking the performance in block 1 as a baseline, the data can be rendered relative to this starting performance. Figure 2b depicts the same data of Figure 2a in terms of performance in the
The effects of VNS on decision-making were not straightforward. In the earlier part of the task (first 4 blocks), there was steadily enhanced performance across blocks when the stimulator was “on”, whereas there was steady decline in performance in the “off” condition. In the final block, however, the trend was reversed: there was a decline in performance when the stimulator was “on”, while performance in the “off” condition improved. Thus, the first pertinent question: why did the decision-making performance worsen during the last block of trials when the stimulator was “on”? There are several possible explanations for this finding. First, convergence of the last data points may simply represent regression to the mean. Second, the problem could be technical, in that we had three stimulation failures, which coincidentally occurred only during the last 25% of the task, and not during any earlier blocks. This could have compromised the impact of stimulation on the choices made during the last few trials of the task. Third, it is possible that early low level VNS was beneficial, and improved performance; however, repeated stimulation may have caused fatigue in the vagus nerve system, or a cumulative stimulation dose effect, so that VNS became disruptive towards the end of the task. This interpretation is consistent with a prior study showing a similar inverted U-shape effect of VNS on memory (Clark et al., 1999).

Fourth, it is possible that the improvement effect of VNS occurred only during the phase when declarative knowledge of what is good or bad was not available, and decisions were guided primarily by non-conscious somatic signals. Indeed, previous studies have established that healthy volunteer subjects began to choose advantageously in the gambling task before they realized which strategy worked best, and they began to generate anticipatory skin conductance responses (SCRs) whenever they pondered a choice that turned out to be risky, before they knew explicitly that it was a risky choice (Bechara et al., 1997). These results suggested that, in normal individuals, non-conscious biases guided behavior before conscious knowledge did (Bechara et al., 1997). The explicit knowledge of which choices were good or bad arrived very late in the task, i.e., during the last block of trials. Thus, in this study, it is possible that VNS benefited decision-making only during the implicit knowledge stage of the task, i.e., prior to the last block during which time decision-making was not under the control of a rule based strategy. However, in the last block of trials, participants may have reached a certain level of conceptual knowledge about the contingencies of the task and they followed some explicit strategy, independent of any effect exerted by the VNS, thereby bringing the performance of both trials (stimulated and unstimulated) to about the same level. This possibility can explain the convergence of performances during the final block of the gambling task. The
limitation of this study is that, to maintain participant blinding, we were unable to assess the conceptual knowledge of tested participants at various stages of the task as was previously done (Bechara et al., 1997), in order to find out at which point individual participants had implicit or explicit knowledge of the contingencies in the gambling task. However, a debriefing of individual participants at the end of each experiment suggests that, half of these participants were able to discriminate explicitly between the good and bad decks, thus indicating that some participants in the final block of the gambling task reached explicit knowledge of the contingencies.

The second important question pertaining to the current findings is: could the worsened performance of participants during the stimulation “off”, relative to the “on”, condition be explained by the possibility that patients were experiencing seizures in the “off”, but not “on” condition? We do not believe that this possibility explains the current results. There were no motor manifestations or arrests in behavior during any of the trials to suggest a seizure. Additionally, the effects of VNS are tonic persisting between stimulations. As a matter of routine, neurologists instruct their patients that it is acceptable to temporarily deactivate the stimulator for events such as eating, public speaking and singing. Such temporary deactivations are not known to precipitate seizures or cause adverse effects.

Another intriguing question in relation to the current findings is: why did the VNS improve, rather than disrupt the somatic signals that influence decision-making? There are two possible mechanisms by which peripheral signals may influence cognition.

One possible mechanism is consistent with the view of Schacter and Singer (Schacter and Singer, 1962) that signals arising in the body are simply a non-specific form of arousal, which interact with knowledge (cognition) to exert an improvement effect. According to this view, stimulation of the vagus provides a state of non-specific arousal, which helps improve decision-making.

Another possible mechanism consistent with the SMH view is that different somatic or emotional states reflect different patterns of physiological activity (Damasio, 1994, 1999, 2003). Meta-analysis of studies linking emotion to changes in autonomic efferent activity suggest that patterns in autonomic activity can reliably discriminate negative from positive emotions (Cacioppo et al., 2000). If different somatic states produce different patterns of signals that need to be transmitted through the vagus, then why did the stimulation not interfere with decision-making? One possibility is that normal function in the right vagus and normal function in the unmyelinated C fibers of the left vagus (C fibers are likely unaffected by low level VNS (Henry, 2002)) are sufficient to carry the patterned signals of somatic states to the brain which is essentially amplified by left VNS with the signals integrated in NTS or downstream when these physiologic and artificial signals reach the telencephalon. Obviously, these potential mechanisms are speculative at this early stage, but they raise intriguing questions for future investigations.

Thus far we have discussed possible mechanisms through which VNS may influence decision-making by altering the brain’s perception of somatic states. Another important avenue through which decision-making may be improved is via transiently improved memory. Considerable work has addressed the role of emotion in memory improvement (e.g., see Roozendaal et al., 1996; McGaugh et al., 1996; Cahill and McGaugh, 1998 for reviews).

Given this line of evidence, it may be argued that the decision-making improvement in this study can be explained by the mechanism of memory improvement produced by VNS (Clark et al., 1999). Indeed decision-making is a process that is partially dependent on memory systems (Bechara, 2002), and impaired working memory can compromise decision-making and performance on the gambling task (Bechara et al., 1999b). Therefore, it is possible that VNS exerts memory improvement, which in turn helps improve decision-making. However, other evidence has shown that therapeutic VNS does not improve memory (Hoppe et al., 2001a), which suggests that the memory-mediated mechanism of decision-making improvement is debatable at this point. Although the vagus nerve may be a common substrate for the improvement effect of emotion on memory and decision-making, our initial studies indicate that at the level of the brain, the neural mechanisms by which emotion improves memory are separate from those by which emotion biases decisions (Damasio et al., 1999; Bechara et al., 2000). The point at which the emotional mechanisms that modulate memory versus decision-making separate remains a topic for future studies.

Another important point we would like to note is that several studies have reported therapeutic VNS being associated with a weak to moderate improvement in dysphoria (Hoppe et al., 2001b; Marnell et al., 2002) and depression (Scherrmann et al., 2001). Although we have no concrete evidence at the present time to substantiate this possibility, this improvement in mood may be a contributing factor to the improved decision-making associated with VNS.

**CONCLUDING REMARKS**

The current results showing a beneficial effect of parasympathetic afferent stimulation on decision-making suggests that these changes exert an important and positive influence on the process of decision-making. The current study is limited by the type of participants we have studied. However
as VNS continues to become more widely accepted, greater numbers of patients with normal cognition will be available for study. Therefore, future studies in these target populations are likely to yield fruitful information. Most important, even in cognitively impaired populations such as the one studied here, the current results have significant clinical implications. The stimulation parameters used in this study were conservatively chosen to avoid perception by the participants. There is no reason to believe that the parameters used here are the most effective in influencing decision-making. Certainly, numerous other parameters could be attempted to define the scope of the effect. Delineating the parameters that enhance and disrupt decision-making may allow research for the use of such neural-prosthetic devices in the cognitive rehabilitation of cognitively impaired patients.

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