

Research Article

Effects of a memory structuring plus vagal breathing intervention on acute stress reactions: Three controlled trials

Yori Gidron*

Chair of psychooncology, Scalab, Lille 3 univ, and Siric Oncolille, Lille, France

Moshe Farchi

Head of Stress, Trauma & Resilience studies, Tel-Hai College, Israel

Eisenman Arie

Head Medical Emergency Department, Western Galilee Hospital Nahariya, Israel

Amar Husien

Rivka Ziv medical Center, Tfad, Israel

Kinge Berends

Dept of Psychiatry, UZ Brussels, Belgium

Ives Hubloue

Dept of Psychiatry, UZ Brussels, Belgium

ABSTRACT

Background: Perceived traumatic events occur often, and if initial responses are untreated, they may develop into post-traumatic stress disorder (PTSD), often seen in primary care. Past studies showed that early psychological interventions such as debriefing are not effective in preventing PTSD. This research tested effects of a memory structuring intervention + vagal breathing (MSI + VB) on perceived traumatic experience (PTE) and acute stress responses (ASR) and preliminarily investigated its mechanisms.

Methods: In Study 1 (N = 77), Study 2 (N = 38) and Study 3 (N = 25), patients attending emergency departments were randomized to the MSI + VB or supportive control. The MSI + VB trains people to perform deep breathing to activate their vagal nerve, and to restructure their trauma memory.

Anxiety (studies 1-3), pain (studies 1-2), heart rate (HR; Studies 1-3), PTE (Studies 2-3) and verbal fluency (reflecting frontal activation; Study 3) were obtained before and 1-2 hours after interventions. In Study 3, PTSD was assessed a month later.

Results: The MSI + VB reduced anxiety, pain and HR (Study 1), reduced PTE levels (Study 2), reduced anxiety, PTE and HR, and tended to lead to lower PTSD intrusive symptoms (Study 3). Controls evidenced reductions in anxiety and pain (Study 2) yet increased HR (Study 3). Finally, increased verbal fluency correlated positively with reduced PTE, across groups (Study 3).

Conclusions: The MSI + VB reduces PTE perceptions and ASR symptoms, and this may be partly explained by increases in verbal fluency, an index of frontal activity.

Introduction

Potentially life-threatening events (e.g., traffic accident, injury, natural disaster) may be perceived as traumatic, and this depends on the cognitive appraisal and fear responses people experience during or soon after exposure to such events. The pioneering study of Speisman et al. [1] already demonstrated the

causal role cognitive appraisals have in determining the stress response. More recent studies showed the role of appraisal with other methods and participants including affecting distress and emotion-modulating brain regions [2-5]. What causes an event to be perceived as traumatic is whether the person experiences feelings of fear and perceives threat and helplessness during or immediately following it (DSM-IV; APA, 1994). We

conceptualize perceived threat, helplessness and subsequent fear collectively as the perceived traumatic experience (PTE). The PTE may lead to psychophysiological reactions collectively termed the acute stress reaction (ASR). ASRs reflect a spectrum of responses including excessive sympathetic responses such as rapid heart rate (HR), emotional responses such as anxiety, cognitive responses such as confusion, and behavioral responses such as regressive behaviors (ICD-10). The natural course of post-traumatic responses following the ASR could include spontaneous remission, development of the acute stress disorder (ASD) up to one month later, and the subsequent development of post-traumatic stress disorder (PTSD) more than a month after the event. Both ASD and PTSD include the symptom cluster of intrusions, avoidance and arousal (DSM-IV, APA, 1994). Importantly, ASR symptoms were found to predict development of PTSD later [6,7]. One study on survivors of an earthquake found a very high incidence of ASR (85.3%), whereas 43% later developed PTSD [8]. Validating the ICD criteria, an incidence rate of 70% for ASR symptoms was found in the first 48 hours after an earthquake [9]. Other investigators propose lower incidence rates of psychological consequences of trauma. For example, the incidence of ASD was found to be between 5 and 20%, depending on the type of event and instruments used [10]. Differences in conceptualizing these entities, their measures and type and time since the event can explain the different prevalence rates. Regardless of the precise prevalence of ASR, these high figures call for developing brief interventions for psychological first aid. However, few interventions have been developed which are based on the neurobiology of trauma. The aim of the present research was to fill this gap.

In primary care, physicians often meet people after potentially traumatic events and also detect PTSD. A review of 27 studies on PTSD in primary care found a range of 2-39% of patients having PTSD. More worrying is that between 0-52% of these cases were ever detected by primary care physicians. These results call for better doctor education in detecting PTSD and in its early prevention [11].

Another potentially perceived stressful context is arrival at the emergency department (ED) for various reasons. A study done on Iranian patients found that 24.6% had severe levels of anxiety while 41.3% had severe stress levels [12]. While not all reasons for arriving at the ED are life threatening, the triggering medical condition, together with the great uncertainty about one's diagnosis, impending procedures and lack of information, could indeed induce various levels of perceived threat and helplessness or the PTE, which can then trigger the ASR [13].

Previous attempts at treating the ASR and in prevention of PTSD have often included various types of debriefing, which mostly have failed to prevent the ASD and PTSD [14-16]. Furthermore, reviews of the effectiveness of early interventions in preventing PTSD have concluded either that there is no evidence for their effectiveness or that only cognitive-behavioral therapy may prevent PTSD [17]. Similarly, a recent review of 19 intervention trials found no evidence for debriefing and some evidence for the effectiveness of early trauma-focused cognitive behavioral treatment [18]. Finally, a recent meta-analysis of

seven trials in women following childbirth found no evidence supporting the effectiveness of debriefing in preventing adverse psychological trauma responses [19]. The conflicting and mainly negative results of these studies may reflect three important issues in this field. First, many of the intervention trials were conducted days, weeks or even months after the first 6 hours following the perceived traumatic event, possibly a crucial "window of opportunity" for intervening [20]. Second, new types of interventions based on the neuroscience of trauma processing as explained below, have not been sufficiently evaluated and contrasted in large samples. Third, many of the studies reviewed above, did not include only those with ASR signs or people at risk for PTSD, which may have led to floor effects.

Taking a more neuro-scientific approach, studies have revealed that events perceived as traumatic are recalled in relatively more fragmented and somatic manners and are processed in a more automatic memory with reduced inhibitory control [21,22]. Furthermore, post-traumatic pathological conditions like PTSD are associated with trauma processing in brain regions reflecting little prefrontal activity and enhanced limbic (amygdala) activation [23]. Finally, symptom reduction in PTSD, following trauma-focused cognitive behavioral therapy, correlated with reduced connectivity between the amygdala and the insular cortex, while performing re-appraisal [24]. This possibly reflected less affective-somatic processing which was coupled with symptom reduction. Such findings call for an attempt to shift the processing of traumatic memories from fragmented and limbic-somatic dominance to more organized, cognitive and prefrontal processing. It is thus possible that interventions need to change from narrative-based and emotion-focused treatments to those that aim to shift the event processing to frontal and self-regulation dominance. This may then provide individuals greater control over their memories and thus reduce the ASR and ultimately, prevent PTSD and enhance recovery.

Rationale and evolution of the memory structuring intervention (MSI)

Following the above, a neuroscience-based intervention, the memory structuring intervention MSI, was developed to try and achieve the processing shift from an implicit, limbic, somatic/emotional and disorganized trauma processing manner to a more explicit/controlled, frontal, verbal and organized processing manner [24]. In the MSI, patients describe their event, with each reported emotion or sensory term (e.g., fear, pain) eliciting the counselor to ask the patient to *verbally elaborate* (labeling) and give a *reason* for that sentiment (causality). Verbally labeling negative emotions (matching faces to words), rather than processing them in a sensory manner only (matching faces to faces), was found to activate the prefrontal cortex [25]. In addition, use of causality predicts symptom improvement in written trauma disclosure studies [26]. Another element of the MSI is restructuring the order of the event because chronological organization was found to be related to symptom reduction as well, which is an antidote to cognitive confusion often seen during the ASR [27]. After the patient completes telling the story once, the counselor reconstructs the story *chronologically*,

verbally *labeling* emotions and sensations, and provides their *causal reasons*. The patient is finally asked to repeat the story in its new structured manner - Chronologically organized, causally linked and with labeled emotions. Initially, in a small-scale study, the MSI prevented PTSD symptoms better than a supportive listening control [28]. However, in a subsequent and larger study, the MSI was found to be non-beneficial for men and effective for women [29]. It is possible that the MSI did not treat an important part of the ASR, namely sympathetic hyper-arousal. Indeed, a meta-analysis of 122 studies suggests that PTSD is associated with elevated psychophysiological responses, particularly heart-rate (HR) and skin conductance, both manifestations of the sympathetic nervous system (SNS) [30]. Furthermore, particularly in males, excessive sympathetic activity predicts negative mental sequela following trauma [31].

As mentioned above, the ASR includes excessive sympathetic activity. In contrast, one can activate the vagus nerve, a major branch of the parasympathetic system, which normally inhibits sympathetic activity [32]. This can be achieved rapidly and simply by slow and paced vagal breathing [33]. Several additional reasons exist for activating the vagus nerve after trauma, including reduction of inflammation and increasing frontal over limbic activity, to alter the reversed pattern seen in acute stress and later in PTSD [34-37]. Indeed, systematic vagal breathing alone was found to reduce PTSD symptoms [38]. For these reasons, vagal breathing (VB) was added to the MSI, to possibly help both men and women. However, the effects of combining the MSI with VB, on ASR and sympathetic symptoms, have not been tested yet.

Purpose of studies & hypothesis

This line of research included three studies which aimed to test the main hypothesis that the MSI with VB could reduce the PTE and ASR symptoms, better than a supportive-listening control intervention. This was part of a larger project examining various cognitive intervention methods in the ED. In all studies, we compared the MSI + VB to supportive listening (control). Study 1 examined these issues in relation to anxiety, heart-rate and pain, symptoms commonly seen in primary care as well. Study 2 additionally examined this in relation to the PTE, using a new measure, as described below. Finally, Study 3 additionally and preliminarily examined the hypothesized mechanism underlying the MSI + VB, namely frontal activation, using a brief neuro-psychological proxy measure, suitable for the ED context.

Study 1

Participants

Four hundred and seventy five patients, who were admitted to the emergency department (ED) of a hospital in northern Israel, were assessed for eligibility. Of these, only 124 (26%) of patients participated in the larger study, of whom $n = 38$ were randomized to the MSI + VB and $n = 39$ to the control condition (the rest to another intervention we shall describe elsewhere). The trial was conducted during January-April, 2010. Patients, who had an acute physical trauma related to orthopedics or internal medicine, took part. Patients with the

following criteria were excluded: 1. Loss of consciousness or head injury; 2. Known pregnancy; 3. Past psychiatric history or present psychotic symptoms observed at the ED; 4. Below age 18 years. The study was approved by the Helsinki ethics committee of both the hospital and of the Tel-Hai College.

Procedure and design

After obtaining approval from the ED staff, patients were approached by 3rd year social work students trained in stress and trauma interventions [39]. Patients were asked to take part in a study on prevention of negative emotional responses for patients admitted to the ED. Patients then provided their written informed consent and were assessed for anxiety, pain and HR before and 1-2 hours after the interventions, to assess the ASR. The study employed a randomized-controlled design. Randomization to the MSI + VB or control conditions was done with a computer-generated list of numbers, allocated to consecutive patients.

Measures

Background information: It included patients' gender, age, ethnicity, primary reason for admission (orthopedic, internal medicine), and whether they had already been treated by a physician prior to seeing the intervening student. Being treated by a physician or not, before receiving the intervention, was thought to possibly affect patients' immediate reactions (state of calmness, pain level), which could influence the ASR as well.

ASR measures: ASR measures included anxiety, pain and heart-rate (HR). These three symptoms reflect part of the symptoms of the ASR (anxiety, excessive arousal and pain; ICD-10), and pain was also thought to be relevant to patients attending the ED for physical reasons, as in the present study. In addition, acute pain is an independent predictor of PTSD symptoms [40]. The anxiety scale represented the distress, perceived pain represented the possible injury or underlying morbidity and potential interference due to the health problem or event, while HR represented the sympathetic nervous system response. Anxiety was assessed with the six-item state-anxiety inventory [41]. In the present study, the internal reliability of the anxiety scale was adequate (Cronbach's Alpha = .73). In addition, pain was assessed using a single 100mm visual analogue scale (VAS) with the anchors 1 = no pain, and 10 = maximal level of pain. HR was measured by a blood-pressure monitor used by the ED staff.

Interventions

Interventions were given by senior students of social work from the Stress and Trauma Studies program at the Tel-Hai College, Northern Israel. Students were trained and received clinical supervision, to ascertain uniformity and adherence to the intervention protocols and to solve unexpected problems. All interventions were provided individually, in the ED with closed curtains, to respect patients' privacy, as approved by the ethics committee.

Memory structuring intervention + vagal breathing (MSI + VB): This protocol included the following stages. 1. Vagal breathing (VB): Patients were guided in VB by doing

approximately 6 breaths/min by inhaling (counting 1-4), holding (counting 1-2) and exhaling (counting 1-7), 6 times, via the nose; 2. The MSI was performed as described above, and included the counselor helping the patient to chronologically structure their memory, label their feelings and sensations and give *reasons* and rationale for such experiences. This lasted approximately 25-30 minutes. The protocol was in line with that of Gidron et al. [42].

To technically simplify the MSI part of the intervention for the counselors, patients first explained the triggering event which brought them to the ED. Counselors then asked them to repeat it chronologically, then to label their feelings and body sensations and then to provide causal links to the story's segments and to their feelings and sensations (e.g., I had pain because my leg broke). Finally, the patients repeated the entire story in chronological order, labeling sensations and feelings and providing causal links, in an integrative manner.

Supportive listening and emotional ventilation (control): Here, patients were encouraged to talk about the triggering medical condition, their thoughts and feelings concerning this condition, and the counselor provided support and empathy, in an unstructured manner. This controlled for attention, empathy and contact with the counselor, thought to be non-specific aspects of any clinical intervention.

Statistical analysis

First, group equality at baseline was tested, using t-tests for continuous data and chi-square tests for categorical data. Subsequently, paired t-tests on the three outcome measures (anxiety, pain, HR) were conducted within each condition separately (i.e., MSI + VB, control), since we only focused here on two measurement points: Pre-treatment and 1-2 hours later.

Results

Patients' scores on all baseline variables were not statistically significantly different between both groups on all continuous and categorical variables, including baseline levels of outcome variables (all p s > .05). These findings support the group equality at baseline and the success of the randomization procedure. Table 1 depicts the basic characteristics of the study sample and Table 2 depicts the scores on the outcome measures, for each intervention group separately.

In patients assigned to the control condition, no significant reductions were found in pain ($t(27) = .65$, $p > .05$), HR ($t(23) = 1.53$, $p = .14$), or in anxiety levels ($t(28) = 1.61$, $p > .05$), compared to baseline levels. In contrast, for patients receiving the MSI + VB, significant reductions were seen in pain ($t(26) = 2.38$, $p < .05$), HR ($t(23) = 4.05$, $p < .001$), and anxiety levels ($t(26) = 2.19$, $p < .05$), compared to baseline levels.

The sample sizes were too small to conduct meaningful analyses by gender as well. However, a similar pattern was found in each gender (data not shown), with no significant changes seen on any outcome in men or women in the control group (all p s > 0.05). In contrast, in the MSI + VB group, men evidenced significant reductions in HR and anxiety ($p < .05$) and showed a trend with pain as well, while women only had

significantly lower HR levels after treatment ($p < 0.05$).

Discussion

Results of Study 1 revealed that patients assigned to the experimental MSI + VB condition showed significant reductions on anxiety, pain and HR, while controls did not evidence such changes. A similar pattern was seen when splitting by gender, with an even better response in men, but due to small sample sizes in each sample, we view these sub-group analyses by gender as exploratory. These results support our hypothesis of the relative greater benefit from undergoing the MSI + VB compared to receiving support and empathy alone. Furthermore, these results support those of Gidron et al. [43] and Gidron et al. [44] in relation to PTSD, but extend them to the early, ASR phase, and to an objective outcome, namely HR. In addition, this study added to the MSI the VB, to possibly overcome gender differences found by Gidron et al. [44]. Our preliminary and exploratory analyses by gender propose that a similar response was seen in both genders, and possibly a more favorable response in men than in women. These results are important due to the crucial need to target the ASR in a short time window of opportunity [45]. In order to replicate and extend the results of Study 1, Study 2 was conducted. It additionally included as an outcome a newly developed direct measure of the perceived traumatic experience, the triggering event, in addition to the symptoms assessed in Study 1.

Study 2

Introduction: Study one found that the MSI + VB reduced levels of pain, HR and anxiety in patients arriving to the ED for acute physical health problems. In contrast, the emotional ventilation and support listening control condition did not yield such an effect. In Study 2, we added a new measure of perceived traumatic experience (PTE) to specifically examine the effects of the MSI + VB on this perception of the triggering event, given the crucial role that appraisal of the event has on stress responses [45-48].

Method

Participants

Forty-one patients arriving at another hospital in North of Israel, took part in this study. The inclusion and exclusion criteria in Study 2 matched those of Study 1. This study was also approved by the second hospital's ethics committee.

Measures

Background information: This included patients' age, gender, and main reason for arriving to the ED (internal medicine or orthopedic).

Acute stress symptoms: Three types of measures were included. First, to assess directly the perception of trauma severity, a newly developed scale whose validation will be reported elsewhere (Farchi & Gidron, manuscript in preparation) was used. This scale, the perceived traumatic experience (PTE) scale, refers to the initial appraisal and response concerning the triggering event and includes fear, perceived threat and helplessness. These symptoms and signs were thought to lead

to other symptoms within 48 hours from the triggering event. Patients were asked to rate each of these three perceptions on a 1-5 scale of intensity (1 = Very little, 5 = Very Much). In its validation, scores of this scale were positively correlated with levels of heart rate and state anxiety, and predicted PTSD symptoms assessed a month later (Farchi & Gidron, manuscript in preparation). Second, we used the same 6-item state anxiety scale for assessing anxiety, as in Study 1 (Marteau et al., [49]) and also asked patients to rate their pain levels, as in Study 1. Finally, a measure of HR was also included in Study 2, however, because of missing data for large segments of the sample, this outcome will not be reported.

Interventions

Study 2 included the MSI + VB and the control intervention conditions. In order to facilitate the counselors' performance of the MSI and to better complete missing aspects of the memory of the triggering event, patients were asked to repeat the story several times and to fill in gaps where missing information was present. Regardless, the principles of chronological organization, causality between the event segments and emotional/sensory labeling were maintained. As in Study 1, controls described their triggering event and received empathy and supportive listening only.

Design and procedure

As in Study 1, this trial was a randomized controlled trial. Participants arriving at the ED were invited by the medical staff to take part in this study. Upon providing their informed consent, they were randomized to the MSI + VB or to the control condition. Their PTE, anxiety and pain levels were assessed before and approximately one hour after their respective interventions.

Statistical analysis

Tests for equality of groups at baseline and changes in the three outcomes (PTE, anxiety and pain) followed those of Study 1.

Results

Table 2 shows the results of Study 2. As can be seen, in the MSI + VB group, only PTE scores significantly decreased over time ($t(16) = 2.22, p < 0.05$). In contrast, in the control condition, pain levels ($t(20) = 3.32, p < 0.005$) and anxiety levels ($t(20) = 1.78, p < 0.05$) significantly decreased over time. We did not perform sub-group analyses by gender due to the small sample sizes.

Discussion

In Study 2, the experimental condition (MSI + VB) had a beneficial effect on the main and new study outcome, PTE symptoms, while the control condition did not affect this outcome. In contrast, controls evidenced significant reductions in pain and anxiety, while the MSI + VB group did not. These results do not fully replicate those of Study 1. Upon inspecting the baseline levels of anxiety in Studies 1 and 2, we could see that patients in Study 1 (in which the MSI + VB alone reduced all outcomes) had considerably higher levels of baseline anxiety

than those in Study 2, across groups. This could have partly explained the inconsistent results between both studies. When running further analyses in Study 2 by splitting the sample into patients with low and high baseline anxiety (data not shown), the MSI + VB was beneficial in reducing PTE levels only for patients with high baseline anxiety. In contrast, the control condition reduced only anxiety levels in those with initially high anxiety levels. To overcome these issues and to prevent any possible "floor effect", which may have occurred in Study 2, Study 3 deliberately included patients with high stress levels upon admission to the ED, as described below.

Study 3

Study 1 found that the MSI + VB was effective in reducing ASR symptoms and Study 2 found it to reduce the PTE scores alone, in people arriving at the ED. Study 3 aimed to extend these findings by preliminarily examining the underlying mechanisms thought to account for the above effects. For the MSI, its major hypothesized mechanism is the shift in processing from a limbic (amygdala), somatic, and emotional processing manner, to a frontal, cognitive and verbal manner of processing the triggering event [50]. The addition of vagal breathing also serves to increase frontal over limbic activity (Dietrich et al., [51]) and to possibly increase connectivity between the amygdala and the frontal cortex (Sakaki et al., [50]). But in both Studies 1 and 2, such processing shift was not measured, nor was its relationship to clinical improvement examined. Furthermore, in studies 1 and 2, patients were not screened before the intervention, to include only those with initially high levels of distress, and this could have potentially resulted in "floor effects". Indeed, high levels of initial ASR is a risk factor for developing PTSD later. Finally, studies 1 and 2 did not present any longer term effects of the interventions on PTSD symptoms. The purpose of Study 3 was to fill in these gaps. We included a brief measure of frontal activity indexed by verbal fluency to begin to examine the underlying mechanism of the combined MSI + VB intervention. Second, we only included patients who showed a certain elevated level of stress upon hospital admission. This was done in order to prevent a "floor effect". Third, we used a standard measure of PTSD administered a month after the interventions.

Method

Participants

In this preliminary study, 25 patients arriving at a main ED hospital in Brussels, Belgium, voluntarily took part in the study. One patient's HR scores were excluded because of baseline and especially post-treatment HR levels which were excessively higher than the tachycardic cut-off of 100bpm (HR = 150bpm), in the experimental group. Patients' age ranged from 18-68 (mean (SD) = 38.9 (14.3) years), 62.5% were women and 37.5% were men. The inclusion criteria included: 1. Experiencing a traffic accident, or physical assault, or being exposed to a threatening event that happened to a significant other; 2. Aged 18-70 years, 3. No loss of consciousness, 4. Scoring high (>5) on a visual analogue scale (VAS) of current stress, during two consecutive time periods 30-60min apart, or, reporting an increase on this

scale between the two measurements. Consistent elevations on such a scale were found in a past study to predict PTSD.

Instruments

As in Studies 1 and 2, background data included patients' age, gender, reason for arriving at the ED, and past psychiatric history (yes/no). The study included four outcome measures. First, to assess PTE symptoms, the 3-item PTE scale (Farchi & Gidron, manuscript in preparation) was used, as described above. It asks about levels of perceived threat, fear and helplessness. Second, to assess state anxiety, the 6-item state anxiety scale was used. Third, to objectively measure the stress responses, we measured patients' HR. To briefly (and indirectly) measure patients' frontal activity in a simple and rapid manner, suitable for the ED context, we used a 1-minute verbal fluency test. In this test, patients had to provide as many words as possible beginning with a certain letter. To prevent a learning effect, different letters were used pre and post-intervention, counterbalanced in order. Such tests were found in past studies to reflect prefrontal cortical activity. Finally, we used the civilian checklist version of the PTSD scale (&&&). This scale includes 17 items reflecting the clusters of intrusions, avoidance and arousal. Each item is ranked on a 0 (never) to 3 = (always) frequency response scale. The PTSD scale was administered approximately a month after the patient was in hospital, by a researcher who was blind to patients' group status.

Interventions

As detailed in Study 1, the intervention here combined both the MSI and VB. Controls only described their event and received support and empathy, as described above. Both interventions were administered by a trained senior medical student.

Procedure

After arriving at the ED, candidate patients were identified by the medical staff. Patients meeting the above inclusion criteria and scoring > 5 on the VAS stress measure over two consecutive measures (or showing an increase over time) were asked to take part in the study, and provided written informed consent. The study was approved by the ethics committee of the university hospital, Brussels. Thereafter, patients were randomized to the combined MSI + VB or supportive listening control conditions, using computer-generated random numbers. All four measures were administered before and approximately 60 min after their allocated intervention. The PTSD scale was administered by phone approximately a month after the interventions, by a researcher who was blind to patients' group status.

Statistical analysis

Equality of groups at baseline after randomization, was examined by t-tests for continuous data and chi-squares tests for categorical data. Paired t-tests were then performed within each group separately, on all study outcomes, as done in Studies 1 and 2. Finally, to gauge at the hypothesized frontal activation mechanism, we examined the correlations between change in verbal fluency (post-treatment – pre-treatment) with changes

in the PTE, anxiety and HR (pre-treatment – post-treatment), using partial correlations, statistically controlling for condition (MSI + VB versus control). These partial correlations examined the associations between improvement in “frontal” activity with improvement in clinical outcomes, beyond patient group. Single-tailed statistical analyses were used because our hypotheses were single tailed.

Results

Concerning group equality at baseline, no significant differences were found between groups all study measures. Thus, the randomization procedure was successful.

Table 1 shows results of all 4 study outcomes measured at baseline and post-treatment for both groups separately. Within the MSI + VB group, patients reported significantly lower levels of PTE scores ($t(12) = 3.5, p = 0.005$), anxiety ($t(12) = 2.2, p = 0.05$) and HR ($t(12) = 2.4, p < 0.05$) at post-treatment than at pre-treatment. However, no significant changes were seen on verbal fluency ($p > 0.05$). In contrast, controls evidenced a significant worsening of HR from pre- to post-treatment ($t(8) = 3.2, p < .05$). No other significant changes were observed in controls (all $ps > 0.05$). We observed one additional finding: At post-treatment, the experimental group scored significantly higher on verbal fluency than controls ($t(20) = 2.3, p < 0.05$).

Finally, patients in the MSI + VB group tended to have significantly lower PTSD intrusion scores ($t(4.8) = 1.65, p < 0.09$) than controls. However, no group differences were found for the subscales of avoidance and arousal or for the full PTSD scale (see Table 1). It is important to note however that only $n = 13$ patients took part at the 1-month follow-up.

To obtain preliminary insight into the mechanisms of these observed effects, correlations between improvements in verbal fluency and improvements in the other outcomes were examined. Because the sample of each group was small, these correlations were performed in the full ($N = 24$) sample, controlling statistically for condition (MSI + VB vs. control). Importantly, improvements in verbal fluency significantly and positively correlated with improvement in PTE scores ($r = 0.56, p = 0.008$; see Figure 3). However, changes in verbal fluency were unrelated to improvements in HR ($r = 0.13, p > 0.05$) or to improvements in anxiety ($r = 0.10, p > 0.05$), controlling statistically for condition.

Discussion

Results of Study 3 show that more improvements were seen in the combined MSI + VB group than in controls. Specifically, only in the MSI + VB condition, were there significant improvements on PTE, HR and anxiety, while in controls there was only worsening in HR levels. Furthermore, trends were seen for lower levels of the PTSD subscale of intrusions in the MSI + VB group than in controls. Together, these results support those of Studies 1 and 2, and extend them to a group with initially high acute stress, in another country. Furthermore, while no changes were seen on verbal fluency over time within each group, at post-treatment, the MSI + VB condition scored significantly higher on verbal fluency than controls. Of greatest

importance, improvement in verbal fluency significantly and positively correlated with improvements in PTE, independent of effects of condition. This result provides for the first time, to the best of our knowledge, preliminary evidence for the importance of frontal activation (as indexed here by verbal fluency) in observing short-term clinical changes in outcomes of relevance to the ASR. These results and those of Studies 1 and 2 will now be elaborated upon in the General Discussion.

General Discussion

This series of three studies tested the effects of an extended memory structuring intervention (MSI) by adding vagal activating breathing (VB), and compared it to supportive listening (control). These were all done in people arriving at the ED in three hospital settings, in two different countries (Israel and Belgium). The results of these three studies showed a relatively consistent benefit for the extended MSI + VB intervention. Specifically, Studies 1 and 3 show significant reductions in anxiety and HR over time in the MSI + VB group, but not in controls. Studies 2 and 3 show significant reductions in PTE over time in the MSI + VB condition, but not in controls. In contrast to our hypotheses, Study 2 showed significant reductions in anxiety and pain in controls, but not in the MSI + VB group. Study 3 also showed that increases in verbal fluency significantly and positively correlated with reductions in PTE, statistically controlling for intervention condition. Finally, Study 3 revealed tendencies for lower PTSD intrusion scores in the MSI + VB group than in controls. Together, these studies point at a general positive effect of the MSI + VB compared to the supportive listening control condition, though not on all outcomes.

These results support those of Gidron et al. [43] and Gidron et al. [44] in relation to the effects of the MSI alone on prevention of PTSD symptoms, especially in women. However, in the present studies, VB was added to the MSI to reduce the excessive sympathetic activity often seen in traumatized patients. Indeed, in a preliminary analysis that was performed in Study 1 in each gender separately, similar benefits from the MSI + VB were observed in men and women. The results of the three studies presented here extend those past ones to the PTE and

the ASR. These outcomes, unlike PTSD, reflect the immediate symptoms after a potentially traumatic event. We thus were able to alter the appraisal of the traumatic event (PTE), which could have tremendous impact on multiple outcomes such as distress and brain activity in regions important for developing PTSD such as modulating the amygdala. The results of Study 3 also show trends for reducing PTSD intrusion symptoms, in line with Gidron et al. [43], however failed to reach statistical significance due to the small sample size at follow-up.

Importantly, the results of Study 3 provide preliminary evidence for the mechanism of the MSI. The extended MSI (MSI + VB) resulted in higher verbal fluency compared to controls, at post-treatment, an outcome which indexed frontal activity. Furthermore, improvements in verbal fluency significantly and positively correlated with reductions in PTE scores, statistically controlling for group status. These results support the hypothesized mechanism of the MSI + VB, where in order to reduce the ASR and to possibly prevent PTSD, a processing shift may need to occur, from a limbic, emotional and somatic processing, to a frontal, verbal and cognitive processing manner (Gidron et al. [43]). However, these results need to be taken with caution since our index of frontal activity was a simple neuropsychological test only, and since these correlations were seen in both groups together, not only in the MSI + VB group.

The improvements in pain and anxiety seen in controls in Study 2 but not in the MSI + VB group were unexpected and do not support the findings of Study 1 and Study 3 showing a benefit for the MSI + VB on such outcomes. These results could partly reflect the fact that the patients in Studies 1 and 3 had relatively higher levels of baseline distress than in Study 2. It is possible that when levels of initial distress are low (as in Study 2), there is less need for a cognitive-physiological type of emotional regulation provided by the MSI + VB, and thus, support, empathy and attention may be sufficient (see Figures 1-3).

The results of Study 3 are unique also because reductions in PTE were observed in patients with initially high stress levels. This is important because such high baseline stress was found to predict PTSD. Furthermore, though not significant, the MSI +

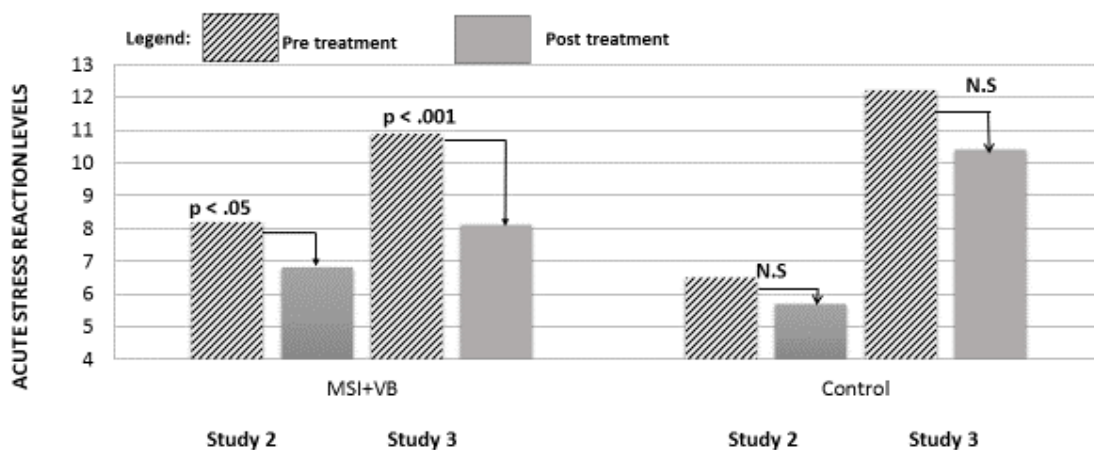


Figure 1. Effects of the MSI + VB versus control on acute stress responses in Studies 2 and 3.

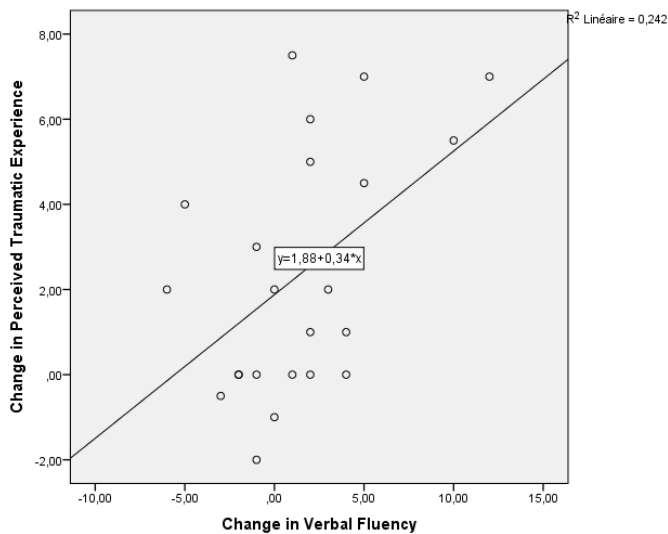


Figure 2. Scatterplot and correlation between increases in verbal fluency and reductions in acute stress reactions in Study 3.

VB group tended to have lower PTSD intrusion symptoms than controls after 1 month. These results can be beneficial for people providing psychological first aid because medical personnel including family physicians can provide the MSI + VB as one possible evidence-based treatment. These could be given to ED patients or to patients attending primary care in the 48 hours post a traumatic event, who show consistently high stress levels. This intervention can be easily learned and implemented in clinics as well as be given over the phone, making it feasible for provision to larger segments of the population in case of a mass disaster such as natural disasters or terrorist attacks.

To summarize each study's major contribution, Study 1 showed a consistent benefit of the MSI + VB for all studied outcomes (pain, anxiety and HR), while Study 2 showed that the MSI + VB clearly reduced PTE levels. Finally, Study 3 showed that the MSI + VB reduced both PTE and HR levels, it may have prevented some aspects of PTSD in the longer term, and it preliminarily revealed new and significant associations between improvements in verbal fluency (proxy measure of frontal activity) and reductions in the ASR.

However, this series of studies had a few limitations. First, the sample sizes were relatively small, though Studies 1 and 2 did exceed those of Gidron et al. [43,44]. Second, no objective neuroimaging measures were included to actually measure brain activity, to directly test the mechanism hypothesized to underlie the effects of the MSI + VB. However, use of a simple neuropsychological measure (verbal fluency) which reflects frontal activity, was seemed as a valid compromise suitable for the ED context. Third, we did not have a control group which included VB alone, not enabling us to determine the effects of VB only on the outcomes. However, we conceived the combination of MSI + VB as an important therapeutic entity, which complement and add to each other. In this combination, the MSI is expected to restructure the traumatic memory and possibly shift brain dominance from limbic to frontal processing, while the VB is expected to induce neurophysiological modulation of the sympathetic response and to possibly help increase connectivity between the amygdala and the frontal cortex.

Fourth, with future larger samples, one should reexamine the therapeutic effects with more rigorous statistical analyses using analysis of variance, statistically controlling for baseline values of each outcome. Finally, no measure of vagal activity (heart-rate variability) was used to ascertain increases in this nerve's activity by VB. However, we did observe reductions in HR (sympathetic activity) in Study 1 and in Study 3, both which are in line with (parasympathetic) vagal nerve activation.

Future studies need to address these limitations, by increasing the sample sizes and including neuroimaging tests, a VB condition only, and measures of vagal nerve activity. Furthermore, future longer follow-ups are needed which will also include measures of PTSD and resilience, to examine the long-term effects of the MSI + VB intervention. These would substantiate the results observed in the present studies. Nevertheless, the relative consistency of results, across hospital settings and two countries, together with future additional confirmatory evidence, proposes that the MSI + VB may eventually constitute a new neuro scientifically-based and evidence-based intervention which can be used as a psychological first aid intervention in the immediate aftermath of potentially traumatic events.

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ADDRESS FOR CORRESPONDENCE:

Yori Gidron, Chair of psychooncology, Scalab, Lille 3 univ, and Siric Oncolille, Lille, France, Tel: +33 32041 6392; Email: yori.gidron2@univ-lille3.fr