Emotional anticipation rather than processing is altered in patients with vasovagal syncope

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Objective: To investigate whether the electrocortical activity underlying the anticipation and processing of emotional stimuli is enhanced in individuals with recurrent episodes of vasovagal syncope (VVS).

Methods: Fifteen fainters and 15 age-matched healthy controls were presented a S1–S2 task, where the content of high-arousal pleasant and unpleasant, and neutral pictures (S2) was forecasted by word cues (S1). Stimulus Preceding Negativity (SPN) amplitude during the S1–S2 interval was computed as a measure of affective anticipation. The event-related potentials (ERPs) to S1 and S2 were measured to assess the processing of emotional warning stimuli and pictures.

Results: Relative to controls, fainters showed smaller P300 to warning cues anticipating emotional (and, particularly, unpleasant) pictures, and smaller SPN during anticipation of unpleasant pictures. No differences between groups were found with regard to ERP amplitudes during picture processing.

Conclusions: These results suggest that the anticipation, rather than the processing, of aversive stimuli is altered in syncopal patients.

Significance: The reduced cortical anticipation in fainters might reflect the use of non-adaptive emotion regulation strategies for reducing the impact of upcoming highly arousing (and, particularly, of unpleasant) events.

1. Introduction

Neurally mediated or vasovagal syncope (VVS) is a syndrome characterized by the co-occurrence of vasodilatation (“vaso”) and vagally-mediated bradycardia (“vagal”), leading to hypotension and transient loss of consciousness and postural tone as a result of cerebral hypoperfusion (e.g., Van Lieshout et al., 1997; Benditt and Goldstein, 2002). VVS is the most common cause of fainting, accounting for up to 40% of syncopal events evaluated in the outpatient setting (Fenton et al., 2000).

VVS ensues when the balance between the mechanisms regulating blood pressure is temporarily disrupted, i.e., excessive venous pooling to the lower extremities due to decreased peripheral resistance is not counterbalanced by a compensatory rise in cardiac output. Vasodilation and bradycardia, instead of compensatory vasoconstriction and tachycardia, lead to hypotension and loss of consciousness (e.g., Van Lieshout et al., 1997; Fenton et al., 2000; Hainsworth, 2004).

Recurrent syncopal events of vasovagal nature may occur in otherwise healthy individuals in response to a variety of determinants. Although the proposed classifications may vary, it has been recognized that the potential triggers of VVS can be distinguished into physical factors, i.e., orthostatic stress and specific stimulation...
of sensory or visceral afferents, and psychological determinants, such as emotional distress, intense fear, sudden and severe painful experiences, or the sight of blood (see Mosqueda-Garcia et al., 2000; Moya et al., 2009). Because emotional factors are often pre-eminent, VVS is often referred to as “emotional fainting” (see Hamer and Bray, 2005). A central, rather than peripheral, neural pathway is believed to play a key role in the activation of emotionally-mediated syncope. This pathway would originate in neocortical and limbic structures of the central nervous system implicated in the evaluation and interpretation of emotional information, and descend from the cortico-hypothalamic centers to the brainstem autonomic nuclei that regulate cardiac and vasomotor activity through sympathetic and parasympathetic efferents (Kaufmann and Hainsworth, 2001; Kinsella and Tuckey, 2001; Diehl, 2005).

At least three different, but partially overlapping, interpretations of the psychological mechanisms involved in VVS have been put forward. According to Graham et al. (1961), VVS is a response to events which are likely to elicit anxiety. In the presence of a threatening situation, an emotional response involving subjective anxiety and increases in heart rate and blood pressure is initially elicited. With cessation of the threat, relief from anxiety is accompanied by a sudden and dramatic drop in both cardiovascular parameters, and fainting may ensue as a consequence.

Drawing from animal models, Engel (1978) ascribed the breakdown of the homeostatic mechanisms that normally maintain the reciprocal relationships between cardiovascular processes and somatic needs to the presence of an irresolvable conflict between contrasting action tendencies, namely fight-flight and conservation–withdrawal. Indeed, VVS typically ensues in situations characterized by uncertainty as to whether active escape or giving up is the most adaptive response to an impending (real or fantasized) threat or danger.

Sledge (1978) examined the psychological antecedents of VVS, and showed that fear, anxiety and feelings of helplessness precede fainting episodes when a threat to the body (e.g., receiving an injection or other medical procedures) or psychological harm (i.e., public ridicule and mortification) was expected in social situations. In all cases, the subject’s interpretation of the social context, and the feeling that “giving in” to the perceived threat is necessary since active countermeasures would be socially inappropriate, highlight the role played by real or fantasized social pressures in the conflict between preparation for action and helpless resignation to the threat.

To summarize the psychosocial factors accompanying or preceding emotional fainting appear to include fear of bodily or psychological harm, anxiety, helplessness, and a sense of resignation to the perceived threat. Surprisingly, while altered anticipatory processing has been recognized as a critical component of some mental disorders, such as anxiety disorders (Barlow et al., 1996), none of the above-mentioned explanations of emotional fainting specifically emphasizes the role played by anticipation. Anticipation has a perceptual connotation, in that the individual awaits the occurrence of a stimulus. Also, anticipation is an active process, because the organism might be behaviorally passive while waiting for perceptual input, but specific brain areas are already active before its actual delivery. The functional role of anticipatory processes is therefore to organize a set of changes in the state of the organism that ultimately allow for a more efficient interaction with expected upcoming stimuli (van Boxtel and Böcker, 2004). However, when brain activity underlying anticipation of relevant stimuli is either exaggerated or abnormally low (as has been observed in individuals with anxiety disorders of several types, depending on the specific experimental conditions used to investigate anticipatory processes; e.g., Proulx and Picton, 1984; Korman and Ryan, 1980; Kimble et al., 2004), the individual’s behavior becomes no longer flexible and adjusted to future environmental demands. On this basis, it is reasonable to hypothesize that in predisposed individuals the cascade of psychological events that culminates in fainting might not only involve abnormal responding, but also altered anticipatory responses to emotionally relevant or, more specifically, unpleasant situations.

In research using the event-related potentials (ERPs) to investigate the neural correlates of psychological processes, anticipation is usually studied by means of experimental paradigms that elicit a slow cortical potential, the Contingent Negative Variation (CNV; Walter et al., 1964; Brunia and van Bokel, 2001; van Bokel and Böcker, 2004). The CNV develops during the time interval between a warning signal (S1) and an imperative stimulus (S2), to which the subject is required to respond (e.g., with a button press). Importantly, a motor response to S2 is a sufficient, but not a necessary condition to elicit a negative potential between S1 and S2 (Brunia, 1988; Chwilla and Brunia, 1991; van Bokel and Brunia, 1994). Non-motor CNV is termed Stimulus-Preceding Negativity (SPN). The SPN has been observed during the anticipation of stimuli with both positive (e.g., erotic pictures; Howard et al., 1992) and negative valence (e.g., a mild electric shock, or unpleasant slides; Lumsden et al., 1986; Rockstroh et al., 1989), and is therefore considered to reflect affective-motivational anticipation (Brunia et al., 2011). Irrespective of valence, the amplitude of the SPN is significantly larger preceding high rather than low arousal pictures, indicating that the SPN is modulated by the intensity of the motivational engagement ascribed to affective stimuli (Poli et al., 2007). The SPN preceding affective stimuli in picture-anticipation tasks shows a frontal maximum, that is particularly evident when the forthcoming stimulus is negative in valence (see Takeuchi et al., 2005). Importantly, cortical negativity is larger before S2 stimuli that are expected to be followed by aversive outcomes (Regan and Howard, 1995; Amrhein et al., 2005), suggesting that it might represent a psychophysiological indicator of expectancy of negative consequences.

In the present study, we investigated emotional anticipation in individuals with recurrent episodes of VVS and healthy controls, using a paradigm where the emotional content of high-arousal pleasant and unpleasant, and neutral pictures (S2) was signaled by congruent word stimuli (S1). The amplitude of the SPN preceding the onset of S2 was measured as an index of emotional anticipation. Moreover, the amplitudes of the P300 and the following Late Positive Potential (LPP) of the ERPs to word and picture stimuli were computed as classic indices of attentional engagement with emotional stimuli (Palomba et al., 1997; Cuthbert et al., 2000; Schupp et al., 2000).

Because in daily life emotional situations can trigger fainting episodes in patients with recurrent episodes of VVS, and considering that anticipating negative consequences from emotional stimuli is reflected in larger electrocortical negativity during anticipation (Amrhein et al., 2005), the hypothesis could be formulated that SPN in anticipation of high-arousal emotional stimuli would be enhanced in syncopal patients as compared with healthy individuals. Syncopal patients were also expected to deploy more attentional resources to emotional stimuli due to their relevance as major trigger factors. This would be reflected in larger P300 amplitude to emotional word stimuli and larger P300/LPP amplitude after emotional picture onset.

2. Methods

2.1. Participants

The study group consisted in 15 consecutive patients, aged 22–53 years, with recurrent syncopal episodes, referred to the Syncope Unit of the Cardiovascular Department of the Umberto I Hospital (Venice-Mestre, Italy) for head-up tilt testing evaluation. In order to be included in the study sample, patients had to meet the
following inclusion criteria: age over 18 years; recurrent syncopal episodes, with at least two episodes in the last 12 months; positive head-up tilt testing with vasovagal response and reproduction of spontaneous symptoms; negative diagnostic work-up for other causes of syncope. Exclusion criteria were the following: presence of structural and/or functional heart diseases, alcohol or drug abuse, declared psychiatric disorders, treatment with psychiatric drugs. The presence of blood-injection-injury fears was a further exclusion criterion, as such content-specific fears may confound possible experimental effects of the unpleasant stimuli used in this study (see below).

All patients were diagnosed with vasovagal reflex syncope, and reported strong emotions, fear or pain as the main triggers of syncopal episodes. Four patients also reported prolonged standing as a partial loss of postural tone accompanied by symptoms of imminent syncope, without complete loss of consciousness.

The two groups did not differ significantly for age (t(28) = −1.37; p = .17).

The demographic and clinical characteristics of patients and controls are reported in Table 1.

### 2.2. Stimuli and procedure

After signing a written informed consent, participants were seated in a comfortable armchair in a sound-attenuated, dimly-lit room at a distance of 1.2 m from the computer screen. During the entire procedure, they were monitored by a closed-circuit video camera. The task involved the presentation of a word (S1), 1 s in duration, that signaled the content of a picture (S2) presented after 5 s and lasting 5 s. Three words (Italian translation of "erotic", "object", and "injury") were selected to match the content of three picture categories: nude couples during sexual intercourse (high-arousal Pleasant), household objects (Neutral), and severely injured bodies (high-arousal Unpleasant). Such high-arousal pleasant and unpleasant picture contents were selected since these have been observed to induce the largest cortical negativity during exposure (Cuthbert et al., 2000).

A total of 45 stimuli (15 pictures per category) were selected from the International Affective Picture System (IAPS; Lang et al., 2008) and presented in two different pseudo-randomized sequences across subjects. Participants were asked to attend to the word and to the subsequent picture. No motor response to S2 was required. The intertrial interval ranged randomly from 8 to 13 s.

The study had been approved by the Ethical Committees of the Cardiovascular Department of the Umberto I Hospital and of the Department of General Psychology, University of Padova.

### 2.3. Physiological recordings and data analysis

The electroencephalogram (EEG) and the electrooculogram (EOG) were recorded using SynAmps amplifiers (NeuroScan, Inc., El Paso, TX). The EEG was continuously recorded from nine tin electrodes (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4) mounted on an elastic cap (Electro-Cap International, Inc.), referred to linked mastoids. We acknowledge that the use of tin electrodes for recording slow potentials might attenuate the low frequencies in the recorded signal (e.g., Picton et al., 1995). Therefore, SPN amplitudes and, possibly, group differences might have been attenuated as well.

The EOG was recorded from four tin electrodes attached above and below the right eye and at the outer canthus of each eye, to monitor eye movements and blinks. Electrode impedance was kept below 10 kΩ.

The sampling rate was 500 Hz (16 bit A/D converter; accuracy = 0.168 uV/LSB) and filters were set at DC-70 Hz.

The EEG signal was epoched into 11300 ms intervals (from 300 ms before S1 until S2 offset), filtered (Semlitsch et al., 1986), baseline corrected using the 300 ms before S1 onset, re-filtered off-line with a lowpass filter at 30 Hz (12 dB/oct, zero phase filter), and linear detrended in order to remove DC drifts. All EEG epochs were visually scored for eye movement and other artifacts, and each portion of data containing artifacts greater than ±70 μV in any channel was rejected for all the recording channels prior to further analysis.

The amplitudes of the P300 component to S1 and S2 and the LPP to S2 were measured with respect to a 100-ms pre-stimulus baseline. Based on visual inspection of grand-average ERP waveforms, the P300 was computed as the mean amplitude between 250 and 400 ms after stimulus onset. Two time windows were considered for the LPP: LPP1 (mean amplitude between 400 and 700 ms after picture onset) and LPP2 (mean amplitude between 700 and 1000 ms after picture onset).

The SPN was defined as the mean amplitude over the 200-ms interval preceding S2, relative to a 300 ms baseline preceding S1 (see Chwilla and Brunia, 1991; Hillman et al., 2000).

Repeated-measures ANOVAs were performed on the amplitudes of each ERP component and of the SPN, with Group (Fainters, Controls) as between-subjects factor, and Category (Pleasant, Neutral, Unpleasant), Region (Frontal, Central, Parietal) and Laterality (Left, Midline and Right) as within-subjects factors.

The corrected p-values for effects within variables with more than two levels are reported together with the Geisser–Greenhouse epsilon (ε) and the uncorrected degrees of freedom. Significant main effects and interactions (p < .05) were followed by Tukey HSD post hoc tests.

Lastly, in the group of Fainters Pearson’s correlations were performed between ERP measures and the number of syncopal episodes (both lifetime and in the past 12 months).

### 3. Results

#### 3.1. P300 to S1 onset

Fig. 1 shows the ERPs in response to Pleasant, Neutral and Unpleasant word cues over Fz, Cz and Pz, in Fainters and Controls.

The analysis on the amplitude of the P300 elicited by word stimuli yielded significant main effects of Region (F(2, 56) = 5.76, p = .013; ε = 68), indicating larger amplitude in the parietal than...
in the frontal region \( (p = .003) \), and Laterality \( (F(2, 56) = 7.68, p = .001; \, \varepsilon = .90) \), indicating larger amplitude over midline and right than left hemisphere sites \( (ps < .01) \).

The main effects of Region and Laterality were modified by the significant Region × Laterality interaction \( (F(4, 112) = 3.81; p = .014; \, \varepsilon = .72) \), showing that in the frontal region P300 amplitude was significantly larger on the right than on the left side \( (p = .001) \); in the central and parietal regions P300 amplitude was larger over midline and right than left side \( (ps < .0003 \text{ and } < .0001, \text{ respectively}) \).

The Group × Category × Laterality interaction \( (F(4, 112) = 3.26, p = .032; \, \varepsilon = .64) \) proved to be significant. With regard to between-group differences, Fainters showed significantly smaller P300 amplitude than Controls to Pleasant word cues over the right side \( (p = .007) \) and to Unpleasant word cues over midline and left sites \( (p = .002 \text{ and } .0002, \text{ respectively}) \). Over the right and the left side,
Fainters responded with smaller P300 amplitude to Pleasant and Unpleasant word cues, which did not differ from each other, than to Neutral word cues (p = .006 and .043, respectively). Over midline sites, Fainters exhibited the smallest P300 amplitude to Unpleasant word cues, followed by Pleasant (p = .037) and Neutral (p = .003). In Controls, no significant differences in P300 amplitude among stimulus categories was found on any side.

3.2. Stimulus Preceding Negativity

Fig. 2 shows cortical activity over Fz, Cz and Pz during the anticipation of Pleasant, Neutral and Unpleasant pictures, in Fainters and Controls.

The significant Category main effect (F(2, 56) = 13.91; p = .0001; \( \varepsilon = .97 \)) showed that SPN amplitude was larger in anticipation of Pleasant and Unpleasant pictures, which did not differ from each other, as compared with Neutral pictures (ps < .001). As indicated by the significant Region main effect (F(2, 56) = 5.94; p = .013; \( \varepsilon = .63 \)), SPN amplitude was larger over the frontal and central regions, which did not differ from each other (p = .10), than over the parietal region (ps < .02). Such main effects were modified by the significant Category × Region interaction (F(4, 112) = 7.15; p = .001; \( \varepsilon = .55 \)), showing that SPN amplitude in anticipation of Pleasant pictures was larger over the frontal and central as compared with the parietal region (ps < .001), whereas no difference as a function of region was observed for SPN in anticipation of Unpleasant and Neutral pictures.

The significant Group × Region interaction (F(2, 56) = 4.49; p = .032; \( \varepsilon = .63 \)) showed that SPN amplitude was significantly smaller in Fainters than in Controls in the parietal region (p = .0002), whereas no group differences emerged in the other regions. SPN amplitude in Fainters was larger in the frontal and central as compared with the parietal region (ps < .04), whereas in Controls no significant differences among regions was observed.

The significant Group × Category × Region interaction (F(4, 112) = 3.12; p = .046; \( \varepsilon = .55 \); see Fig. 3) showed that over the frontal region Fainters responded with smaller SPN amplitude than Controls in anticipation of Neutral pictures only (p = .046). Fainters displayed a larger SPN amplitude in anticipation of both Pleasant and Unpleasant pictures as compared with the SPN preceding Neutral pictures (p < .001). In Controls, only the SPN preceding Pleasant pictures was significantly larger relative to the SPN preceding Neutral pictures (p = .0002). In both Fainters and Controls, the amplitude of the SPN in anticipation of Pleasant and Unpleasant pictures did not differ from each other. Over the central region, Fainters responded with smaller SPN amplitude than Controls in anticipation of Unpleasant pictures (p = .026). Fainters again showed larger SPN in anticipation of Pleasant and Unpleasant pictures, which did not differ from each other, as compared with SPN preceding Neutral pictures (ps < .007). In Controls, only SPN preceding Unpleasant pictures was larger relative to SPN preceding Neutral (p = .001). Over the parietal region, Fainters showed smaller SPN amplitude than Controls in anticipation of Unpleasant pictures (p = .0001). SPN amplitudes preceding the three picture categories did not differ from each other in Fainters. In Controls, SPN preceding Unpleasant pictures was significantly larger relative to SPN preceding Neutral (p = .002).

3.3. Correlations between SPN amplitude and number of fainting episodes

No significant correlations were observed for Fainters between SPN amplitude and the number of lifetime syncopal episodes or the number of episodes in the past year (rs ranged between -.005 and -.42, ps ranged between .98 and .11).

3.4. P300 and LPP to S2 onset

No significant main effects or interactions involving the Group factor were observed.

A significant main effect of Category was found for P300, LPP1 and LPP2 (F(2, 56) = 38.65, p = .0001; \( \varepsilon = .94 \); F(2, 56) = 60.38, p = .0001; \( \varepsilon = .89 \); and F(2, 56) = 63.68, p = .0001; \( \varepsilon = .96 \), respectively), showing larger amplitude for Pleasant and Unpleasant as compared with Neutral pictures (all ps < .001). A significant Region main effect for the three ERP components was also found (F(2, 56) = 32.81, p = .0001; \( \varepsilon = .55 \); F(2, 56) = 47.31, p = .0001; \( \varepsilon = .57 \); F(2, 56) = 6.09, p = .015; \( \varepsilon = .57 \), respectively), indicating larger amplitude in the parietal as compared with central and frontal regions (ps < .004). For LPP1 and LPP2 a significant Laterality main effect (F(2, 56) = 5.26, p = .011; \( \varepsilon = .87 \) and F(2, 56) = 6.43, p = .004, \( \varepsilon = .87 \), respectively) indicated larger amplitude on the right as compared with the left side (ps < .02).

In order to test whether group differences as a function of category could emerge in the early ERP components, namely N1 and P2, additional analyses were performed on the mean amplitude in the 50–130 ms and 130–200 time-windows, based on visual inspection of grand-averaged ERP waveforms.

Results did not show any significant main effect of the Group factor or significant Group × Category interactions for any component (all Fs < .20, all ps > .54). For the P2 component, a main effect of Category was found (F(2, 56) = 6.42, p = .005, \( \varepsilon = .86 \)), showing larger amplitude for Pleasant than Neutral pictures (p < .003). No significant Category main effect emerged for N1.

4. Discussion

Although it has long been recognized that fainting episodes can be triggered by emotional factors, the underlying neural mechanisms are far from being fully elucidated. Even more so, the involvement of anticipatory mechanisms in the cascade of events that may lead to syncope has been suggested (e.g., Sledge, 1978), but to our knowledge has never been empirically investigated so far.

The present study was aimed at investigating whether individuals with recurrent episodes of vasovagal syncope (VVS) show enhanced anticipation and processing of emotional stimuli. To this purpose, electrocortical activity was recorded during a picture anticipation task, where words forecasted the presentation of high-arousal pleasant and unpleasant, and neutral pictures.

Contrary to our hypothesis, emotional anticipation and processing were not found to be enhanced in syncopal patients as compared with healthy individuals. However, we obtained findings indicating that the pattern of brain activation during anticipation of affective stimuli was markedly different in patients with VVS and controls.

Patients responded with smaller P300 amplitudes than controls to positively valenced words over left hemisphere sites, and to negatively valenced words over both midline and right hemisphere sites. This finding indicates that, relative to healthy controls, syncopal patients deployed less attentional resources towards warning cues that anticipated the occurrence of high-arousal affective stimuli, both pleasant and unpleasant. Thus, the critical factor that modulated attention to warning cues in fainters was the emotional salience, rather than the hedonic value of the stimuli. This pattern of abnormal responding, which encompasses pleasant and unpleasant stimuli, may be related to the fact that most patients reported strong emotional events, and not unpleasant stimuli (e.g., fear, pain) only, as the main triggers of VVS syncope. This finding suggests that it is the emotional impact of stimuli and events, and not unpleasantness only, to be of relevance in this context. It can be hypothesized that the reduced P300 amplitude to
emotional word cues reflects the patients’ attempt to reduce attentional deployment as a means to down-regulate their emotional response to the upcoming arousing stimuli. Although this hypothesis is admittedly speculative, some support to its plausibility comes by the observation that intentional self-distraction from highly arousing emotional stimuli results in reduced activation of emotion-processing brain regions (Ochsner and Gross, 2005; Kalisch et al., 2006; Thiruchselvam et al., 2011). Although in the present study the participants were not given instructions to modulate their emotional responses, the patients may nevertheless have recruited regulatory processes during the anticipation of upcoming stimuli, with or without conscious awareness.

Whereas healthy subjects showed no differences in P300 amplitude to the three word categories, as already observed by Poli et al. (2007), the patients showed reduced P300 amplitude in response to words anticipating emotional pictures (both pleasant and unpleasant), as compared to neutral words. This was observed over both the right and the left side. Overall, a right hemisphere advantage

![Image of electrocortical activity](image-url)
for the processing of emotional words might be expected based on
reports of a right-hemisphere superiority in the perception of emo-
tional stimuli, regardless of valence (see Borod, 1992). Alternat-
ively, a right hemisphere advantage for negative stimuli and a
left hemisphere advantage for positive stimuli could be expected
based on the valence hypotheses of hemispheric specialization for
emotional perception (see Davidson, 1995). However, data on the
processing of emotional words are mostly inconsistent with both
hypotheses, and rather suggest that the right and the left hemi-
spheres play complementary roles in the processing of words with
emotional meaning (Abbassi et al., 2011). Consistently, in our study
no hemispheric lateralization emerged with regard to the process-
ing of the emotional words used as warning stimuli.

With regard to the SPN, a cortical measure of emotional antici-
pation, the results of the present study showed that affective mod-
ulation, i.e., larger amplitude of the SPN in anticipation of emotional
relative to neutral pictures, was evident in both individuals with
recurrent episodes of VVS and healthy controls. In particular, in
syncopal patients cortical negativity was larger in anticipation of
both pleasant and unpleasant as compared with neutral pictures
at frontal and central sites. In controls, larger negativity in anticipa-
tion of pleasant than neutral pictures was evident frontally,
whereas larger negativity in anticipation of unpleasant than neutral
pictures was observed centro-parietally. Overall, such findings indi-
cate that brain activity during anticipation reflected the motiva-
tional salience of high-arousal affective stimuli, irrespective of
their valence (Simons et al., 1979; Lumsden et al., 1986; Poli
et al., 2007). This conclusion might seem at odds with what sug-
gested by Böcker and colleagues (2001), who reported larger SPN
amplitudes following threat cues, i.e., during the anticipation of an
aversive shock, than following safe cues. This finding has been inter-
preted as an indication that stimulus relevance per se is not a
sufficient condition for the slow cortical negativity to develop
and, rather, that the aversive nature of S2 is likely to be a necessary
condition for the larger part of the negativity preceding aversive
stimuli (see also Damen and Brunia, 1994). This inconsistency be-
tween results might be explained by differences in the stimulus
conditions employed, in that safe cues in the context of a threat-
of-shock paradigm might not represent a genuine appetitive
condition and, possibly, are not as arousing as threat cues. However,

Importantly, SPN amplitude during anticipation of unpleasant
pictures was significantly smaller in syncopal patients than in con-
trols. Such effect was specifically observed in central and parietal
regions. Considering that a large body of research has consistently
documented that slow cortical negativity during anticipation can
be reduced by distracting stimuli (Tecce and Hamilton, 1973;
Knott, 1985; Rockstroh et al., 1986; Dourou et al., 1987; Wagner
et al., 1996; Travis and Tecce, 1998; Kimble et al., 2004), our find-
ing would again suggest that syncopal patients might have sponta-
neously activated cognitive regulation strategies, such as
deploying their attention away from the emotional aspects of the
anticipated unpleasant stimuli. Self-distraction would result in
the reduction of cortical excitability preceding the occurrence of
expected unpleasant stimuli, as reflected in the smaller SPN ampi-
tude as compared with controls. The finding that the SPN ampi-
tude was not correlated with the number of fainting episodes
during lifetime or during the past year suggests that reduced cor-
tical activation during anticipation reflects more an altered cogni-
tive process rather than a specific pathological feature in direct
relationship with the likelihood of recurrent fainting. However,
because participants were not given instructions to use cognitive reg-
ulation strategies, nor were they asked after the experimental
session whether they spontaneously engaged in self-distraction,
our interpretation is necessarily provisional at this stage.

Interestingly enough, the electrocortical activity elicited by
emotional pictures was similar in syncopal patients and healthy
individuals. In fact, the amplitude of P300 and late positive poten-
tials to S2 stimuli was only modulated by the motivational rele-
ance of affective pictures (i.e., larger positivity to emotional,
either pleasant or unpleasant, than neutral pictures), irrespective
of group. The larger amplitude of late positive ERP components
for emotional than neutral pictures, together with the right-parie-
tal topography, replicate well-established findings in the literature
(e.g., Schupp et al., 2000).

Our finding of comparable ERP responses to emotional pictures
in syncopal patients and controls might seem at odd with the

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Fig. 3. Mean amplitude of the Stimulus-Preceding Negativity in Fainters and Controls during the anticipation of Pleasant, Neutral, and Unpleasant pictures over the frontal,
central, and parietal regions.
reduced electrocortical activity in the stages of processing of the warning cue and picture anticipation. However, it has been observed that anticipatory distraction, that we hypothesize having modulated the patients’ cortical activity before picture presentation, does not influence subsequent emotion processing, i.e., it does not reduce subsequent activation in brain areas involved in emotional processing (Erk et al., 2006). On the other hand, one might argue that emotional fainters mostly faint during, and not before, emotionally relevant situations, and therefore one would expect that patients differ from controls during exposure to emotional stimuli. Indeed, previous research (Calandra-Buonaura et al., 2008) has found no difference in ERPs or cardiovascular measures between fainters and controls during the viewing of emotional pictures presented for 6 s. Consistent with these findings, our data point towards comparable emotional processing in fainters and controls during 5-s exposure. It is possible that the activation of syncope upon exposure to emotional stimuli involves dysfunctional interaction between subcortical emotional processing and brainstem regions mediating autonomic cardiovascular regulation. Therefore, event-related cortical potentials might not be able to detect such alterations. Indeed, recent research reported lower regional brain volumes within medulla and midbrain in patients with neurocardiogenic syncope compared to non-fainting controls, and highlighted negative correlations between volumes in the caudate nucleus, fanning frequency, and experienced anxiety levels (Beach et al., 2009). Alternatively, exposure to sustained stimulation might be needed to highlight abnormal emotional responding, which in most VVS patients develop on a temporal scale ranging from 30 s to several minutes (Grubb, 2005).

Overall, the potential clinical implications of the findings of the present study are at least twofold. Firstly, the use of non-adaptive emotion regulation strategies for reducing the impact of highly arousing (and, particularly, of unpleasant) events, that we hypothesize to underlie the reduced cortical anticipation in VVS patients, might be involved in the pathophysiology and/or the maintenance of emotional fainting. In fact, the failure to activate flexible self-regulatory responses to emotional stimuli is known to be detrimental to psychological and physical health. Indeed, inefficiency in selecting, attending and responding to emotional information in the environment is thought to lie at the core of various forms of pathology, including depression, panic disorder, generalized anxiety disorder, hypertension, and coronary heart disease (Thayer and Lane, 2000). Further research should better elucidate how emotional anticipation and processing are related to emotion regulation strategies in individuals with VVS, and which neural networks and pathways come to interact dysfunctionally in anticipating emotional information and modulating cardiac and vasomotor activity (Fenton et al., 2000; Kaufmann and Hainsworth, 2001; Kinsella and Tuckey, 2001).

Secondly, our findings might offer clues to expand existing psychological interventions with individuals with VVS (Gracie et al., 2004, 2006). The treatment of VVS is still a matter of controversy, and specific interventions are only recommended in a minority of patients (Kuriachan et al., 2008). Conventional non-pharmacological management of recurrent VVS mainly relies on education and reassurance (Wieling et al., 2004), but in cases where symptoms have proved resistant to conventional treatments, cognitive-behavioral interventions may be beneficial (Newton et al., 2003). The selective alteration of anticipate, but not of the processing, of emotional stimuli suggests that cognitive-behavioral interventions in VVS patients might usefully target the cognitive, affective and physiological responses inherent in the anticipation of emotional events, rather than the responses that take place once such events are actually occurring. For instance, the use of attention-focusing strategies during in vivo or imaginal exposure to emotional stimuli has been proven to reduce fear responses in phobic individuals (see Mohlman and Zinbarg, 2000). Future research should evaluate whether such strategies might facilitate an effective regulation of psychophysiological responses during emotional anticipation in VVS patients.

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**References**


