HHS Public Access

Author manuscript

Biol Psychiatry. Author manuscript; available in PMC 2019 April 01.

Published in final edited form as:

Biol Psychiatry. 2018 April 01; 83(7): 618–628. doi:10.1016/j.biopsych.2017.10.004.

Face Perception in Social Anxiety: Visuocortical Dynamics Reveal Propensities for Hypervigilance or Avoidance

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Abstract

Background—Theories of aberrant attentional processing in social anxiety, and anxiety disorders more broadly, have postulated an initial hypervigilance or facilitation to clinically relevant threats and consequent defensive avoidance. However, existing objective measurements utilized to explore this phenomenon lack the resolution to elucidate attentional dynamics, particularly covert influences.

Methods—We utilized a continuous measure of visuocortical engagement, the steady-state visual evoked potential in response to naturalistic angry, fearful, happy and neutral facial expressions. Participants were treatment-seeking patients with principal diagnoses of social anxiety circumscribed to performance situations (n=21) or generalized across interaction contexts (n=42), panic disorder with agoraphobia (n=25), and 17 healthy participants.

Results—At the principal disorder level, only circumscribed social anxiety patients showed sustained visuocortical facilitation to aversive facial expressions. Control participants as well as patients with panic disorder with agoraphobia and generalized social anxiety showed no bias. More finely stratifying the sample according to clinical judgment of social anxiety severity and interference revealed a linear increase in visuocortical bias to aversive expressions for all but the most severely impaired patients. This group showed an opposing sustained attentional disengagement.

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Financial Disclosures

The authors declare no competing financial interests relevant to this research. Dr. McTeague reports receiving stock options in Joyable.com for consulting unrelated to this work. All other authors report no biomedical financial interests or potential conflicts of interest.

Conclusions—Rather than shifts between covert vigilance and avoidance of aversive facial expressions, social anxiety appears to confer a sustained bias for one or the other. While vigilant attention reliably increases with social anxiety severity for the majority of patients, the most impaired show an opposing avoidance. These distinct patterns of attentional allocation could provide a powerful means of personalizing neuroscience-based interventions to modify attention bias and related impairment.

Keywords

ssVEP; EEG; social anxiety; panic disorder; agoraphobia; RDoC

Introduction

Heightened sensitivity to facial expressions, particularly those connoting threat or scrutiny, has often been observed in social anxiety disorder. This includes speeded behavioral responses to spatial cues (1), increased reflexive eye-movements (2) and enhanced early (i.e., 100–200 ms) and later (i.e., 300–500 ms) event-related potential components (ERPs) (3–5). Functional neuroimaging findings implicate excessive recruitment of limbic, paralimbic and medial prefrontal fear circuitry in conjunction with extrastriate visual cortex (6–8).

While heightened sensitivity to aversive facial expressions is common in social anxiety, a corpus of work has suggested marked inconsistency—at times revealing no bias for aversive faces or even a bias for neutral faces (9, 10). Aberrant perceptual sensitivities in social anxiety, and anxiety disorders more broadly, have often been interpreted in accordance with the vigilance-avoidance hypothesis—that perception of threat-relevant stimuli is characterized by initial hypervigilance and consequent defensive avoidance (11, 12). However, the measurements utilized to explore this phenomenon (i.e., fMRI, ERPs, reaction time, eye-tracking, self-report) lack the ability to continuously quantify threat-related changes in visuocortical engagement that may unfold at different latencies and for different durations. Opposing attentional shifts such as initial hypervigilance and reflexive avoidance, when averaged into a single epoch, may contribute to inconsistent findings.

To track dynamic attention to angry, fearful, happy and neutral facial expressions, here we used scalp-recorded steady-state visual evoked potentials (ssVEPs) as a continuous measure of selective attention (i.e., the attentional spotlight) with near optimal time resolution (13). The ssVEP is an oscillatory electrocortical response to a stimulus modulated in luminance or in contrast (i.e., flickered). It oscillates at the known, specific frequency of the driving stimulus (14, 15), allowing its separation from noise and quantification in the time-frequency domain (16). Generators of the ssVEP have been localized to extended visual cortex (14), with strong contributions from primary visual areas (17). Importantly, ssVEPs reflect repeated excitations of the visual system evoked by the same “flickered” stimulus. Temporal changes in driven neural mass activity indexed by the ssVEP reflect initial sensory processing as well as subsequent re-entrant, top-down modulation (18, 19) likely from fronto-parietal and limbic connections (20–22). In keeping with top-down contributions from these regions, modulation of the ssVEP by motivation has been observed as a function

of instructed attention (23), fear conditioning (24, 25) and emotional arousal (26, 27) in patterns that vary with individual differences including depression (28), fearfulness (29), and anxiety (30, 31).

Unlike ssVEPs provoked by emotional scenes and fear conditioned cues, we have observed in a series of prior studies that ssVEPs to facial expressions are not modulated as a function of emotion—except in the case of social anxiety (30–32). For example, in a study of undergraduate students selected to be high and low on social anxiety, we observed no modulation in the low symptom group, and sustained enhancement to emotional (angry, fearful, happy) expressions relative to neutral that robustly increased with social fear and avoidance severity (32). These findings prompt the hypothesis that affective expressions should evoke heightened ssVEPs in those with social anxiety disorder. We have however found that treatment-seeking adult clinical samples are marked by substantial heterogeneity in defensive reactivity. Instead of uniform defensive hyper-reactivity, we have observed that a substantial portion of patients with social anxiety as well as other anxiety disorders, typically those with the most severe disorder-related distress and interference, show a paradoxical hypo-reactivity to threat cues (33–35). If visuocortical dynamics mirror these findings, we hypothesize that a portion of the sample with the most extreme levels of distress and impairment (36) would display attentional avoidance (either sustained or subsequent to initial hypervigilance) in response to angry faces.

While the latent structure of social anxiety appears dimensional (37, 38), a more discrete boundary between circumscribed (i.e., performance only) and generalized social anxiety subtypes has often been observed in subjective and objective measures (35, 36). Here we also examine if ssVEP modulation in response to facial expressions would vary by social anxiety subtype. Although facial expressions may hold particular salience for individuals with social anxiety, fears of scrutiny are prominent in many disorders. Limbic and visuocortical sensitivity to emotional facial expressions has been established across a range of disorders, particularly other anxiety disorders (39–41). To assess the specificity to principal social anxiety, we included a sample of individuals with principal panic disorder with agoraphobia, without comorbid social anxiety disorder. This clinical comparison was selected because persistent apprehension about experiencing panic symptoms in settings where escape is difficult and/or embarrassing renders cues connoting possible scrutiny especially pertinent (42).

Methods and Materials

Participants

Participants were assessed at the University of Florida Fear and Anxiety Disorders Clinic: 88 treatment-seeking adults with DSM-IV principal diagnoses of social anxiety disorder circumscribed to performance situations (n=21) or generalized across interaction contexts (n=42), principal panic disorder with agoraphobia (PDA; n=25), and 17 community control participants—all without psychosis, somatoform, substance use or eating disorders or major physical disease.

The University of Florida Institutional Review Board (IRB-01) approved the study. Participants provided informed consent, completed questionnaires and interview in the morning and psychophysiological assessment in the afternoon.

Diagnostic Classification

Diagnostic groups were established using the Anxiety Disorder Interview Schedule for DSM-IV (ADIS-IV) (43). For multiple Axis I disorders, diagnostic primacy was determined according to the severity rating of the Clinical Global Impression Scale (CGI-S) (44); ranging from 0, *No features present*, to 7, *Most severely ill patients*) reflecting both distress and interference for respective disorder presentations. The CGI-S was modified to consider functional interference and related distress not more appropriately subsumed under another disorder (see supplement). Interviewers rated CGI-S for all disorders assessed in the ADIS (anxiety, mood, adjustment, somatoform, substance use, and psychotic disorders) and any Axis II disorders assessed as warranted by SCID-II screener (45) elevations. Controls denied current or lifetime diagnoses of psychiatric illness and/or treatment and did not receive any CGI-S ratings that indicated more than minimal symptoms (i.e., severity rating=1). A doctoral level-clinical psychologist with expertise in anxiety disorders was present in all interviews (MCL) and inter-rater reliability (via videotape) was calculated for 25% of patients, yielding 100% agreement for principal diagnosis among three masters or doctoral-level clinical psychologists.

Consistent with the DSM-5 performance specifier, circumscribed social anxiety was operationalized as disabling and disturbing anxiety about negative evaluation limited to performance contexts[1]. Generalized social anxiety was defined as significant disturbance in at least two of the following domains: formal performances, informal speaking and interaction, observation of behavior, and assertive interaction[2] (46, 47). To assess the specific nature of predominant symptom phenotypes on observed effects in ssVEP patterns, patients meeting criteria for social anxiety were exclusive of those with PDA and vice versa[3].

Stimuli

Experimental methods were similar to those described previously (32). In brief, 96 pictures were selected from the Karolinska Directed Emotional Faces (KDEF) (48) of actors (12 female, 12 male) posing 4 different expressions (neutral, happy, fearful, angry) and were pre-processed to have equal overall luminance and color composition (mean luminance of 28 cd/m^2; Michelson contrast of 0.83). To gather normative affective ratings on the Self-Assessment Manikin (SAM) (49), 242 unselected individuals rated the stimuli (Table S1).

[1]For example, idiographic performance fears included taking examinations, musical performance, athletic participation, speaking in group meetings at work, giving a speech, or interviewing.

[2]Circumscribed social anxiety patients endorsed fear (ADIS-IV Fear Severity Rating, 4 and above) and/or avoidance (Avoidance Severity Rating, 4 and above) of at least one formal, structured performance situation (i.e., public speaking, participating in meetings and classes, or idiographic situations). In addition, these individuals exceeded the same threshold for distress and/or functional interference regarding apprehension/avoidance of performance situations, but did not similarly rate other social contexts.

[3]As only one participant was excluded owing to comorbid generalized social anxiety and PDA, this criterion likely did not impact the generalizability to a naturally occurring treatment-seeking sample.

Experimental Design

Participants were seated in a sound-attenuated, dimly lit room and the Electrical Geodesics (EGI) HydroCel EEG 129 sensor net was attached. Participants were instructed to view each picture for the duration of presentation, keeping their eyes comfortably focused on the center of the screen.

Faces were presented 116 cm from the participant on a 51 cm CRT monitor with a vertical refresh rate of 70 Hz, subtending a visual angle of 5° horizontally and 6.9° vertically. Using Psychtoolbox (50), faces appeared in a random order, each flickering at a rate of 17.5 Hz (28.57 ms on and 28.57 ms off) for 3428 ms (60 cycles), with a gray background set to the mean luminance of the faces. Faces were followed by a randomly variable 2–4 second inter-trial interval during which a central crosshair (1° visual angle) appeared. Each face was shown once, for 96 trials total over approximately 11 minutes.

EEG Recording & Data Collection

EEG was continuously recorded and digitized at 250 Hz, using Cz as a recording reference. As suggested (51) for the EGI high input-impedance (200 MOhms) amplifier, electrode impedances were kept below 50 kΩ. Data were filtered online by 0.1-Hz high-pass and 100 Hz low-pass elliptic filters, and off-line at 30 Hz low-pass (48 dB/octave, 18^{th} order Butterworth filter). An established procedure (52), as implemented in the EMEGS software suite (53) was used to identify artifact-free epochs, extracted relative to the onset of each picture, using 300 ms pre- and 4400 ms post-picture onset. See supplement for additional details.

ssVEP Analyses

To illustrate data quality, grand mean ssVEPs recorded over central occipital sensor Oz for the neutral face condition are shown in Figure 1. For ssVEP analysis, condition-based averages were submitted to time-frequency analysis using the Hilbert transform: Data were filtered with a 10^{th}-order Butterworth band-pass filter (width: 0.5 Hz) around the driving frequency of 17.5 Hz. The time-varying ssVEP amplitude was extracted as the modulus of the band-pass filtered ssVEP signal and the Hilbert-transformed analytic signal.

Statistical Analysis

Two complementary strategies were employed to evaluate group differences in ssVEP amplitude: an initial step assessed broad differences in time-averaged ssVEP amplitudes, the second step examined the ssVEP dynamics at each sample point. First, ssVEP amplitude was extracted as a posterior regional mean of the viewing period. For each participant and condition, the time-varying ssVEP amplitude was averaged between 800 and 3200 ms, across an occipital electrode cluster comprising electrode Oz and its 8 nearest neighbors. A linear mixed model analysis implemented in SPSS (SPSS, Inc., Chicago, Illinois) was conducted on the average ssVEP amplitude with fixed effects of facial expression (neutral, happy, fearful, angry), sex (male, female), and diagnostic group (control, circumscribed social anxiety, PDA, generalized social anxiety), and their interaction terms. Age was entered as a continuous covariate of interest, including its interaction terms with the categorical fixed effects. ssVEPs are sensitive to rated emotional arousal (26); thus contents

were entered in order of increasing arousal for KDEF stimuli (i.e., neutral, happy, fearful, angry), demonstrated in the present normative sample and other studies (4). The subject factor was modeled as a random variable, nested within diagnostic group and nested within sex. Follow-up analyses to decompose omnibus effects were conducted with repeated measures analysis of variance (ANOVA), evaluating differences between facial expressions within each group and enabling planned contrast analyses of interactions between group and expression (54). Greenhouse-Geisser correction was applied where appropriate (55). Significant effects were followed up using paired t-tests or planned contrasts. Univariate ANOVAs and Tukey Honestly Significant Difference (HSD) tests for planned comparisons determined group differences in demographic and questionnaire data.

A second set of analyses capitalized on the rich temporal and spatial information contained in the dense array EEG recordings. In these analyses, *t*-values (comparing specific expressions) or F-contrasts comparing emotional (happy, fearful, angry) expressions to the neutral expression were determined for each EEG sensor, for the mean Hilbert-transformed ssVEP in the time window described above (800 to 3200 ms after face onset), and—importantly—for each time point individually. The latter analysis addresses hypotheses regarding hypervigilance-avoidance sequences vis-à-vis temporally sustained facilitation or suppression of threat cues. Thresholds for statistical significance were determined using a permutation technique (56, 57). Permutation distributions for t-values and F-values were generated based on randomly shuffling within each group. The maximum t- or F-value for each of 5000 random permutations entered a permutation distribution, and the top and bottom 2.5% tails of these distributions served as critical values for statistical significance.

Results

Principal Diagnosis and ssVEP Modulation

Linear mixed model analysis of ssVEP amplitude showed an interaction of facial expression and diagnosis, $F(9,297)=2.54$, $p=0.008$[4]. No further main effects or interactions were observed, including those of sex or age. Follow-up analyses to disentangle the omnibus interaction revealed no differences in ssVEP amplitude as a function of expression in control participants, $F(3,48)=0.41$, $p=.72$, or patients with generalized social anxiety, $F(3,123)=0.38$, $p=.76$, or panic disorder with agoraphobia, $F(3,75)=0.83$, $p=.48$. Meanwhile, patients with circumscribed social anxiety showed pronounced sensitivity to facial expression, $F(3,60)=4.53$, $p=.019$. Specifically, ssVEP amplitude was enhanced when patients with circumscribed social anxiety viewed fearful, $t(20)=2.45$, $p=.024$, and angry, $t(20)=2.30$, $p=.032$, compared to neutral expressions and fearful compared to happy expressions[5], $t(20)=2.50$, $p=.022$ (Table 1). Between-group tests of emotional relative to neutral expressions (i.e., difference score) revealed a reliable difference specific to responses during fearful versus neutral expressions, $F(3,101)=2.98$, $p=.035$, with circumscribed showing greater enhancement than generalized social anxiety. In contrast, tests of between-group

[4]Initial inspection of means and distributions indicated that age was not evenly distributed across diagnostic categories. When age was added as an additional random factor nested in group, the pattern of modulation of ssVEP amplitude by diagnosis did not differ.
[5]The reliable ssVEP enhancement to fearful in relation to happy expressions among circumscribed social anxiety patients was consistent with the reliably increased arousal ratings obtained for the fearful relative to happy expressions (see supplement for details).

differences in ssVEP amplitude by expression revealed no differences, underscoring that modulation rather than raw amplitude of the ssVEP varied across groups.

Regarding temporal dynamics contributing to these group effects, the time course for the occipital sensor cluster employed for statistical analysis is shown in Figure 2. Hypersensitivity to angry and fearful faces in circumscribed social anxiety patients emerged early in the viewing epoch and persisted. The lack of enhancement to emotional expressions in the other three groups was similarly persistent throughout viewing. As a follow-up to the circumscribed group effects, Figure 3 displays the ssVEP time course for each expression at sensor POz. To illustrate the finding that both angry and fearful expressions prompted temporally sustained ssVEP amplification, the white line shows the time-varying F-value of the contrast (angry=fearful > neutral) computed for this sensor.

Topographical statistical mapping of permutation-controlled t-tests was consistent with mixed model and ANOVA results. Differences in ssVEP amplitude across posterior locations of the scalp were solely observed for circumscribed social anxiety patients, shown for comparisons between neutral versus angry and fearful faces, respectively (Figure 4). Topographical analyses also demonstrated that condition differences in the circumscribed social anxiety group were strongest at parieto-occipital sensors, superior to the maximum of the ssVEP, shown in Figure 1.

The pattern of ssVEP enhancement to aversive expressions specific to circumscribed social anxiety was not explained by self-reported symptoms. The results are reported in detail in Table 2 and the supplement. In short, we observed a linear increase in broad negative affectivity and functional impairment from control to circumscribed, PDA, and generalized social anxiety at the extreme. Anxious arousal/agoraphobia was most pronounced for PDA, followed by generalized and circumscribed social anxiety and lastly the control group. Social fear/avoidance was most extreme for the generalized followed by circumscribed social anxiety, PDA, and lastly the control group. Neither medication usage (see supplement), diagnostic comorbidity, nor demographics (Table 2) corresponded with ssVEP modulation.

Transdiagnostic Social Anxiety Severity and Impairment and ssVEP Modulation

Next, we considered whether finer-grade clinical judgments of social fear and avoidance severity and interference (as opposed to diagnostic grouping) might reveal distinctions in attentional patterns. These analyses were performed transdiagnostically. Participants across principal disorders were ranked according to CGI-S social anxiety ratings.

The mean expression-related differences in ssVEP amplitude during angry versus neutral expressions (expressed as % amplitude of neutral response) were examined according to CGI-S rankings (Figure 5; Figure S2–S3). The pie chart at each CGI rank reflects the proportion of each disorder contributing to a given severity and impairment level of social anxiety. As observed in Figure 5, no differences between angry and neutral expression-evoked ssVEPs were observed for individuals not impaired by social anxiety. A linear increase across groups was observed starting from the 1) not impaired to 2) minimally impaired to 3) moderately impaired, followed by individuals 4) markedly impaired by social

anxiety showing the greatest bias to angry expressions. Patients rated as even more (i.e., severely) impaired showed a difference relative to neutral expressions nearly on par with the markedly impaired group—in the opposite direction (i.e., neutral evoking larger ssVEP amplitudes than angry expressions). Reliability of the overall pattern was confirmed by univariate ANOVA, which demonstrated ssVEP modulation as a function of CGI-S, $F(4, 100)=3.02$, $p=.021$, best described by a quadratic trend, $F(1,100)=4.82$, $p=.031$. No such trend was observed for fearful expressions, $F(4, 100)=0.95$, p=0.438[6]. The opposing patterns in the marked and severe groups represented sustained hyper- and hypo-sensitivity, respectively, to angry expressions as opposed to fluctuating attentional over- and under-engagement (Figure 6). Follow-up tests of all symptom severity, prognosis, and comorbidity indices in Table 2 suggested more similarities than differences between these groups.[7] Follow-up tests of LSAS-SR total score, similarly separated into quintiles showed no reliable differences, suggesting that self-reported social anxiety did not track this attentional bias as closely as clinical judgment.

Discussion

In the current study, continuous visuocortical responses to naturalistic emotional and neutral facial expressions were assessed in individuals with circumscribed and generalized social anxiety disorder and panic disorder with agoraphobia as well as healthy control participants. At the principal disorder level, only circumscribed or performance social anxiety groups showed attentional facilitation to static aversive facial expressions. Furthermore, these group-level patterns were consistent throughout viewing. Circumscribed social anxiety patients showed a sustained pattern of hypervigilance. The other groups, despite elevated self-reported social anxiety and broad distress, showed no visuocortical sensitivity to emotional expressions.

Finer-grade clinical judgments of social anxiety severity and impairment were more predictive of visuocortical anomalies to facial expressions. By stratifying—transdiagnostically—on the basis of CGI severity ratings of social anxiety, we observed that interpersonal apprehension and related interference predicted a linear increase in sustained perceptual sensitivity to aversive facial expressions. That is, with the exception of the most impaired group, which showed sustained attentional disengagement or avoidance of aversive relative to neutral facial expressions. Despite the opposing patterns of attentional bias observed in the two most extreme ranks, both were composed of principal social anxiety

[6]A posthoc test of the interaction of CGI rank and expression (neutral, angry) underscored the reliability of this effect, $F(4,100) = 2.79$, $p=.03$. Additional follow-up pairwise comparisons of the ssVEP amplitude difference in response to angry relative to neutral expressions across groups, $F(4,100) = 3.02$, $p=.02$, further revealed that the markedly impaired group showed ssVEP enhancement to angry relative to neutral expressions that exceeded the responses of the not impaired, $p=.044$, and severely impaired groups, $p=.02$. All other pairwise comparisons did not differ.

[7]Consistent with the worse CGI-S score for social anxiety conferred to the severely impaired relative to markedly impaired group, the severely impaired group endorsed more social fearfulness as rated on the LSAS-SR (Total: Markedly M=86.96; SD=17.21; Severely M=100.38; SD=21.57, $p=.04$; Fear: Markedly M=45.67; SD=8.95; Severely M=52.92; SD=10.57, $p=.03$). Repeating symptom, comorbidity, and prognosis analyses in Table 2 between these subgroups, however, revealed additional differences only in MASQ Anxious Arousal (Markedly M=26.22; SD=7.37; Severely M=34.54; SD=8.81, $p=.003$) and General Anxiety (Markedly M=26.41; SD=7.16; Severely M=31.69; SD=8.79, $p=.049$). To reduce the array of questionnaires to underlying dimensions, we also conducted a principal components analysis using the dimensional symptom measures and then compared the two groups on the resulting factors: 1) general distress/negative affectivity, anxious/hyperarousal, and 3) social fear and anxiety (details in Supplemental Results). The two most impaired groups did not differ on these broad factors.

patients. Surprisingly, the percentage at each of these two CGI ranks belonging to circumscribed versus generalized subtypes was equivalent, despite the substantial differences in prognosis and symptomatic distress typical of these classes (36). Considering subjective symptom severity, further suggested that while the severely impaired group reported more social fearfulness, anxious arousal, and non-specific anxiety on select measures[6], that these groups were predominantly similarly extreme in their subjective distress. The difference in CGI ranking was based on the extent of impairment in psychosocial functioning. That is, marked impairment was characterized by significant (but not gross) impairment in important areas of functioning. Severe impairment was characterized by at least severe impairment in several or total impairment in one domain. Essentially, clinician judgment of psychosocial impairment was uniquely related to reliable and opposing patterns of selective attention to aversive expressions.

Individuals who demonstrated heightened sensitivity to angry expressions also demonstrated facilitation to fearful expressions. Vigilance to other aversive expressions has frequently been observed in social anxiety in both ERP and hemodynamic imaging studies (10, 67), particularly disgust expressions (68). Rather than specific expressions, aversive expressions as a whole may prompt threat of scruitiny and contempt in social anxiety.

Proposals that affective modulation of primary visual responses result from re-entrant signals ultimately originating in fronto-parietal and limbic cortices (20, 67), have borne out in recent concurrent ssVEP-fMRI investigations (21, 69). Chronic social anxiety may tune visuocortical neurons sensitive to facial cues via altering thresholds and gains in the networks representing expectations of interpersonal failure and its consequences. Work with ERPs may assist in identifying the extra-visual processing stages that contribute to these effects (70). Limbic and paralimbic regions shown to drive re-entrant modulation of the ssVEP are those consistently shown during fMRI studies to be hyper-reactive to social cues in social anxiety patients (10, 68).

Similar to posttraumatic stress (71, 72), there may be subtypes of social anxiety with different corticolimbic biases, correspondingly different patterns of re-entrant modulation of visual cortex, and thus different attentional phenotypes. Our prior work with startle, autonomic, and facial expressivity measures (35) has suggested that hyper-versus hypo-reactivity to social threat cues in social anxiety is related to disorder duration, with more enduring dysfunction related to response attenuation. Whether hyper-versus hypo-reactivity may reflect a transition in response dispositions as a function of chronicity or is more reflective of invariant trait dispositions will await a longitudinal investigation. Regardless of the respective pathogenesis of the attentional biases, fMRI studies of social anxiety treatment outcome hint that reactivity patterns may relate to prognosis: Successful cognitive-behavioral intervention for social anxiety down-regulates defensive activation of limbic and visuocortical regions to clinically relevant cues while up-regulating dorsolateral and medial prefrontal areas suggestive of enhanced control (73–75). Notably, symptom amelioration is more pronounced among those patients who at pre-treatment show stronger visuocortical and paralimbic reactivity to aversive cues (73, 76) as well as weaker fronto-parietal activation and connectivity during simultaneous cognitive demands (76–78). Steady-state

visuocortical response to social cues may be a prognostic indicator of whether a patient is primed for the sensory, cognitive, and emotional engagement optimal for CBT response.

The finer discernment of visuocortical anomalies observed on the basis of transdiagnostic CGI ratings of social anxiety highlights the relevance of these symptoms and related attentional biases across disorders. Interpersonal apprehension and avoidance are elevated in a range of psychiatric disorders including other anxiety (79, 80), eating (81), personality (82) and substance use disorders (83), autism (84), unipolar and bipolar depression (85), and psychosis (86), as well as numerous physical health conditions (87). Relative to discrete diagnosis, the graded clinical impression weighting the extent of interpersonal fear, distress, and interference yielded superior prediction of attentional dysregulation—a potential intermediate phenotype.

With the rollout of the Research Domain Criteria (RDoC) initiative (88) to promote a science of psychopathology based around dimensions of brain-behavior relationships as opposed to subjectively based diagnostic categories, numerous clinical scientists have called for clearer specification of the clinical targets (89). This has included calls for incorporating the metrics of prognosis, caseness, and disability (90) while also attending to the need for improved reliability of experimental indices, brain and behavior alike (91). The current findings suggest a potential point of reconciliation—linking objective measures to subjective dimensional indices that account for not only symptom domain severity but also broader impairment. In the current study, follow-up analyses utilizing self-reported social fear and avoidance (i.e., LSAS-SR Total) to stratify patients in a manner akin to the CGI rankings obscured the attentional patterns revealed by clinician judgment. The present study requires replication and extension, particularly in light of the established inconsistency of impairment ratings such as the Global Assessment of Functioning, which contributed to its exclusion from DSM-5. Furthermore, although inter-rater reliability for principal disorders was 100% in the current sample, reliability was not calculated for CGI ratings. In summary, systematic efforts to operationalize and clarify clinical judgment of global severity and impairment in relation to more objective RDoC-style domains could be especially productive (92, 93).

The steady-state visual evoked potential is a strong candidate measure for advancing clinical science at the intersection of brain and behavior. With selective sensitivity to visuocortical processing ssVEPs are limited in reflecting processes occurring in other brain areas. However, their fine temporal and dynamic resolution for covert attention fluctuations during sustained stimulation (13), its prediction of behavioral performance (13), and its established reliability (94–96), even at the single-trial level (97, 98) highlight their usefulness in assessing biased visual processing. Single-trial analyses of ssVEPs have revealed attentional differences as a function of nuanced cues in static facial expressions (i.e., direct versus averted gaze (99)). The fidelity of ssVEPs could be especially productive for individually tailoring attention bias modification interventions, and thus potentially reconcile inconsistent findings (100–102). Similarly, dysfunctional attentional biases might be pliable to highly resolved, ssVEP-guided real-time neurofeedback (103). Real-time feedback of overt eye movements has recently shown promise to ameliorate biases to aversive faces and symptoms in social anxiety (104). The added capability to index covert biases in real-time with ssVEPs could enhance novel neuroscience-guided interventions.

Conclusion

Rather than initial hypervigilance or facilitation to aversive facial expressions and consequent defensive avoidance, social anxiety appears to confer a sustained bias for hypervigilance or avoidance. Furthermore, while the extent of sustained vigilance to aversive expressions reliably increases with social anxiety severity for the majority of patients, the most impaired show an opposing avoidance. These distinct patterns of attentional allocation could provide a powerful means of personalizing neuroscience-based interventions to modify attention bias and related impairment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported in part by National Institute of Mental Health grants R01 MH084932 and R01 MH097320 to Andreas Keil, K23 MH104849 to Lisa M. McTeague and R01 MH084932, R01 MH097320, and R21 MH082702 to Peter J. Lang. Special thanks to Christopher T. Sege, M.S. for comments on this manuscript.

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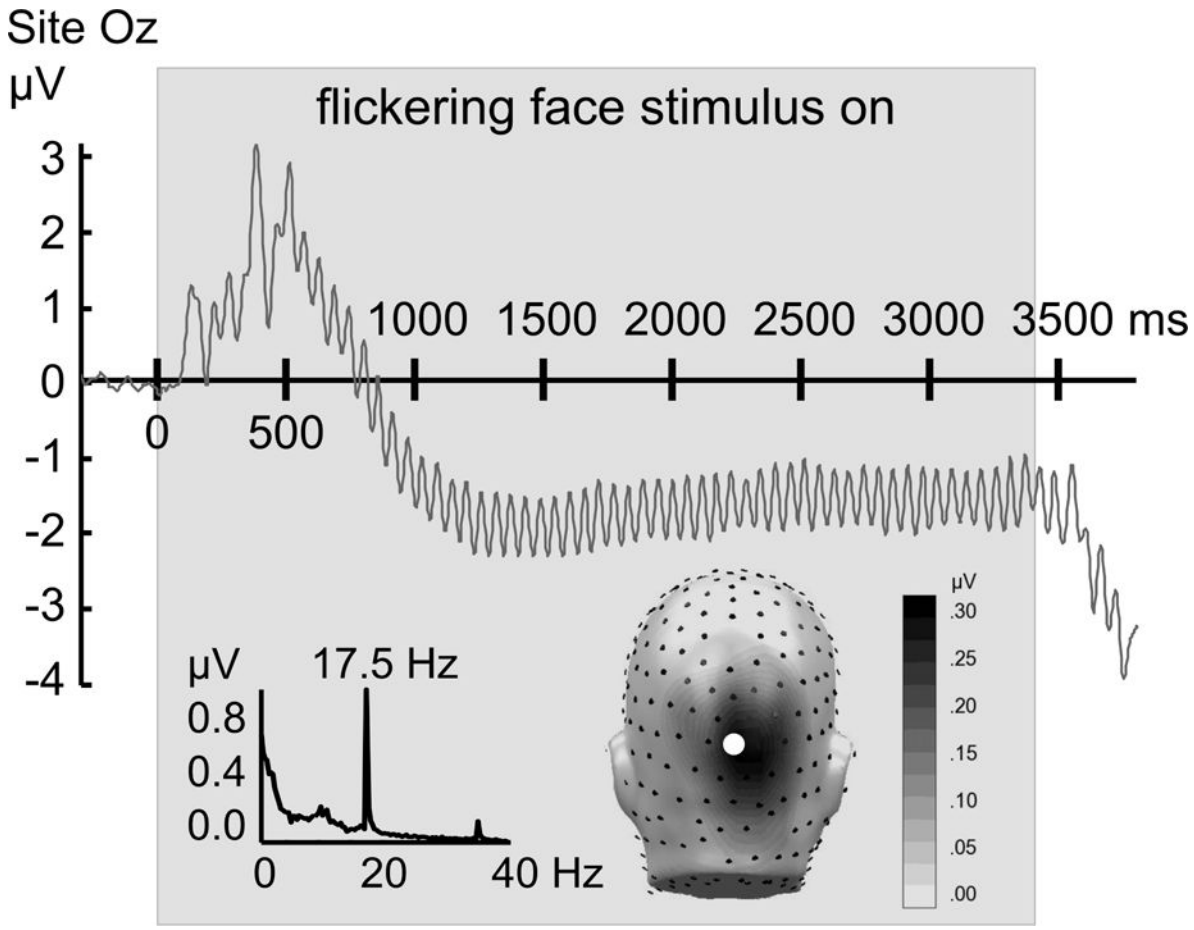

Figure 1.

Top: Time domain representation of the ssVEP, averaged across participants (N=105) when viewing neutral faces flickering at a rate of 17.5 Hz, recorded from sensor Oz. The gray box indicates the duration of the flickering faces. Insets display the frequency spectrum of the same data (left lower panel), with a pronounced peak at the flickering frequency (17.5 Hz) and the first harmonic frequency (35 Hz) clearly visible. The inset on the right shows a back view of the spectral amplitude topography of this response as projected to a standard head. The location of sensor Oz is highlighted as a white circle. Note the focal parieto-occipital distribution of the ssVEP signal evoked by flickering pictures.

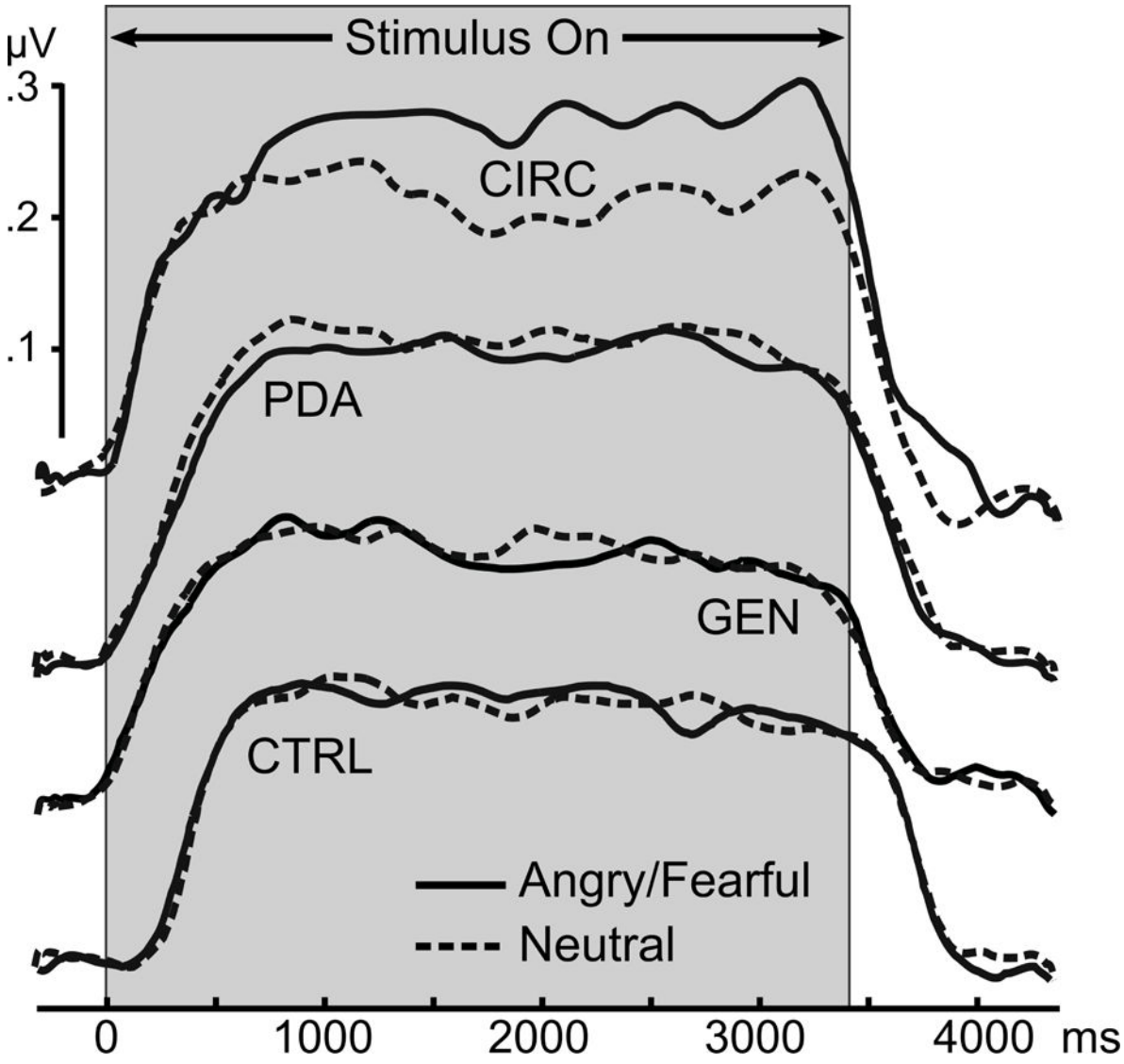

Figure 2.

Grand mean time-varying envelope of the ssVEP signal (from a posterior sensor cluster including Oz and its 8 nearest neighbors) evoked by the flickering faces, comparing aversive expressions (averaged across angry and fearful expressions) with neutral expressions, for the four principal diagnostic groups. CTRL=Control (N=17); CIRC=Circumscribed social anxiety (N=21); GEN=Generalized social anxiety (N=42); PDA=Panic disorder with agoraphobia (N=25).

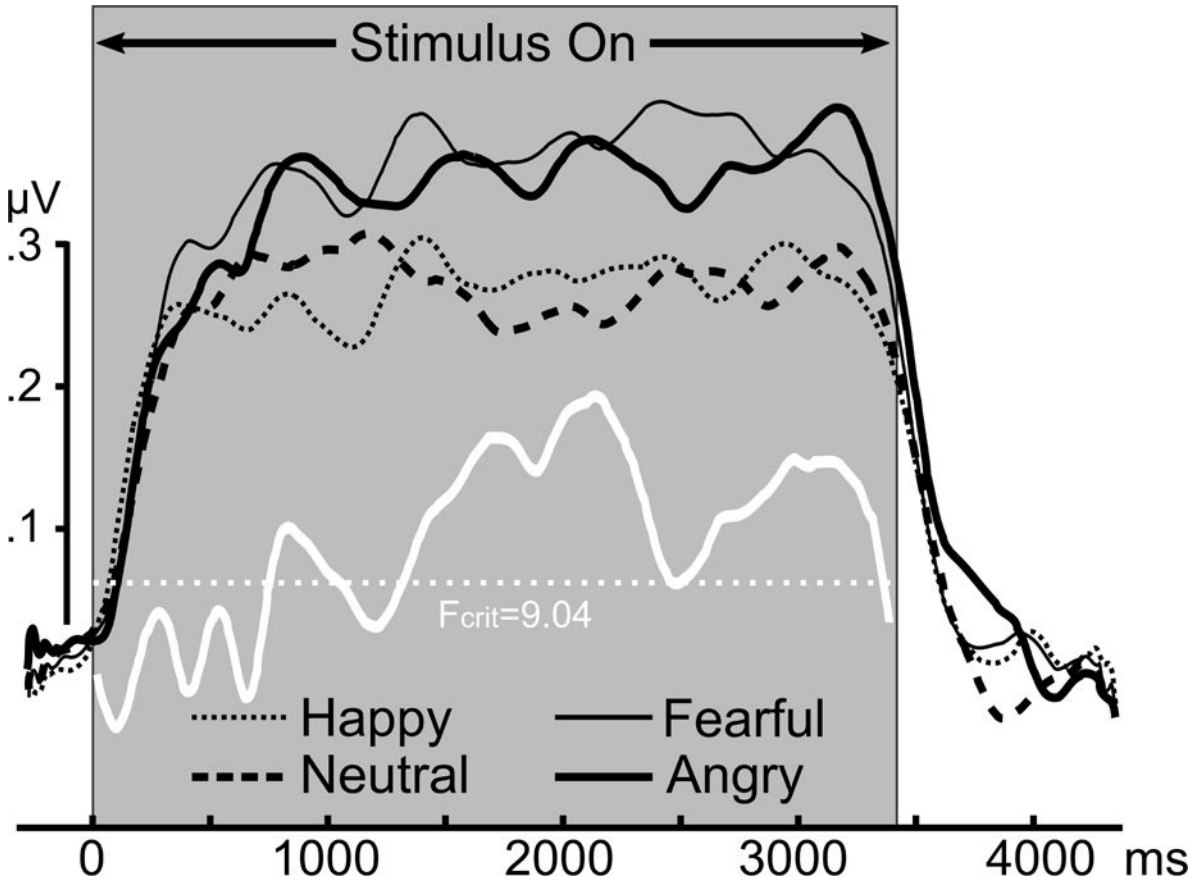

Figure 3.

Grand mean time-varying envelope of the ssVEP signal evoked by the flickering faces with four different expressions, for participants diagnosed with circumscribed social anxiety (N=21) recorded from parieto-occipital electrode site POz. The white line shows the permutation-controlled F-contrast comparing neutral with angry and fearful contents (fearful = angry > neutral).

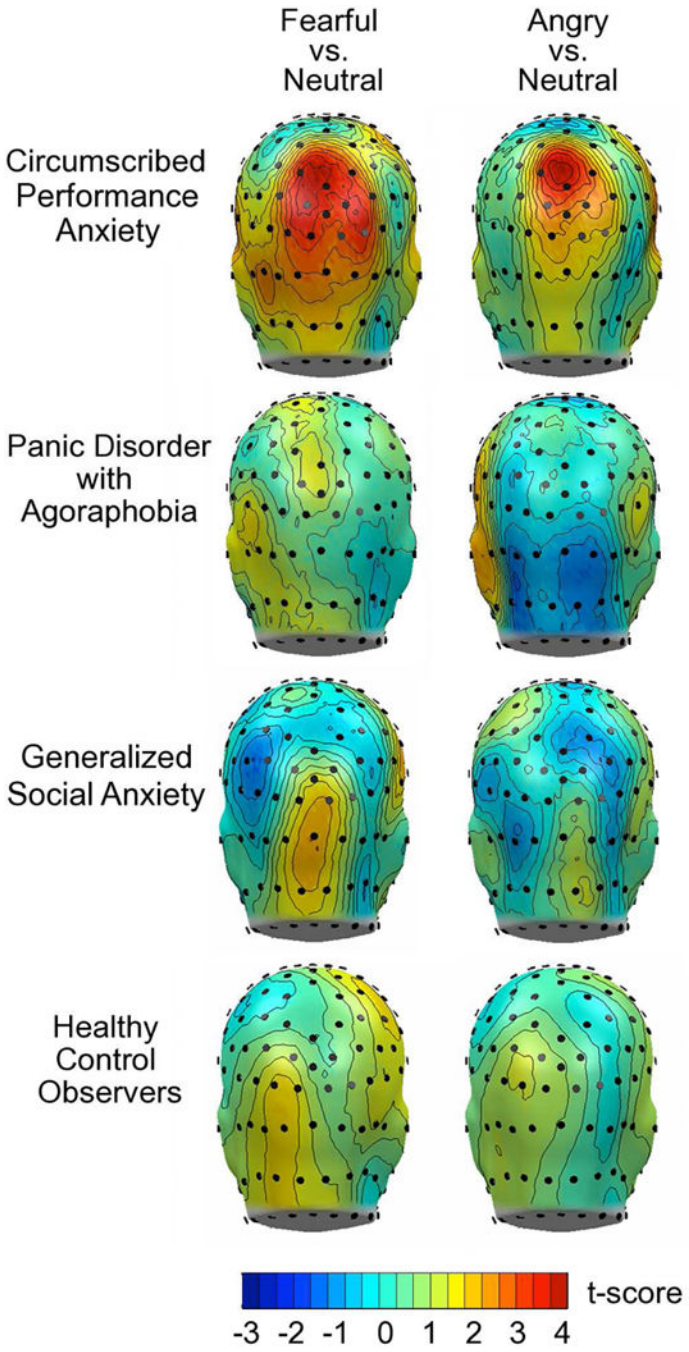

Figure 4.

Mass univariate comparisons by principal disorder of mean ssVEP amplitude across the viewing epoch, evoked by fearful versus neutral and angry versus neutral faces. Red colors indicate significant differences (exceeding a critical t-value of 3.68). Note that reliable ssVEP enhancement during aversive relative to neutral face processing is observed only in participants in the principal circumscribed social anxiety group.

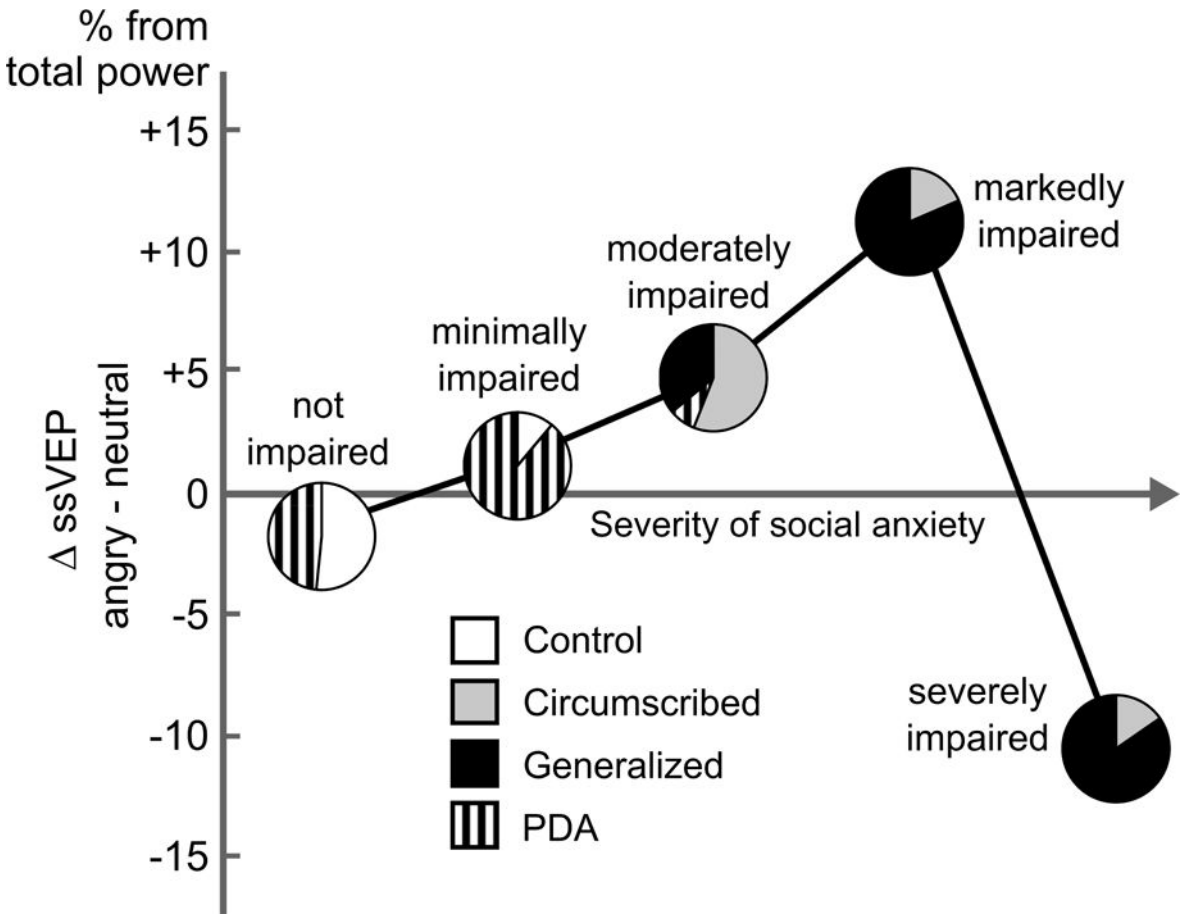

Figure 5.

Differential sensitivity of the visual cortex to angry faces, as a function of social anxiety severity as rated on the Clinical Global Impression Scale (CGI-S) for all participants. Mean difference in ssVEP amplitude is shown transdiagnostically for increasing levels of social anxiety severity, for unimpaired (N =31), minimally impaired (N=9), moderately impaired (N=25), markedly impaired (N=27), and severely impaired (N=13) individuals. Relative contribution of each diagnostic category to the respective severity level is indicated by pie charts.

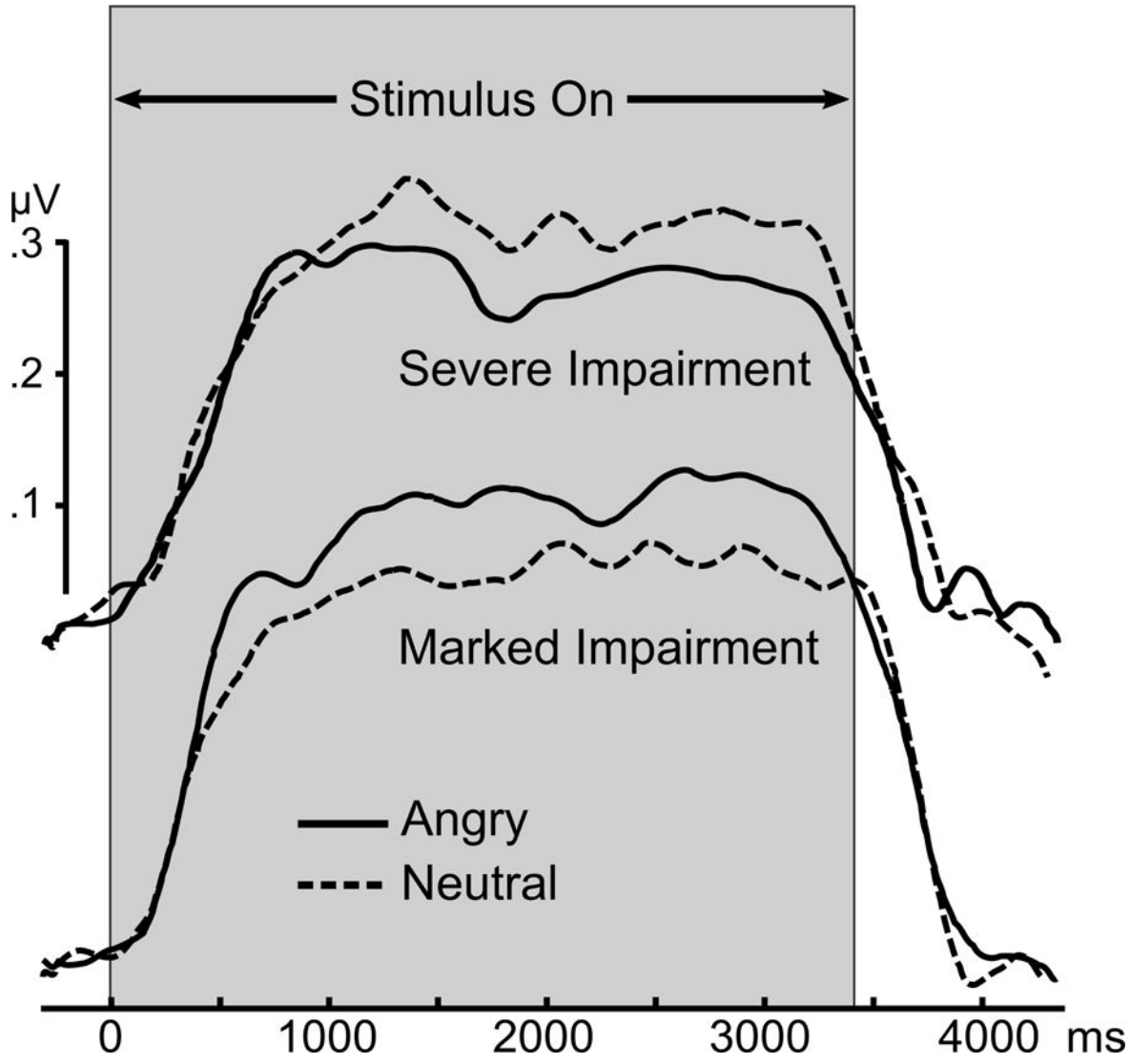

Figure 6.

Grand mean time-varying envelope of the ssVEP signal (from a posterior sensor cluster including Oz and its 8 nearest neighbors) evoked by the flickering faces, comparing angry expressions with neutral expressions, for the two groups characterized as most impaired by social anxiety (markedly impaired (N=27) and severely impaired (N=13) individuals).

Table 1

Steady-state visual evoked potential (ssVEP) amplitude (means and standard deviations) by facial expression for Control, Social Anxiety and Panic Disorder with Agoraphobia Groups

Facial Expression	Control (n=17)	Principal Social Anxiety: Circumscribed (n=21)	Principal Panic Disorder with Agoraphobia (PDA) (n=25)	Principal Social Anxiety: Generalized (n=42)
Neutral	0.24 (0.14)	0.24 (0.21)	0.28 (0.21)	0.22 (0.14)
Happy	0.23 (0.13)	0.24 (0.23)	0.28 (0.24)	0.23 (0.13)
Fearful	0.24 (0.13)	0.29 (0.25)[a]	0.29 (0.24)	0.22 (0.13)
Angry	0.25 (0.14)	0.28 (0.22)	0.27 (0.22)	0.22 (0.13)

[a]=within-group comparison to neutral is significant at $p < .05$. No pairwise between-group comparisons were significant.

Table 2

Questionnaire, interview, and demographic responses (means and standard deviations) for Control, Social Anxiety and Panic Disorder with Agoraphobia (PDA) Groups

Measure	Control (n=17)	Principal Social Anxiety: Circumscribed (n=21)	Principal Panic Disorder with Agoraphobia (n=25)	Principal Social Anxiety: Generalized (n=42)	Group Effect
Social anxiety-related distress					
LSAS-SR Total	19.53 (15.90) *b c d*	53.19 (22.49) *a d*	55.96 (34.36) *a d*	92.21 (19.63) *a b c*	$F(3, 101)= 33.08$, $p< .001$
LSAS-SR Fear	10.59 (7.96) *b c d*	29.38 (11.43) *a d*	30.64 (15.90) *a d*	48.57 (9.81) *a b c*	$F(3, 101)=46.78$, $p< .001$
LSAS-SR Avoidance	8.94 (8.34) *b c d*	23.81 (12.14) *a d*	25.32 (18.79) *a d*	43.64 (10.42) *a b c*	$F(3, 101)= 33.08$, $p< .001$
FSS Social	37.35 (11.64) *b c d*	63.05 (12.84) *a d*	53.40 (17.97) *a d*	78.67 (13.77) *a b c*	$F(3, 101)=38.17$, $p< .001$
Panic-related distress					
PDSS Total	0.06 (0.24) *b c d*	5.71 (4.48) *a c*	14.28 (5.30) *a b d*	9.10 (6.78) *a c*	$F(3, 101)=25.19$, $p< .001$
ASI Total	15.06 (9.56) *c d*	25.14 (14.72) *c*	39.16 (10.27) *a b d*	28.88 (12.04) *a c*	$F(3, 101)=14.52$, $p< .001$
MASQ Anxious Arousal	20.65 (3.43) *c d*	26.05 (7.73) *c*	34.64 (9.93) *a b d*	28.76 (8.35) *c*	$F(3, 101)=10.78$, $p< .001$
FSS Agoraphobia	22.59 (5.12) *c d*	27.62 (8.24) *c*	44.08 (11.75) *a b d*	32.86 (10.98) *a c*	$F(3, 101)=18.51$, $p< .001$
Broad negative affectivity					
MASQ Mixed Symptoms	25.35 (5.44) *b c d*	36.10 (13.23) *a*	41.40 (14.75) *a*	43.52 (10.42) *a*	$F(3, 101)=10.68$, $p< .001$
MASQ General Anxiety	16.47 (4.52) *c d*	22.0 (6.47) *c d*	30.48 (5.80) *a b*	28.05 (7.85) *a b*	$F(3, 101)=18.99$, $p< .001$
MASQ General Depression	18.24 (4.49) *b c d*	28.90 (11.98) *a c*	31.84 (12.08) *a*	37.12 (10.46) *a b*	$F(3, 101)=13.40$, $p< .001$
MASQ Anhedonia	46.65 (10.91) *b c d*	64.10 (16.37) *a d*	73.24 (13.87) *a*	76.24 (14.01) *a b*	$F(3, 101)=19.60$, $p< .001$
BDI-II Total	3.18 (5.27) *b c d*	11.52 (8.49) *a d*	17.76 (10.73) *a d*	18.98 (9.86) *a b*	$F(3, 101)=13.53$, $p< .001$
STAI-Trait	34.0 (7.99) *b c d*	48.24 (11.85) *a d*	52.72 (10.03) *a b*	58.31 (9.34) *a b*	$F(3, 101)=25.33$, $p< .001$
PSWQ	37.35 (8.89) *b c d*	52.67 (15.33) *a d*	59.64 (11.34) *a*	65.40 (10.33) *a b*	$F(3, 101)=25.32$, $p< .001$
Transdiagnostic functional interference					
IIRS Total	18.06 (9.48) *b c d*	37.95 (16.19) *a c d*	52.40 (15.75) *a b*	51.98 (13.92) *a b*	$F(3, 101)=27.21$, $p< .001$
Clinician judgment of distress/impairment					
CGI-S: Social Anxiety	1.06 (0.24) *b d*	4.43 (0.68) *s c d*	1.48 (0.65) *s b c*	5.07 (0.75) *s b c*	$F(3, 101)=253.61$, $p< .001$
CGI-S: Panic Disorder	1.0 (0) *c*	1.05 (0.22) *c*	4.60 (0.58) *a b d*	1.10 (0.48) *c*	$F(3, 101)=432.32$, $p< .001$

Measure	Control (n=17)	Principal Social Anxiety: Circumscribed (n=21)	Principal Panic Disorder with Agoraphobia (n=25)	Principal Social Anxiety: Generalized (n=42)	Group Effect
CGI-S: Agoraphobia	1.0 (0) *c*	1.0 (0) *c*	4.72 (0.79) *a b d*	1.02 (0.15) *c*	$F(3, 101)=550.38$, $p< .001$
CGI-S: Total Axis I/II	29.76 (0.90) *c d*	32.23 (3.56) *c d*	39.04 (5.06) *s b*	36.83 (4.04) *s b*	$F(3, 101)=25.34$, $p< .001$
Treatment Prognosis		2.43 (0.81) *d*	2.80 (1.19) *d*	3.52 (1.21) *b c*	$F(2, 85)=7.54$, $p< .01$
Interview Measures					
Axis I disorders (Count)	0 (0)	1.29 (0.46) *d*	1.60 (0.96) *b d*	1.83 (0.82) *b*	$F(3, 101)=26.37$, p< .001
Comorbid major depressive disorder (%)		14.3	28.0	19.0	X^2 (2)=1.42, *ns*
Demographics					
Age at assessment (Years)	23.94 (6.07) *b*	34.10 (11.71) *d*	34.52 (11.34) *b*	25.14 (7.38) *b*	$F(3, 101)=9.21$, p< .001
Gender (% Female)	47.10	57.10 *d*	60.0 *d*	28.6 *b*	X^2 (3)=8.14, $p< .05$
Race (% Caucasian)	41.20 *b c d*	76.20 *a c*	96.0 *a*	78.60 *a*	X^2 (3)=17.03, $p< .01$
College graduate (%)	41.20	66.70 *d*	44.0	28.60 *b*	X^2 (3)=8.41, $p< .05$

Note. LSAS-SR= Liebowitz Social Anxiety Scale-Self-report Version (58); FSS=Fear Survey Schedule (59); PDSS=Panic Disorder Severity Scale (60); ASI=Anxiety Sensitivity Index (61); MASQ=Mood and Anxiety Symptom Questionnaire (62); BDI-II=Beck Depression Inventory-II (63); STAI= State-Trait Anxiety Inventory (64); PSWQ=Penn State Worry Questionnaire (65); IIRS=Illness Intrusiveness Rating Scale (66); CGI-S=Clinical Global Impressions-Severity rated for respective disorders (7-point scale ranging from 1, Normal/No illness or impairment, to 7, Among the most severely ill patients) (44); Total Axis I/II=sum of ratings of all Axis I disorders assessed on ADIS (anxiety, mood, adjustment, substance use, somatoform, psychosis) as well as Axis II disorders assessed based on elevated SCID-II screener scores (44). Treatment Prognosis=clinician-rated estimate of treatment outcome (scale ranging from 1, *Excellent*, to 7, *Poor*); Superscripts=Results of Tukey HSD or chi-square pairwise between-group comparisons:

a=comparison to control is significant at $p< .05$;

b=comparison to circumscribed social anxiety is significant at $p< .05$;

c=comparison to PDA is significant at $p< .05$.

d=comparison to generalized social anxiety is significant at $p< .05$.