Cortical neurophysiology of anticipatory anxiety: an investigation utilizing steady state probe topography (SSPT)

M. Gray, A.H. Kemp, R.B. Silberstein, and P.J. Nathan*

Neuropsychopharmacology Laboratory, Brain Sciences Institute, Swinburne University of Technology, 400 Burwood Road Hawthorn 3122, Victoria, Australia

Abstract

The precise role of the cortex in human anxiety is not well characterised. Previous imaging research among healthy controls has reported alterations in regional cerebral blood flow (rCBF) within the prefrontal and temporal cortices during periods of anxious anticipation; however, the temporal dynamics of this activity has yet to be examined in detail. The present study examined cortical Steady State Probe Topography (SSPT) changes associated with anticipatory anxiety (AA), allowing examination of the temporal continuity and the excitatory or inhibitory nature of AA activations. We recorded Steady State Visually Evoked Potentials (SSVEPs) at 64 scalp locations, skin conductance, and self reported anxiety among 26 right-handed males while relaxed and during the anticipation of an electric shock. Relative to the baseline condition, the AA condition was associated with significantly higher levels of self-reported anxiety and increased phasic skin conductance levels. Across the seven second imaging window, AA was associated with increased SSVEP latency within medial anterior frontal, left dorsolateral prefrontal and bilateral temporal regions. In contrast, increased SSVEP amplitude and decreased SSVEP latency were observed within occipital regions. The observed SSVEP latency increases within frontal and temporal cortical regions are suggestive of increased localised inhibitory processes within regions reciprocally connected to subcortical limbic structures. Occipital SSVEP latency decreases are suggestive of increased excitatory activity. SSVEP amplitude increases within occipital regions may be associated with an attentional shift from external to internal environment. The current findings provide further support for the involvement of frontal, anterior temporal, and occipital cortical regions during anticipatory anxiety, and suggest that both excitatory and inhibitory processes are associated with AA alterations.
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Introduction

Human anxiety consists of a complex pattern of cognitive, affective, physiological and behavioural changes in response to threat, loss, or perceived negative outcome (Beck and Clark, 1997). Anxiety reactions cross into the spectrum of clinical disorders when they are situationally inappropriate or excessive in duration or degree. Within any one-year period, 5.7% of the Australian population meet the DSM-IV criteria for an anxiety disorder, a level closely matched in both UK and US samples (Andrews et al., 2001), highlighting the importance of gaining a better understanding of the neural underpinnings of anxious symptomatology.

Research within a range of anxiety disorders employing symptom provocation, pharmacological or behavioural challenges, and resting state comparison methodologies has highlighted the fact that in addition to the activity of limbic and brain stem structures, higher cortical areas are functionally significant to the pathophysiology of anxiety. The most consistently reported cortical brain regions with functional significance to anxiety are found within the prefrontal cortex, the temporal cortex (particularly anteriorly) and insula, and within the occipital lobes. Alterations in activity within the prefrontal cortex have been observed amongst a range of patient populations including social phobia (Davidson et al.,

* Corresponding author. Neuropsychopharmacology Laboratory, Brain Sciences Institute, Swinburne University of Technology, 400 Burwood Road Hawthorn 3122, Victoria, Australia. Fax: +61-3-92145525.

E-mail address: pnathan@bsi.swin.edu.au (P.J. Nathan).

2000), simple phobia (SP) (Paquette et al., 2003; Johanson et al., 1998; Fredrickson et al., 1995; Wik et al., 1993), panic disorder (PD) (Boshuisen et al., 2002; Bremner et al., 2000; Meyer et al., 2000; Malizia et al., 1998; Nordahl et al., 1998, 1990; De Cristofaro et al., 1993), post traumatic stress disorder (PTSD) (Shaw et al., 2002; Osuch et al., 2001; Mirzaei et al., 2001; Semple et al., 2000, 1993; Liberzon et al., 1999; Shin et al., 1999; Zubieta et al., 1999), and obsessive compulsive disorder (OCD) (Rauch et al., 2002; Lucey et al., 1997; Schwartz et al., 1996; Rubin et al., 1992; Zohar et al., 1989; Baxter et al., 1987). The results of the above studies are consistent with the hypothesis that prefrontal cortical regions (particularly within the right hemisphere) are involved with the regulation and control of anxiety by regulating the activity of subcortical limbic areas including the anterior cingulate and amygdala (Davidson, 2002; Davidson and Irwin, 1999).

Alterations in temporal lobe function associated with anxious symptomatology have also been frequently reported. Increased temporal lobe rCBF activity was reported among patients with generalised anxiety disorder (GAD) (Johanson et al., 1992; Wu et al., 1991), OCD (Breiter et al., 1996), SP (Rauch et al., 1995; Davidson et al., 2000), PD (Boshuisen et al., 2002) and PTSD (Shin et al., 1999). Increased rCBF was observed within the right insula of SP (Rauch et al., 1995) and OCD patients (Breiter et al., 1996) and among SP, OCD and PTSD patients (Osuch et al., 2001; Shin et al., 1999; Rauch et al., 1997). Decreased rCBF has been reported within the parietotemporal cortex (Meyer et al., 2000; Bisaga et al., 1998) and anterior insula (Boshuisen et al., 2002) of PD patients, and within the temporal polar cortices of SP patients (Fredrickson et al., 1995). Anxious symptomatology has also been associated with alterations in occipital lobe activity. Reduced rCBF within primary and secondary visual cortical areas has been reported among SP patients (Wik et al., 1996, 1993) and PTSD patients (Mirzaei et al., 2001). Increases in occipital rCBF have also been reported among subjects with PTSD (Rauch et al., 1996), SP (Paquette et al., 2003; Fredrikson et al., 1993 1997), GAD (Wu et al., 1991) which were attenuated after benzodiazepine treatment (Buchsbaum et al., 1987), and subjects with OCD (Zohar, 1989).

Pharmacological challenges, whilst providing another avenue for investigation of the neural basis of anxious symptomatology, are somewhat difficult to synthesize because of the use of various panicogens (CCK-4, pentagastrin, yohimbine, lactate, and CO_2 inhalation) in both clinical and normal groups. Although each of these agents may be used to induce anxious symptomatology to varying degrees within patients and controls, each has a differing influence on the adrenergic and vascular functioning of the central nervous system. As a result, the specific results appear somewhat contradictory, however regional cortical alterations within PFC, temporal lobes and insula, and occipital cortex are commonly reported (Boshuisen et al., 2002; Cameron et al., 2000; Javanmand et al., 1999; Bremner et al., 1997; Benkelfat et al., 1995; De Cristofaro et al., 1993;

Stewart et al., 1988; Gur et al., 1987), highlighting the involvement of these cortical regions during periods of anxiety.

While clinical anxiety represents an excessive or inappropriate response to perceived threat, the underlying neural circuitry associated with the basic components of anxiety reactions may be common to both healthy and pathological anxiety. Research within healthy adults aims at delineating the specific neural circuitry involved in the normal emotional self regulation associated with the various aspects of anxiety reactions, providing a baseline for comparison with the disordered and excessive reactions observed within clinical populations. Evidence suggests that although disorder specific abnormalities are observed within unique systems, there is a core system comprised of elements of the paralimbic belt which is common to anxiety states within both a range of clinical anxiety populations, and within physiological or normal anxiety (Rauch et al., 1997). Cortical activations associated with anxiety within healthy control subjects are generally consistent to those observed amongst clinical populations. Experimentally induced anxiety has also been associated with activity within the prefrontal cortex (Simpson et al., 2001; Liotti et al., 2000; Critchley et al., 2001; Chua et al., 1999). The results of Simpson et al. (2001) suggests a dynamic interrelationship between decreased rCBF within the PFC, attentional focus and subjective levels of anxiety. These authors propose that the ability to remain relaxed during anxiety provocation was associated with successful suppression of prefrontal cortical activity in the face of threatening aversive environmental stimuli. Activations within the temporal poles and within the right superior temporal sulcus and bilateral insula have also been reported within healthy anxious subjects, as have activations within occipital cortical regions (Paquette et al., 2003; Liotti et al., 2000; Kimbrell et al., 1999; Reiman et al., 1989).

Anticipatory Anxiety (AA) is one of the most basic forms of anxiety, and while being experienced by normal individuals, also occurs within a number of clinical anxiety disorders such as PD and phobias. AA refers to human anxiety that is focused on an imminent threat or danger and is typically associated with sympathetic arousal and fight or flight reactions. AA can be differentiated from the more long term and distally focused anxiety, such as worry, which may largely constitute disorders such as GAD in a similar fashion to Heller et al.'s (1997) differentiation of Anxious Arousal from the more generalised Anxious Apprehension. AA has previously been induced within healthy male controls via the expectation of an unpleasant electric shock (Simpson et al., 2001; Chua et al., 1999; Reiman et al., 1989). AA is also associated with arousal of the central autonomic nervous system, previously gauged by examination of electrodermal activity (Chua et al., 1999; Kopacz and Smith, 1971). These previous investigations amongst healthy controls have employed Positron Emission Tomography (PET) to investigate the alterations in cerebral metabolic function associated with AA. Whilst providing data

with an exceptional spatial resolution, PET data is less able to provide fine-grained information on when these changes occur and insight into the temporal continuity of AA activations.

In the current study, we aimed to examine electrical brain activity associated with AA using an electrophysiological technique called Steady State Probe Topography (SSPT). SSPT is a variant of EEG which allows the examination of cortical electrical activity on a millisecond timescale. Previous studies also have indicated that SSVEP is relatively insensitive to noise contamination from sources including Electroccculargraphic (EOG), eye blink, 50 Hz mains, and electromyographic (EMG) noise (Silberstein et al., 1998; Regan 1989). Furthermore, studies within our laboratory suggest that SSVEPs are sensitive to cognitive (Silberstein et al., 1998, 1996) and emotional alterations (Kemp et al., 2003, 2002, in press). In addition, the differing neural basis of PET and SSVEP data may provide complementary information the metabolic demands and excitatory or inhibitory nature of localized cortical activity.

Methods

Subjects

Twenty-six healthy males (age = 23.4 yrs, ±4.0) participated in the present study. Prior to inclusion in the study, all subjects underwent a medical examination, screening for physical illness, and past or present neuropsychiatric disorders. Subjects were non-smokers and were free of psychotropic or prescribed medications. All subjects were strongly right handed as assessed by the Edinburgh Handedness Inventory (Oldfield et al., 1971). Subjects were recruited via university notice board advertisements, and were generally well educated (education = 15.2 years, ±2.0 yrs). All subjects gave written informed consent to take part in the study, which was approved by the Swinburne University Human Research Ethics Committee.

Behavioural measures

Upon arrival subjects completed the Stait Trait Anxiety Inventory (STAI) State and Trait versions (Spielberger et al., 1970), and the Beck Depression Inventory (BDI) to assess levels of anxious and depressive symptomatology (Beck et al., 1961). Subjects also completed a Visual Analogue Scale (VAS) measure of anxiety prior to scanning, after the baseline scan and again after the anxiety-inducing scan. The VAS consisted of three 100 mm lines anchored at each end with the words relaxed/anxious, calm/nervous, and tense/peaceful.

Experimental tasks

Subjects completed a simple computer based Continuous Performance Task, the CPT-AX under two conditions; a relaxed followed by an anticipatory anxiety condition. The CPT-AX task, previously described in Silberstein et al. (2000, 1998, 1996), was included in order to ensure a basic level of cognitive activity which was consistent between task conditions. Subjects were instructed to view a computer monitor upon which a random letter appeared every 1.5 sec, remaining on the screen for 1.2 sec after which it was replaced by a central fixation cross. Subjects held a button box and were required to make a button press on the unpredictable appearance of the letter X, only when this was preceded by the letter A. The ratio of targets to non-targets was set at 1:4. The letters subtended a vertical and horizontal angle of approximately 1.2 degrees when viewed at the fixed distance of 2.3 meters. During the relaxed task condition, a 1.2 cm blue border framed the stimulus presentation screen. Subjects were assured that they would not receive any electric shocks during the baseline task. During the anticipatory anxiety condition, SS performed the same CPT-AX task. As in the control condition, this task began with a blue-bordered screen. Every 25 sec, this border changed from blue to red, for a period of 11 sec. This occurred 11 times throughout the task. SS were informed that during this task they may receive electric shocks at any time during the red border display. Five shocks were administered at varying latencies after red border onset, ensuring that subjects could not predict the exact timing of electrical stimulation.

Procedure—experimental design

Subjects sat in a quiet recording room 2.3 meters from the task computer monitor. Brain electrical activity was recorded through an electrode cap containing 64 electrodes (10–20 international location system and other midpoint electrodes), with linked ear electrodes as a reference and a nose electrode as ground. Half-mirrored goggles were fitted which emitted a flickering mild white light (13 Hz) while allowing subjects to see the computer monitor before them. Subjects completed the baseline task while SSPT data was collected. An isolated stimulator CMS1-200 (Dogwood scientific equipment) was used to deliver electrical stimulation via electrodes applied to the dorsal aspect of the subjects' right hand immediately prior to completion of the AA condition. Shocks were set at a predetermined level of 30 mA, 115 v (maximum).

SSPT signal processing

The key features of the SSPT signal processing employed is described in Silberstein et al. (1995, 1990). Brain electrical activity was amplified and filtered with a 0.74 Hz high pass filter and a 74 Hz low pass filter prior to digitization (16 bit accuracy). Electrical activity was recorded at a sampling rate of 500 Hz. SSVEPs, induced via a spatially uniform 13 Hz visual flicker were extracted from the brain electrical activity by calculating the sine and cosine Fourier Transform (FT) coefficients at each stimulus cycle during each task recording. FT coefficients were smoothed to re-

duce noise by averaging overlapping blocks of 10 stimulus cycles. All data were checked for artifact within each electrode as described in Silberstein et al. (1995).

SSVEP data analysis

The SSVEP was first epoched to provide measures of cortical activity within the relaxed and AA conditions. During the relaxed condition, nine seven-second periods were randomly selected and averaged to form an epoch of relaxed task SSVEPs for each subject. Similarly, nine seven-second epochs were selected during the AA condition. These epochs were chosen so that they began upon the presentation of the red-bordered screen and ended before shock delivery. Electrical stimulation was delivered within the first 1.5 sec of the red border presentation during the remaining AA periods, and as a result these were not included as AA SSVEP epochs. The task characteristics during the relaxed and AA epochs were matched, so that each contained the same number of A and X targets as well as the same number of AX responses required. SSVEP data is comprised of both amplitude; the size of the SSVEP signal recorded at each electrode site, and phase components; alterations in the time between sinusoidal steady state visual stimuli presentation, and their expression as SSVEP within the cortex. SSVEP amplitude was normalized by subtracting the average amplitude for all electrodes from each electrode time series (discrete waveform) data, for each subject. SSVEP phase was normalized by subtracting the mean phase for each electrode from its time series for each subject. Cross subject averages were then constructed for each task condition, providing averaged SSVEP maps for each of the 91 data cycles (13 Hz × 7 sec) within both the relaxed baseline and AA conditions.

Topographic mapping of SSVEP data

Difference maps, subtracting the relaxed condition SSVEP from the SSVEP obtained during the AA condition, were generated to provide a measure of electro-cortical activity observed during periods of anticipatory anxiety. SSVEP phase variations are presented in millisecond (msec) latencies; (change in phase/$2 \times \pi$) × (1000/13). Hotellings T statistics indicating the statistical strength of differences in amplitude and phase combined were also calculated. Previous spatial component analysis of SSVEP data suggests that 5 independent factors are represented in SSVEP data (Silberstein et al., 1995). As a result, Hotellings T *p* values (2-tailed) have been divided by 5 before being reported. Hotellings T statistics are presented as topographic maps illustrating the statistical significance of differences in amplitude and latency at each electrode. Contour lines illustrate areas of statistical significant at 0.05 and 0.01 and 0.001 alpha levels.

Statistical cluster plot & component mapping

A statistical cluster plot displaying Hotellings T data across all electrodes (y-axis) and time-points (x-axis) was generated to investigate the location and time course of significant SSVEP differences. One benefit of statistical cluster plots is their ability to display data at each time point across all electrodes, providing a clear summary of temporal patterns of significance. While datasets comprised of numerous point wise *t*-tests will contain randomly distributed type 1 error, clusters of statistical significance are likely to reflect real effects, and may provide a useful guide for further examination (Murray et al., 2002; Guthrie and Buchwald, 1991). Electrodes are approximately separated into frontal (electrodes 0–20, including Fp1, Fp2, F7, F3, Fz, F4, and F8), parieto-temporal (electrodes 21–52, including T3, C3, Cz, C4, T4, T5, P3, Pz, P4, and T6) and occipital (electrodes 53–63, including O1, Oz, and O2) locations. The two clusters of significant differences within frontal/temporal electrodes clearly evident in the statistical cluster plot were further examined by generating early and late epochs (each 1 sec at 13 Hz), applying the original normalisation routine, and averaging the resulting data sets to form topographic maps.

Electrodermal data analysis

Electrodermal measures of skin conductance (SC) were recorded throughout the baseline and AA conditions for 14 of the 26 subjects using the Psylab SC5-SA skin conductance and temperature coupler. Electrodes were located on the distal phalanx of index and middle fingers, and a hypoallergenic gel ensured contact between the skin and electrode. Skin conductance was recorded at 40 Hz and digitized to 24-bit accuracy at the electrode site, producing SC data with an absolute accuracy of 0.1 micro siemens. Mean Skin Conductance Level (SCL) was chosen as an electrodermal index of sympathetic nervous system arousal, as this measure is able to reflect differences in both the amplitude and the frequency of non-specific skin conductance responses, as well as general phasic increases in galvanic SC. In order to ensure SCLs were not artificially inflated by shock delivery, we selected the four red-bordered epochs during which no shocks were actually delivered. These were averaged together to provide a measure of AA SC for each subject. Relaxed SC was constructed from the average of the entire baseline condition.

EMG artifact investigation

In order to ensure the results from our study were not contaminated by electromyographic (EMG) noise, we examined the influence of EMG activity on SSVEP profiles. A subset of 15 subjects were quasi-randomly selected to complete an EMG artifact condition immediately following the recording of the baseline AX condition. Subjects instructed to complete the baseline AX task a second time while

clenching their jaw every 2 to 3 sec. Apart from this, the task instructions were identical, as were data analysis procedures.

Results

The BDI scores ($M = 5.3$, SD $= 5.7$) indicated that no subjects suffered from depressive symptomatology to any discernable extent. These scores are within the normal BDI range for male college students. Likewise the trait STAI scores ($M = 36.4$, SD $= 7.6$) also indicated that all subjects were within the normal ranges (Spielberger et al., 1970). State STAI scores ($M = 32.3$, SD $= 6.8$) indicated that subjects were reasonably relaxed before testing commenced. VAS scores indicated that subjects were significantly more anxious during the anxiety induction task $t(21) = 8.194$, $p < 0.001$, see Fig. 1.

EMG artefact results

Mann-Whitney U non-parametric tests for independent samples indicated that the 15 subjects included in the EMG control study were not significantly different from the remaining 11 subjects in terms of STAI (state or trait measures), BDI scores, or VAS levels during either the relaxed or anticipatory conditions. Hotellings T analysis failed to reveal any significant differences at any electrode site between SSPTs recorded during the baseline and the EMG artifact condition.

Behavioural self-report measures and SCL

Again, Mann-Whitney U analysis indicated that the 14 subjects for which SCL data was recorded were not significantly different from the remaining subjects in terms of STAI (state or trait measures), BDI scores, or VAS levels during either the relaxed or anticipatory conditions. Analysis of SC data revealed significant increases in sympathetic nervous system arousal during the AA condition, relative to the baseline $t(13) = 3.256$, $p = 0.006$, see Fig. 1.

SSVEP data

We first examined the SSVEP difference data across the seven-second epoch as a whole. Fig. 2 (left) shows the mean SSVEP maps specific to the AA condition. Hotellings T data is presented as a topographic map illustrating the statistical significance of AA specific differences in SSVEP data (considering both amplitude and latency differences). Across the entire 7 sec epoch, AA was associated with significant alterations in SSVEPs within the medial (midline) anterior frontal cortex, left dorsolateral prefrontal cortex, bilateral temporal lobes, and left occipital cortex. Fig. 2 also illustrates differences in both the amplitude and latency components of the SSVEP's. Warmer colours indicate re-

duced SSVEP amplitude and latency in the AA condition relative to the baseline scan. Significant alterations within frontal and temporal electrodes are associated predominately with increases in SSVEP latency. SSVEP amplitude increases are evident only within the occipital cortex. Widespread latency reductions are evident within bilateral occipital lobes; however, only a smaller portion of the left occipital lobe reached statistical significance.

In order to examine the temporal nature of the observed alterations in SSVEPs, we generated a Hotellings T statistical cluster plot which displays the significant SSVEP differences for all electrodes (y-axis) across time (x-axis) (see Fig. 2, right). An examination of the statistical cluster plot indicates that the majority of significant frontal and temporal differences occur in two bursts, an initial early component (692–1692 ms) and a later component (5000–6000 ms) indicated by the white banded regions in Fig. 2. The occipital activations conversely are relatively stable and consistent throughout the windowing period, and are therefore reasonably illustrated within the 7 sec epoch mean topographic maps. In order to examine frontal and temporal activations, we generated SSVEP mean topographic maps for both these early and late components (see Fig. 3).

Within both the early (692–1692 ms) and late (5000–6000 ms) epochs, significant differences are again primarily driven by alterations in SSVEP latency. During the early component epoch (692–1692 ms), SSVEP latency increases reached significance within midline prefrontal electrodes and left dorsolateral prefrontal electrodes. Further examination reveals the largest latency increases within temporal electrodes (particularly left hemisphere) and left dorsolateral electrodes. As in the entire epoch mean (Fig. 2), occipital latency reductions are evident, reaching significance within the left occipital lobe. SSVEP amplitude changes are relatively modest, with minor amplitude reductions within the left frontal lobe and amplitude increases within the right frontal and temporal lobes and within bilateral occipital lobes. During the later component epoch (5000–6000 ms), significant differences are observed within large regions of the bilateral frontal lobes, within the right temporal lobe, and bilateral occipital lobes. Occipital amplitude and latency increases are more pronounced during the later component. Relative to the early component, SSVEP latency increases are attenuated within the temporal lobes, particularly within the left hemisphere, whilst within prefrontal electrodes, larger latency increases are evident, particularly within bilateral anterior frontal electrodes.

Further examination of the temporal profile of SSVEP latency changes within the temporal lobes revealed some evidence of hemispheric differences. Fig. 4 displays the SSVEP latency changes recorded at 3 temporal lobe electrodes within each hemisphere across the entire 7 sec epoch. During the early component, the left hemisphere latency increases are larger, more uniform, and more sharply defined than within the right hemisphere.
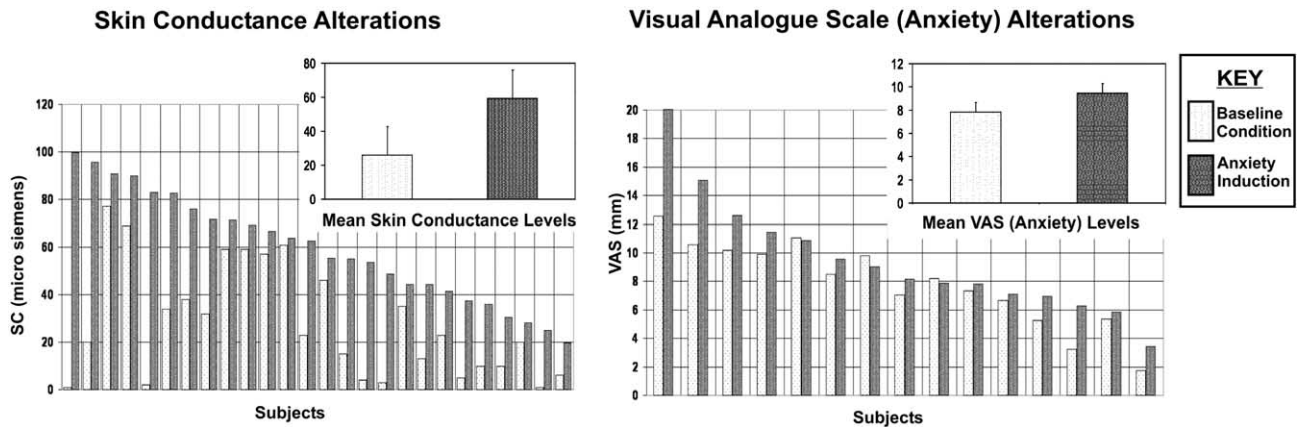
Skin Conductance Alterations

Visual Analogue Scale (Anxiety) Alterations

Fig. 1. Skin conductance and visual analogue scale (Anxiety) measures during baseline and anticipatory anxiety conditions.

Discussion

The current study examined the temporal processing of AA within healthy male subjects. Our findings suggest that AA is associated with two predominant electrophysiological changes; (1) significant SSVEP latency increases within prefrontal and temporal cortical regions, and (2) significant SSVEP latency decreases and amplitude increases within occipital regions. Whilst occipital SSVEP latency decreases and amplitude increases were evident throughout the anxious anticipatory epoch, frontal and temporal lobe latency increases were more transitory, appearing within the first sec, and again within the fifth sec of the imaging window. These cortical activations were associated with concomitant increases in self-reported anxiety and electrodermal activity.

In terms of regional cortical alterations, the present findings are consistent with a large amount of previous research amongst both patient groups and healthy controls. Anxiety associated prefrontal increases in rCBF have been frequently reported by metabolic imaging studies (Paquette et al., 2003; Rauch et al., 2002, 1997; Meyer et al., 2000; Zubieta et al., 1999; Shin et al., 1999; Malizia et al., 1999; Liberzon et al., 1999; Johanson et al., 1998; Nordahl et al., 1998, 1990; Breiter et al., 1996; Semple et al., 1993; Rubin et al., 1992; Wu et al., 1991; Swedo et al., 1989; Baxter et al., 1987). Previously reported increased rCBF within anterior temporal lobes and insula are also consistent with the significant SSVEP alterations we observed within temporal lobe electrodes (Boshuisen et al., 2002; Osuch et al., 2001; Meyer et al., 2000; Liotti et al., 2000; Chua et al., 1999; Shin et al., 1999; Rauch et al., 1997, 1996, 1995; Breiter et
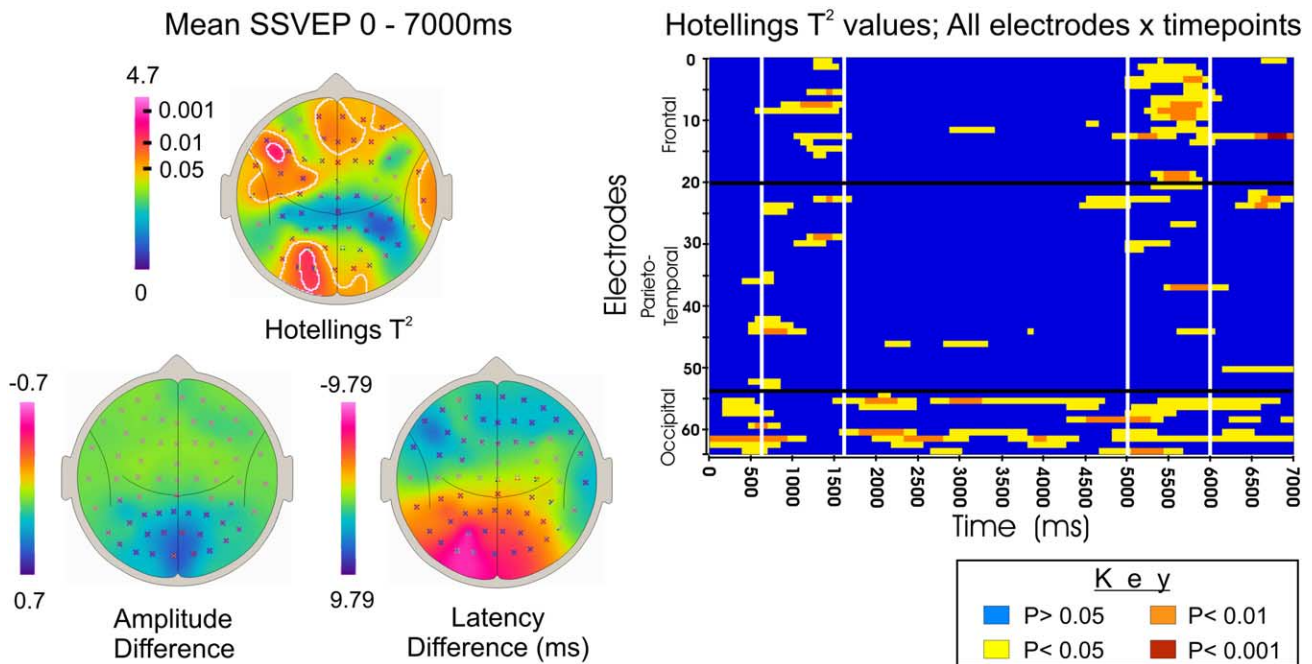

Fig. 2. SSVEP amplitude and latency changes and Hotellings T values during anticipatory anxiety induction (left) and statistical cluster plot illustrating the selection of the early and late epochs (right).
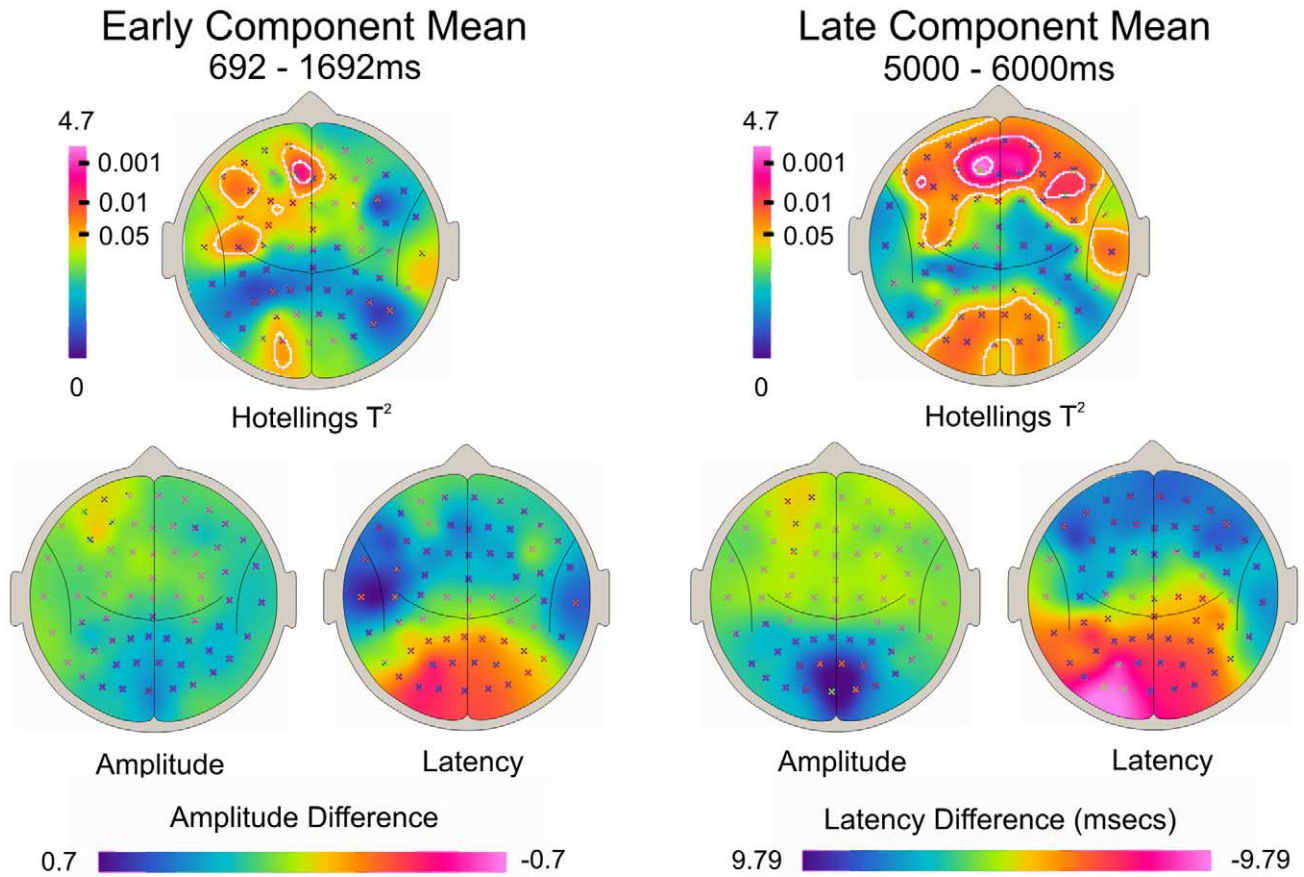
Fig. 3. Mean SSVEP amplitude, latency and Hotellings T during early and late components.
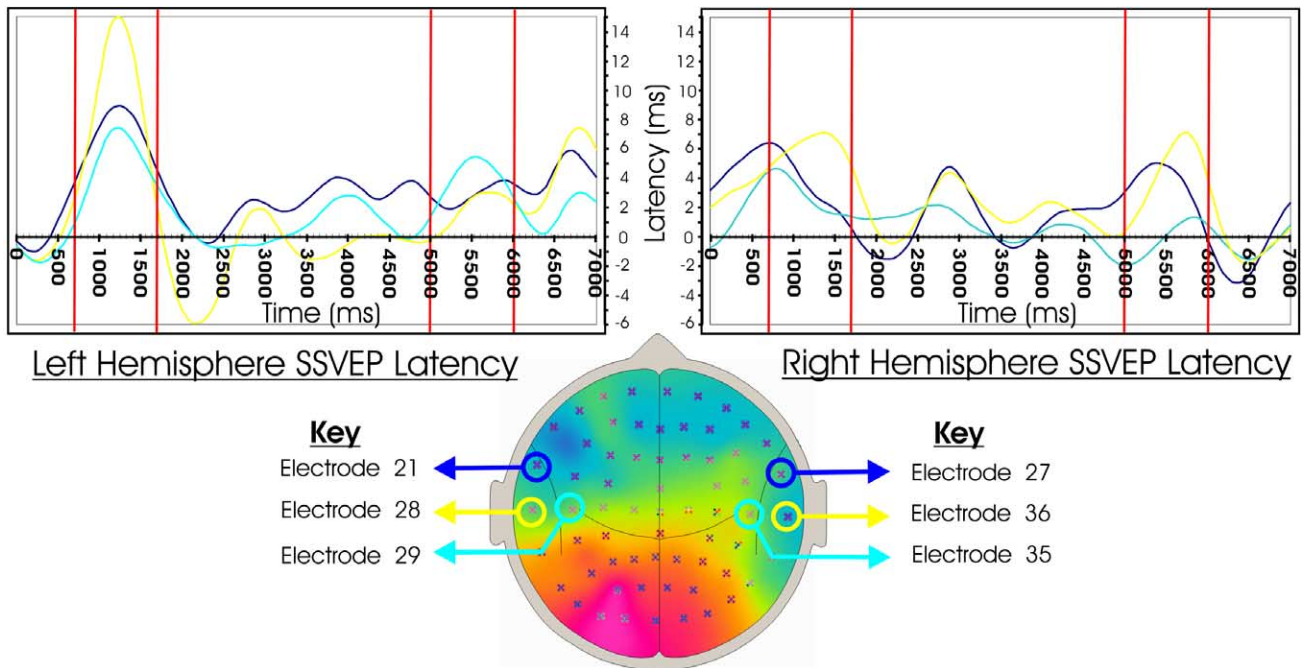

Fig. 4. SSVEP latency changes within temporal lobe electrodes across the seven second imaging epoch. Early and late components are indicated by red banded regions.

al., 1996; Johanson et al., 1992; Wu et al., 1991; Reiman et al., 1989). Likewise, regional anxiety associated changes within the occipital cortex previously reported are also evident in the present results (Paquette et al., 2003; Mirzaei et al., 2001; Fredrikson et al., 1997; Rauch et al., 1996; De Cristofaro et al., 1993; Wu et al., 1991, Zohar et al., 1989; Stewart et al., 1988; Buchsbaum et al., 1987).

SSVEPs are comprised of both amplitude and latency components, each of which reflect different aspects of regional cortical network activation. Variations in SSVEP latency have been previously interpreted as an index of variations in neural information processing speed, and are likely to result from alterations in the loop transmission time of local cortico-cortical feedback loops (Kemp et al., 2002; Silberstein et al., 2001, 1995). Previous research within our institute has illustrated correlations between reaction time during a visual vigilance task and SSVEP latency (Silberstein et al., 1996). In addition, SSVEP latency reductions within prefrontal electrodes observed within normal children during attentional tasks are attenuated among children with attention deficit hyperactivity disorder (Silberstein et al., 1998), further strengthening the association between latency decreases and normal excitatory processes. Alterations in SSVEP latency are understood to result from the excitatory and inhibitory neuromodulation of regional cortico-cortical resonances (Silberstein et al., 2000, Regan, 1989). The release of neurotransmitters such as acetylcholine (ACh) are believed to reduce the cortico-cortical loop time in a similar way to the increases in thalamocortical transmission speeds following cortical ACh release observed within animal research (Metherate and Ashe, 1993). Likewise increases in latency are likely to be associated with inhibitory neuromodulation of cortico-cortical feedback loops, possibly via inhibitory interneurons such as golgi, basket and stellate cells (Attwell and Iadecola, 2002; Koos et al., 1999). SSVEP amplitude is, in some respects, analogous to EEG amplitude within the alpha bandwidth, such that regional event related desynchronisation results in relative EEG alpha and SSVEP amplitude reductions (Pfurtscheller and Lopes da Silva, 1999). Conversely, increases in the number of neurons recruited into synchronously activated cortico-cortical rhythmic activity results in cortico-cortical loop gain, or relative SSVEP amplitude increases.

The present findings of increased SSVEP latency within frontal electrodes may be interpreted as evidence of an increase in neurochemically modulated inhibitory cortical activity. These results suggest that previously reported PFC increases in rCBF may be associated with increased localised inhibition. Regions within the prefrontal cortex have long been understood to have a role in the modulation and inhibition of subcortical limbic structures including the amygdala and cingulate (Carr et al., 2003; Quirk and Gehlert, 2003; Davidson et al., 2002; Cardinal et al., 2002; Niemer and Goodfellow, 1966). The amygdala is well known to be necessary for the development of conditioned fear (LeDoux, 1996) and communicates with regions within

the prefrontal cortex including the orbitofrontal cortex via direct excitatory efferents and the dorsolateral prefrontal cortex through a smaller number of excitatory efferents as well as pathways through the orbitofrontal cortex (Barbas, 2000). Glutamatergic projections from the PFC are believed to project to GABAergic neurons which synapse on the amygdala, allowing both the PFC and amygdala to modulate each other during cognitive-emotional processing (Davidson et al., 2002; LeDoux, 1996). Disruption of this co-modulation may underlie increased PFC activation observed within clinical populations (Barbas, 2000). The increased SSVEP latency within dorsolateral and anterior PFC electrodes amongst our healthy subjects during AA may be associated with increased inhibition within localised PFC circuits occurring in response to increased excitatory input from the amygdala, although without the ability to concurrently image amygdala activity, this interpretation must remain speculative. The significant SSVEP alterations within the left dorsolateral PFC evident in the epoch mean data and also within both the early and late frontal components lies approximately over Brodmann's area 8, an area which is known to receive robust projections from visual association cortices within primates, and may be associated with visual attentive aspects of the PFC's selection of emotionally appropriate responding (Barbas, 2000). In addition, anxiety induced increases in inhibitory activity within prefrontal regions accords well with deficits in processes subserved by prefrontal information processing during anxiety, including attentional biases and working memory deficits (Ninan and Berger, 2001; Mogg and Bradley, 1998; Beck, 1976).

Increases in localised inhibitory processes associated with the observed significant SSVEP latency increases within the right temporal lobe are consistent with many previous reports of anxiety associated rCBF increases within the temporal lobes of both patients and healthy controls (Paquette et al., 2003; Boshuisen et al., 2002; Liotti et al., 2000; Meyer et al., 2000; Chua et al., 1999; Rauch et al., 1997, 1995; Breiter et al., 1996; Johanson et al., 1992; Wu et al., 1991; Reiman et al., 1989). The frequently reported activity within temporal cortices observed during the imaging of human anxiety has previously been related to visceral processing by the agranular neurons within the medial wall of the temporal lobe and insula (Chua et al., 1999; Mesulam and Mufsom 1982a). The temporal poles and insula form part of the paralimbic cortex, reciprocally connected to the amygdala, orbitofrontal and dorsolateral PFC and cingulate gyrus, and are thought to integrate internal and external environmental information useful for selection of appropriate responses during situations involving threat, helplessness or danger (Barbas, 2000; Pandya, 1995, Reiman et al., 1989; Mesulam and Mufsom, 1982b). Our findings of increased SSVEP latency within temporal lobe electrodes suggests that within these regions AA is again associated with increased localised inhibitory modulation of cortico-cortical oscillatory activity. Our findings of larger latency increases and more frequently significant right temporal

lobe alterations, relative to the left hemisphere within both the later component and overall epoch means are consistent with the more frequent reports of rCBF increases within the right temporal lobe, relative to the left associated with anxiety specifically, and emotional processing generally (Heilman, 1997; Heller et al., 1997; Ross, 1981). It is interesting to note, however, that the largest SSVEP latency increases were observed within the left hemisphere during the early component. This is consistent with largest rCBF increases within the left insula of healthy males anticipating an electric shock reported by Chua et al. (1999). Davidson et al. (2002) suggests that the left PFC particularly may be involved with inhibitory control of amygdala activity. Our results indicate that this latency increase was more clearly defined within the left hemisphere, providing some evidence of hemispheric differences in the temporal lobe involvement during AA.

The results from the EMG artefact condition have particular relevance to the observed changes within the temporal lobes. Acute periods of anxiety are commonly associated with increases in muscle tension, which significantly increases the risk of EMG artefact during electrophysiological recordings of brain activity. Previous reports on anxiety induced alterations in temporal lobe function have had to defend against claims of EMG artefact (Benkelfat et al., 1995; Drevets et al., 1992). Our findings of no significant SSVEP differences between the baseline and EMG artefact conditions suggest that the observed results are indeed related to temporal lobe function.

A significant amount of research has reported increased activation of the occipital cortex associated with both the visual processing of emotionally valanced stimuli (Kemp et al., 2002; Phan et al., 2002; Lane et al., 1999; Lang et al., 1998; Morris et al., 1998), and with anxiety, within patient groups and anxious controls (Paquette 2003; Fredrikson et al., 1997, 1993; Rauch et al., 1996; Breiter et al., 1996; De Cristofaro et al., 1993; Wik et al., 1993; Wu et al., 1991; Zohar et al., 1989; Gur et al., 1987). Wik et al., (1996) observed anxiety related decreases in rCBF within primary visual cortical regions amongst phobics which may be associated with anticipatory coping. Within occipital electrodes, we also observed significant SSVEP alterations during periods of anxious anticipation. These were generally observed within the left hemisphere, and were localised with decreases in SSVEP latency observed within occipital electrodes. Regions of the limbic cortex including the anterior temporal lobes, orbitofrontal and dorsolateral PFC and the magnocellular portion of the basal nucleus of the amygdala are reciprocally connected to the primary visual cortex and widespread regions of the extra-striate cortex (Weller et al., 2002; Linke et al., 1999; Barbas, 1995). This connectivity is likely to underlie visual cortex alterations observed not only during anxiety induction, but also more generally during emotional processing (Phan et al., 2002; Davis and Whalen, 2001; Lang et al., 1998; Morris et al., 1998; Breiter et al., 1996). The decreased SSVEP latency observed within occipital electrodes is consistent with an increase in lo-

calised excitatory processes, possibly associated with increased modulation of visual processing by regions of the limbic system including the amygdala (LeDoux, 1996). Our previous studies have reported SSVEP amplitude decreases within extra-striate visual areas associated with increased visual vigilance during continuous performance attentional tasks (Nield et al., 1998; Silberstein et al., 1990). In contrast, the present results indicate SSVEP amplitude increases within extra-striate cortex during periods of AA. We hypothesise that this may be due to a shift in attentional focus away from the visual aspects of the task in the face of intense emotional induction. This is consistent with previous findings that while highly trait anxious controls shift attention towards anxiety inducing stimuli, normal controls tend to divert attention from anxiety inducing stimuli (Wilson and MacLeod, 2003; Mogg and Bradley, 2002; Clark, 1999; Vasey et al., 1996).

Scalp recorded SSVEP's are generated by the synchronised firing of pyramidal neurons lying within layers 2 and 3 of the cortex (Silberstein et al., 2001; Regan, 1989). Alterations in rCBF measured by metabolic imaging methodologies, such as PET and fMRI are understood to be driven by the synaptic energy requirements of re-establishing ionic concentrations and neurotransmitter repackaging (Arthurs et al., 2002, Attwell and Iadecola, 2002, Attwell and Laughlin, 2001; Jueptner and Weiller, 1995). Logothetis and colleagues have recently shown in a fascinating series of articles that rCBF as indexed by the BOLD response is closely correlated with local field potentials within the occipital cortex, strengthening the association between excitatory driven BOLD responses and cortical local field potentials (Logothetis et al., 2003, 2001; Logothetis, 2002). A number of researchers have argued that both inhibitory and excitatory activity is associated with increased rCBF resulting from ion recycling and ion gradient restoration (Arthurs et al., 2002, Jueptner and Weiller, 1995, Nudo and Masterton, 1986, Ackermann et al., 1984). Although metabolic imaging methodologies and electro-cortically recorded field potentials gauge information processing within cortical regions, the differing neurological basis of each methodology may provide complementary perspectives on regional cortical activity. Our findings of region specific excitatory and inhibitory processes in areas previously associated with rCBF increases suggests that further research could benefit from the simultaneous investigation of SSVEP latency and rCBF alterations within the same region of the cortex.

In summary, the results from the present study support alterations in regions previously found to undergo increases in rCBF during anxious anticipation, including the anterior and dorsolateral PFC, anterior temporal cortices, and the extra-striate cortex. While previous research has reported increases in rCBF within prefrontal, temporal and occipital cortical regions, our results suggests an increase in localised inhibitory processes within the PFC and anterior temporal lobes, and an increase of localised excitatory processes within regions of the extra-striate occipital cortex during

anticipatory anxiety. These findings may provide further insight into the nature of the neurophysiological mechanisms underlying anticipatory anxiety.

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