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Steady state visually evoked potential (SSVEP) topography in a graded working memory task

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Abstract

The steady state visually evoked potential (SSVEP) elicited by a diffuse 13-Hz visual flicker was recorded from 64 scalp sites in 30 subjects performing a low and high demand version of an object working memory task. During the perceptual component of the task, the SSVEP amplitude was reduced at left and right parieto-occipital sites. During the hold or memory component of the task, the SSVEP amplitude exhibited a load-dependent increase at frontal and occipito-parietal sites, while the SSVEP latency exhibited a load-dependent reduction at central and left frontal sites. We suggest that SSVEP amplitude changes index cortical information processing modes in that perceptual processes are associated with an SSVEP amplitude reduction, while holding information in active short-term or working memory is associated with an SSVEP amplitude increase. We also discuss changes in SSVEP amplitude and latency in terms of changes in the behavior of cortico–cortico and thalamo–cortico loops that utilize cortical layer I. Such cortico–cortico and thalamo–cortico loops are also proposed to constitute a neurophysiological mechanism for holding information in working memory. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Steady state potential; Object working memory; Re-entrant loops

1. Introduction

The steady state visually evoked potential (SSVEP) elicited by a diffuse visual 13 Hz flicker

demonstrates specific topographic changes in amplitude and phase during different cognitive tasks. For example, increased visual vigilance is associated with an occipito/parietal and centro/parietal reduction in the magnitude of the SSVEP elicited by the irrelevant visual flicker. By contrast, cognitive set change tasks such as the Wisconsin Card Sort Task are associated with SSVEP amplitude reductions at pre-frontal sites during the set change (Silberstein et al., 1990, 1995). We have suggested that such changes in SSVEP am-

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plitude appear analogous to the site-specific reductions in alpha EEG amplitude associated with cognitive and motor tasks (Pfurtscheller and Klimesch, 1990).

The availability of an external reference signal in the stimulus also permits an estimation of changes in SSVEP latency (Silberstein et al., 1998, 2000). We have suggested that an SSVEP latency reduction may index increased neural information processing speed, possibly reflecting an increase in excitatory processes or a reduction in inhibitory processes (Silberstein et al., 2000). This interpretation is consistent with observations that the reaction time in a visual vigilance task (Continuous Performance Task, CPT) was correlated with frontal SSVEP latency (Silberstein et al., 1996, 2000). Subsequent studies examining vigilance-related changes in SSVEP latency in schizophrenia (Line et al., 1998; Silberstein et al., 2000) and ADHD (Silberstein et al., 1998) have also been consistent with this suggestion.

In this study, we examined the changes in the SSVEP amplitude and latency topography during

an object working memory task where one or two abstract objects were held in working memory. Working memory is the term describing a type of active memory that is relevant for only a short period of time (Baddeley, 1986; Goldman-Rakic, 1996). Functional neuroimaging findings have implicated the prefrontal cortex as playing an important role in holding information in working memory (Rymya et al., 1999; Smith et al., 1995; Swartz et al., 1995). In the next section, we briefly review a neurophysiological model of the SSVEP generators that will be used as the conceptual framework to introduce our hypothesis that an increased working memory load will be associated with an increase in SSVEP amplitude and a decrease in SSVEP latency at prefrontal sites.

1.1. Re-entrant loops and the SSVEP

While the precise neural basis of the SSVEP elicited by a visual stimulus in the 4–14 Hz range is unclear, the relatively long latency of this response (250–300 ms) and its topography makes it

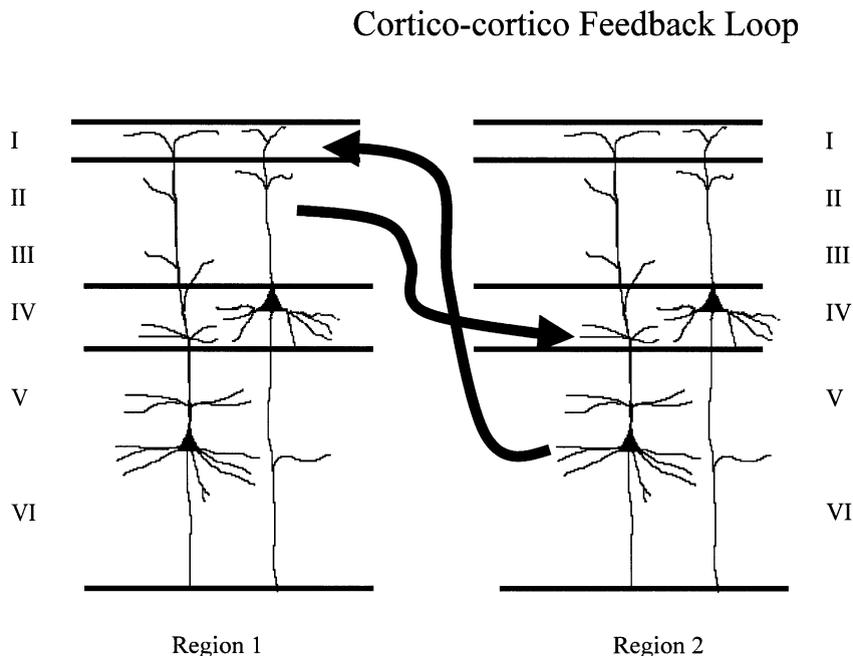


Fig. 1. Feed-forward and feedback cortico-cortico fibers that constitute the re-entrant loops. Feed-forward fibers originating in layers II and III of R1 preferentially terminate in layer IV, while the feedback fibers originating in layer V of R2 preferentially terminate in layer I.

unlikely to be a result of direct projection from specific thalamic relay nuclei (Regan, 1989; Silberstein, 1995a). The amplitude of the SSVEP exhibits a maximum or resonance when the stimulus frequency is in the low frequency or 8–12 Hz range, and one of the authors has proposed a neurophysiological mechanism for the SSVEP (Silberstein, 1995b). In this model the cortico–cortico loops and thalamo–cortico loops play an important role in the genesis of driven EEG rhythms in the 8–18 Hz range. Cortico–cortico loops have been described extensively, especially in the visual system (Pandya and Yeterian, 1985). In broad terms, neocortical processing regions that have a reciprocal relationship tend to be characterized by ‘feed-forward’ fibers originating predominantly in neocortical layer II and III and terminating in layer IV. By contrast, the ‘feedback’ fibers originate in layer VI and project to layer I, see Fig. 1 (Fellerman and Van Essen, 1991).

In addition to the cortico–cortico loops, there also exist a range of thalamo–cortical loops. Those most relevant to the current discussion involve the intra-laminar nucleus (ILN) of the thalamus. This is a ‘non-specific’ nucleus that projects diffusely to neocortical layer I (Herkenham, 1986; Berendse and Groenewegen, 1991; Purpura and Schiff, 1997). The ILN also receives extensive neocortical projections originating, predominantly, in layer VI. It has been suggested previously that these re-entrant loops may contribute to EEG resonant processes such as the SSVEP in the 8–18 Hz range and have been termed Regional Resonances (Silberstein, 1995b). The resonant frequency or its inverse, the resonant period, of such loops is determined by the sum of the axonal and synaptic delays in the loops or the loop time. When inhibitory cells constitute a component of the feedback loop, the resonant period is twice the mean loop time (Silberstein, 1995b; Marmarelis and Marmarelis, 1978). The loop time will vary with axonal length (changing axonal delay) and the number and location of synapses in the loop (changing synaptic delay), but rough estimates suggest regional resonances in the 8–18 Hz range (Silberstein, 1995b). The amplitude of the SSVEP in this range is a function of the stimulus

frequency that in turn influences the number and activity of synchronously activated neural elements that have been recruited into the loop. Increases in the synaptic transmission efficiency of elements in such re-entrant loops or increased ‘loop gain’ will thus be associated with an increase in the amplitude of rhythms generated by such mechanisms.

While changes in the loop-gain are proposed to influence the SSVEP amplitude, changes in the synaptic and axonal transmission times of the re-entrant loop (loop-time) will be associated with changes in the phase difference between the visual sinusoidal stimulus and the SSVEP. In particular, we suggest that a reduction in the loop time will be associated with an increase in the resonant frequency. The effect of an increase in resonant frequency can be inferred from the effects of stimulus frequency on the SSVEP. When the stimulus frequency increases through the alpha frequency range (8–13 Hz), the SSVEP amplitude peaks and the SSVEP phase with respect to the visual stimulus exhibits an increased phase lag of approximately -2π rad (Spekreijse et al., 1977), see Fig. 2. If the stimulus frequency is fixed, then an increase in the resonant frequency will be observed as a phase advance (or less of a phase lag) and this may be represented by a decrease in the SSVEP latency. It should be noted that the relationship between changes in the resonant frequency and changes in apparent SSVEP latency proposed above is a consequence of the phase properties of the SSVEP and is not dependent on any neurophysiological model of the SSVEP.

For convenience of discussion, re-entrant loops or regional networks may be viewed as one of three general categories of neural networks (or cell assemblies), the others being local and global networks, as indicated in Fig. 3. We define local networks as neural groups having local preferential functional connections that persist for times at least as long as cognitive processing times, say several tens of milliseconds or more. By ‘local’ we mean that the underlying network delays (and preferred or resonant frequencies) are due mainly to rise and decay times of post-synaptic potentials, independent of network size in a manner

Steady State Visually Evoked Potential amplitude, and phase difference

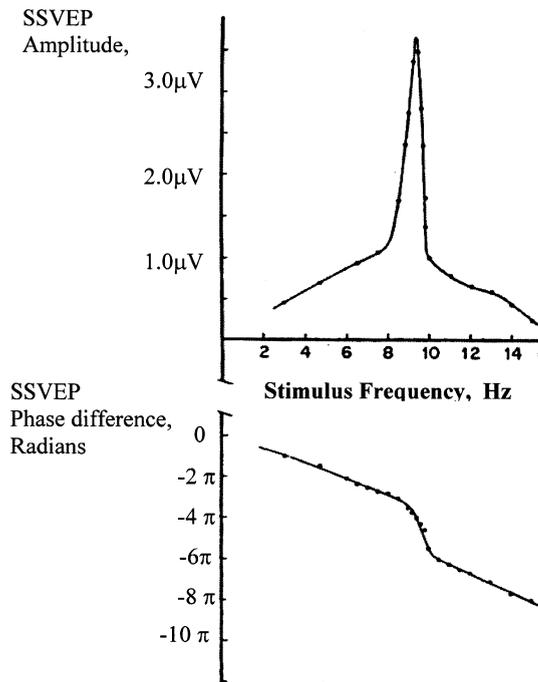


Fig. 2. Occipital SSVEP elicited by an unstructured visual stimulus from 3 to 15 Hz. Note the steeper phase lag in the vicinity of the amplitude maximum or resonant frequency. Changes in the resonant frequency of the system will thus influence the recorded SSVEP phase. For a fixed stimulus frequency near the resonant frequency, an increase in the resonant frequency will be associated with a phase advance (or increased phase), while a decrease in the resonant frequency will be associated with a phase lag. Diagram following Speckreijse et al. (1997).

similar to simple electric circuits (Nunez, 1989, 1995; Nunez and Silberstein, 2000; Silberstein, 1995b). Such local networks may occur at small or intermediate scales, e.g. from fractions of millimeters to several centimeters. They may involve positive and negative feedback between cortical and thalamic or between exclusively cortical tissue (Lopes da Silva, 1999). Such networks are believed to be embedded within a background of global dynamic activity, analogous to social networks embedded within a culture (Nunez and Silberstein, 2000; Nunez, 2000). By contrast to

local network delays, global dynamic behavior is believed to depend strongly on axonal delays along cortico–cortico fibers, analogous to more complex electric circuits like transmission lines (Nunez, 1995; Burkitt et al., 2000). Scalp electrodes appear to be most sensitive to widespread global activity, which involves multiple interactions between widespread cortical regions, as indicated by the black arrows in Fig. 3.

The re-entrant loops or regional networks are also conjectured to be embedded within the global dynamics. The specificity of connections and delays due to both local feedback and propagation along cortico–cortico fibers are potentially important in such regional networks. Thus, phase differences between ‘activity’ (e.g. synaptic activity space-averaged over the volumes of local networks) in regional networks is expected to depend on both the separation distance of participating cortical regions and interconnection ‘strength’ (e.g. synaptic gain) between local networks in Fig. 3. SSVEP amplitude and phase, as measured by electrodes close to such local networks, are generally believed to provide crude approximations to network amplitude and phase. There is no guarantee that synaptic activity exterior to networks will not swamp any putative network activity associated with a specific cognitive event. However, we believe that the SSVEP data reported here show sufficiently robust correlation with memory tasks to warrant our tentative interpretations in terms of such networks.

1.2. Working memory and the SSVEP

We have previously suggested that cortico–cortico and thalamo–cortico re-entrant loops involving cortical layer I may have a functional role in neural information processing, specifically, such re-entrant loops are proposed to offer a mechanism for holding information actively ‘on-line’ by re-circulating the information in the loop (Silberstein, 1998). The efficiency of such loops is critically dependent on the transmission efficiency of the participating loops. Reductions in synaptic transmission efficiency at layers 1 or 4 will result in the loss of information held actively in such loops. By contrast, increases in the trans-

Global, Local and Regional Resonances

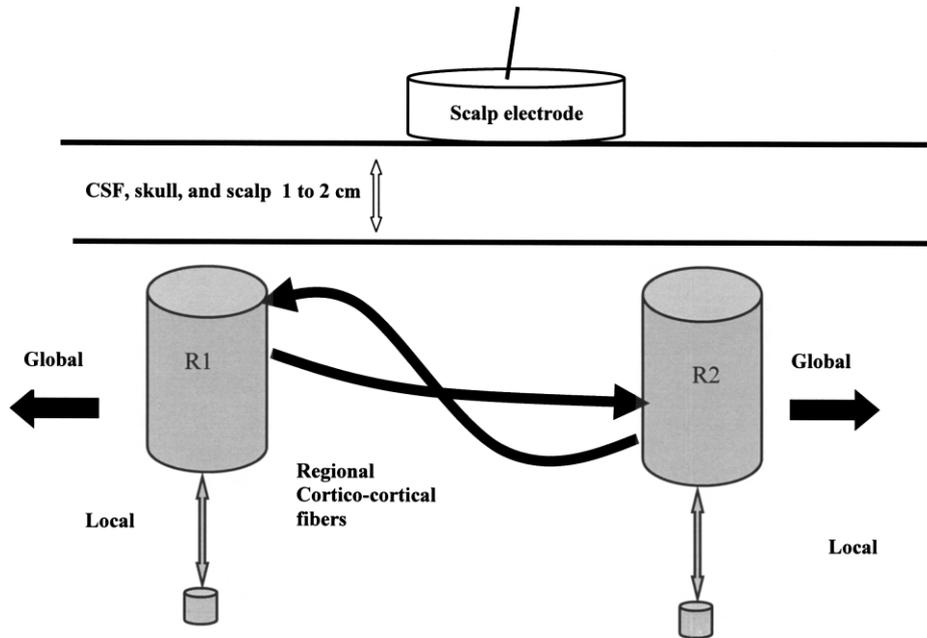


Fig. 3. Re-entrant loops that are proposed to give rise to regional resonances are one of three major resonant systems, local, regional and global. Local resonances depend on the synaptic delays and time course of post-synaptic potentials within neural networks. Global resonances, represented by the thick black horizontal arrows, are determined by axonal delays over the entire cortical surface. Both synaptic delays and axonal transmission times determine the resonant characteristics of regional resonances. Such regional networks are embedded within the global dynamic system. Scalp electrodes are believed to record a mixture of local, regional and global dynamic activity.

mission efficiency will be associated with a reduced rate of information loss. We therefore suggest that cognitive tasks requiring information to be held actively on-line will be associated with increased transmission efficiency of the participating re-entrant loops, and that this in turn will be associated with increases in the loop gain and reductions in loop time. By contrast, those cognitive tasks requiring processing of sensory information such as a sustained visual vigilance task will be associated with reduced re-entrant loop transmission efficiency as transmission through layer 1 is inhibited and specific sensory inputs to layer 4 are enhanced (Silberstein, 1995b). Such sensory processing tasks will therefore be associated with a reduction in the amplitude of the SSVEP.

The increase in SSVEP amplitude and reductions in SSVEP latency during the hold compo-

nent of a working memory task should be most prominent at prefrontal and parietal sites, regions that have been shown to participate in short-term active information storage or working memory (Goldman-Rakic, 1996). Specifically, we hypothesize that the hold component of an object working memory task requiring subjects to hold one or two abstract shapes in working memory will be associated with SSVEP amplitude increase and latency reduction at prefrontal and parietal sites. By contrast, we hypothesize that the intake or sensory component of the working memory task will be associated with an SSVEP amplitude reduction at occipito-parietal sites.

2. Methods and materials

The study was approved by the Human Experi-

mentation Ethics Committees of Swinburne University of Technology.

2.1. Subjects

Thirty right-handed male university students aged 19–35 (mean = 24.2, S.D. = 3.7 years) participated as subjects. Inclusion criteria for this study were that the subjects be right-handed as determined by the Edinburgh Inventory and possess normal uncorrected vision.

2.2. Cognitive tasks

Subjects performed an object working memory task where each trial comprised either 1 irregular polygon and 3 filled circles (low demand trials), or two irregular polygons and 2 filled circles (high demand trials), or 4 filled circles (internal control trials) for 2 s. Irregular polygons were selected to minimize the chance of subjects using verbal strategies in the task (Vanderplas and Garvin, 1959). During the subsequent 4.2-s hold period, the screen was blank except for a small cross in the center of the screen that acted as a fixation point. Subjects were then presented with an irregular object (the probe) and required to indicate whether the object matched one of the polygons prior to the hold period. A button push with the right hand indicated a match while a non-match was indicated by a left button push. Each trial lasted 12 s and subjects performed 32 high demand trials (HD) and 32 low demand trials (LD) in a block. Subjects also performed 32 trials of a control task (C) in a separate block. The timing of HD, LD and C trials are described in Fig. 4. Subjects performed a working memory block and a block of C trials in succession. Reaction time for each trial was recorded to an accuracy of 1 ms.

2.3. Stimulus parameters

Each of the polygons or circles subtended a horizontal and vertical angle of approximately 1.0° when viewed by the subjects from a fixed distance of 1.34 m. Polygons and circles had an illuminance of 13.0 Cd/m^2 against the video

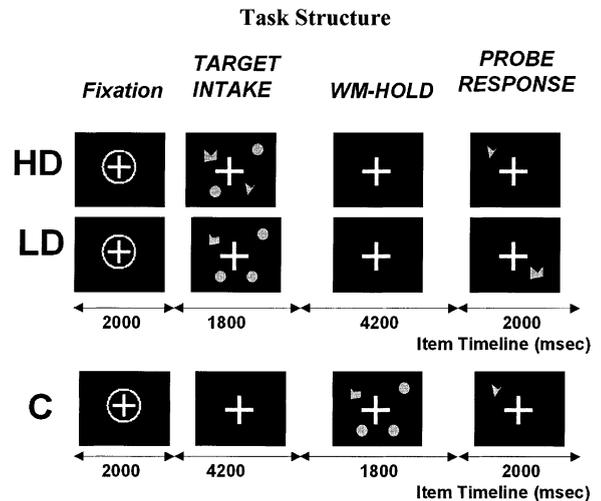


Fig. 4. Structure of high (2 objects) and low (1 object) demand versions of the object working memory task. Objects were presented for an interval of 1.8 s followed by a fixation cross for 4.2 s during which the shape of the objects must be held in working memory. At the end of the hold phase, a probe is presented and subjects are required to indicate whether the probe shape matches (one of) the target shape(s). In the control task (C), the objects are presented immediately before the probe.

monitor background of 1.2 Cd/m^2 . The stimulus used to evoke the SSVEP was a 13-Hz sinusoidal flicker subtending a horizontal angle of 160° and a vertical angle of 90° . The modulation depth of the stimulus when viewed against the background was 45%. A set of goggles, which permitted the sinusoidal flicker to be superimposed on the viewing field, was used to present the stimulus (Silberstein et al., 1990). The goggles comprised two sets of light emitting diode (LED) arrays viewed through half-silvered mirrors. The light intensity generated by the LED arrays was controlled by a 13-Hz sinusoidal voltage waveform, and the non-linearity between voltage input and light intensity was less than 0.5%.

2.4. Recording

Brain electrical activity was recorded from 64 scalp sites which included all international 10–20 positions with additional sites located midway between 10 and 20 locations. The specific locations of the recording sites have been previously

described (Silberstein et al., 1990). The average potential of both earlobes served as a reference and a nose electrode served as a ground. Brain electrical activity was amplified and band-pass filtered (3 dB down at 0.1 and 80 Hz) prior to digitization to 16-bit accuracy at a rate of 500 Hz.

2.5. Signal processing

The major features of the signal processing have already been described (Silberstein et al., 1995). Briefly, the SSVEP was determined from the 13-Hz Fourier coefficients evaluated over 10 stimulus cycles at the stimulus frequency of 13 Hz, thus yielding a temporal resolution of 0.77 s. The 10-cycle evaluation period is shifted 1 stimulus cycle and the coefficients recalculated for this overlapping period. This process was continued until the entire period of activity for each block was analyzed. An identical procedure was applied to data recorded from all 64 recording sites. To assess the changes in the SSVEP associated with different components of the cognitive tasks, the following procedure was employed. For the HD, LD and C trials, 12-s epochs of SSVEP real and imaginary components commencing 8 s before the probe were averaged, for all correct responses. For each subject and each electrode site, the mean SSVEP amplitude and phase (expressed as a single complex number) was determined from these 12-s SSVEP epochs of the C trials. This yielded 64 measures of the mean SSVEP amplitude and phase (one for each electrode) during the mean C trials for each subject. The 64 amplitude measures were then averaged to yield an average SSVEP amplitude for each subject that we termed the Normalization Factor (NF). Pooled effects were examined by weighted averaging the mean SSVEP time series for HD, LD and C trials for all 30 subjects. The weighted averaging procedure involves normalization of the SSVEP amplitude time series prior to averaging or pooling across subjects. This is necessitated by the large inter-subject variation in the SSVEP amplitude (Silberstein et al., 1990). Normalization was achieved by dividing the mean SSVEP amplitude time series for HD, LD and C trials for each subject by the appropriate NF. The pooled SSVEP

amplitude is then represented as a multiple of the normalization factor. Variations in the SSVEP phase are then expressed in terms of latency variations.

2.6. Artifact detection and compensation

A specific advantage of the SSVEP is its relative noise and artifact insensitivity (Regan, 1989; Silberstein, 1995a). This is a consequence of the fact that signal power of artifacts such as the electro-oculogram and blinks is located primarily at low frequencies and is negligible above 8 Hz (Gevins et al., 1977; Gasser et al., 1985) while muscle electrical activity is distributed over a range of frequencies (Regan, 1989). By contrast, the SSVEP power is concentrated almost exclusively at the stimulus frequency, that is 13 Hz and its harmonics (Regan, 1989). The signal processing technique we have used to extract the SSVEP is only sensitive to a narrow frequency band centered on the stimulus frequency and is thus, less influenced by artifact frequency components that differ from the stimulus frequency. The relative insensitivity of the SSVEP to common artifacts permits one to relax the rejection criteria for artifact contamination that are normally employed when evaluating EEG power spectra. For each subject, the mean SSVEP time series for C, HD and LD tasks were visually inspected and any recording site that was identified as a failure was replaced by the mean of its three nearest neighboring recording sites.

2.7. Mapping and statistical considerations

Topographic maps illustrating the differences in SSVEP latency and amplitude between HD and C, LD and C and HD and LD were produced using a spherical spline interpolation procedure (Nunez et al., 1994). Statistical Parametric Mapping (SPM) based on a Multivariate Permutation Test (MPT) utilizing the student's *t*-test was used to illustrate the topography of the statistical strength of the effect. The use of MPTs to evaluate differences in event-related potential topography was first suggested by Blair and Karniski (1993, 1994). This method has become increas-

ingly popular in the field of functional brain imaging as they are distribution free, require no assumptions about the underlying correlation structure of the data and produce exact P -values for any number of subjects and observations (time points and electrodes) (Holmes et al., 1996).

In this study, an MPT based on the student's t -test was used to estimate the probability of falsely rejecting the null hypothesis (type-1 error) associated with task differences in the SSVEP latency and amplitude. Thus, 128 [64 recording sites by two comparisons (high demand and low demand)] hypotheses were tested for the relative amplitude and latency hypotheses, 1 s into the intake component and 1 s into the hold component. Specifically, the MPT was used to compare the SSVEP observed during the mean of the C task with that of the HD and LD tasks in the intake and hold components. It should be noted that the MPT explicitly takes into account the correlation between SSVEP values at different recording sites and yields exact P -values corrected for multiple comparisons (Eddington, 1987; Holmes et al., 1996). Topographic maps illustrating the distribution of $-\log_{10}(P)$ values for comparisons of relative amplitude and latency changes were produced with iso-probability contours corresponding to $-\log_{10}(P)$ values of 1.3 (5%), 2.0 (1%) and 2.3 (0.5%). Electrode sites where the MPT yields $-\log_{10}(P)$ values that are equal to or greater than 1.3 are thus, individually significant at the 5% level or better while those sites exceeding $-\log_{10}(P)$ values of 2.0 and 2.3 are individually significant at the 1.0 and 0.5% level, respectively.

3. Results

Subjects performed better on the LD trials than the HD trials. An average of 21.8 (S.D. = 4.0) trials out of 32 were correctly performed for the HD task and 23.8 (S.D. = 3.1) for the LD task. A paired t -test indicated that this difference was significant at the 0.0001 level ($t = 4.27$, d.f. = 29, and $P < 0.0001$).

3.1. Brain electrical activity

Task-related changes in SSVEP latency and relative amplitude were observed at all recording sites. At frontal sites the SSVEP relative amplitude was low during the intake component and increased during the hold component (see Fig. 5). The increased relative amplitude during the hold component was load-dependent, with the HD trials exhibiting higher relative amplitude than the LD trials. While the SSVEP relative amplitude increased during the hold interval, the SSVEP latency decreased, reaching a minimum approximately 500 ms after the start of the hold component. The SSVEP latency reduction was also load-dependent with the HD trials associated with a larger SSVEP latency reduction.

3.2. SSVEP latency and amplitude topography

3.2.1. Intake component

During the intake component of the task, there was a trend for SSVEP relative amplitude reduction at prefrontal, right and left parietal sites although the effect was only statistically significant for the HD task at the left parietal. During this time, there was a tendency for the SSVEP latency to be reduced at left temporal and right parietal sites although these changes do not reach statistical significance, see Fig. 6.

3.2.2. Hold component

Fig. 7 illustrates the changes in SSVEP relative amplitude and latency with respect to the mean of the C task, 1 s into the hold task for both the HD and LD versions. The SSVEP relative amplitude is markedly increased at occipital sites for both the LD and HD task. While the SSVEP relative amplitude increase at occipital sites is statistically significant for the HD and LD versions, the effect was statistically more robust for the HD version. A statistically significant increase in SSVEP relative amplitude is also apparent at prefrontal sites for both the LD and HD tasks, although the effect is stronger and more extensive for the HD version (see Fig. 7).

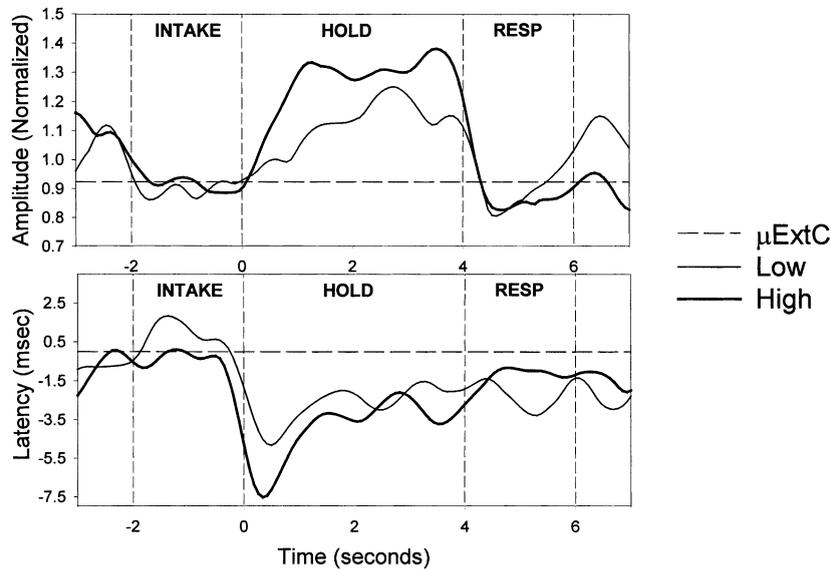


Fig. 5. The upper pair of traces illustrate the changes in SSVEP relative amplitude at the mid-frontal site Fz (electrode 16). While both the low and high demand versions are associated with an increase in the SSVEP relative amplitude, the increase is larger for the high demand version. The horizontal dotted line indicates the mean SSVEP relative amplitude for the control task. The lower pair of traces illustrates differences in SSVEP phase, expressed as latency, between the external control task and the high and low demand versions of the working memory task. During the hold interval, the latency is reduced in both tasks although the effect is larger with the HD task.

Statistically significant reductions in SSVEP latency were observed at left prefrontal and central parietal sites for only the HD task. A similar tendency was observed for the LD task, although this did not reach statistical significance except for two left fronto-central sites.

4. Discussion

4.1. Intake component

While the principal focus of this paper concerns the SSVEP changes during the hold component of the task, we briefly comment on the changes during the perceptual or intake component. During the intake component of the task, we observed an SSVEP relative amplitude reduction at left and right occipito-parietal sites. Such reductions are consistent with our hypothesis and previous SSVEP findings that report an occipito-parietal SSVEP amplitude reduction during a visual vigilance task (Silberstein et al., 1990; Nield et al.,

1998). Such reductions appear analogous to the transient reduction in spontaneous alpha activity (event-related desynchronization) associated with increased vigilance (Pfurtscheller and Aranibar, 1977). The SSVEP relative amplitude reduction in the perceptual component is also consistent with the notion of reduced loop-gain during a perceptual task (Silberstein, 1995b).

These and previous observations of an SSVEP relative amplitude reduction in a period of increased vigilance, may appear at odds with reports of increased SSVEP relative amplitude in increased visual attention (Morgan et al., 1996; Hillyard, et al., 1997). In the study reported by Hillyard et al. (1997), subjects were required to attend to a rapid sequence of letters appearing on small rectangular flickering background squares. Two flickering squares were presented, one at the left and one at the right visual field, and the squares were oscillating at different frequencies. When subjects were required to indicate the appearance of a target letter at either the left or right square, the amplitude of the SSVEP at the

Change in SSVEP Amplitude During Intake

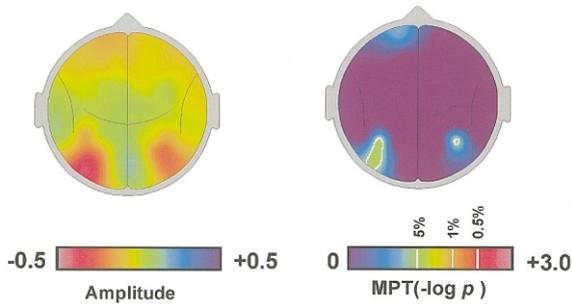
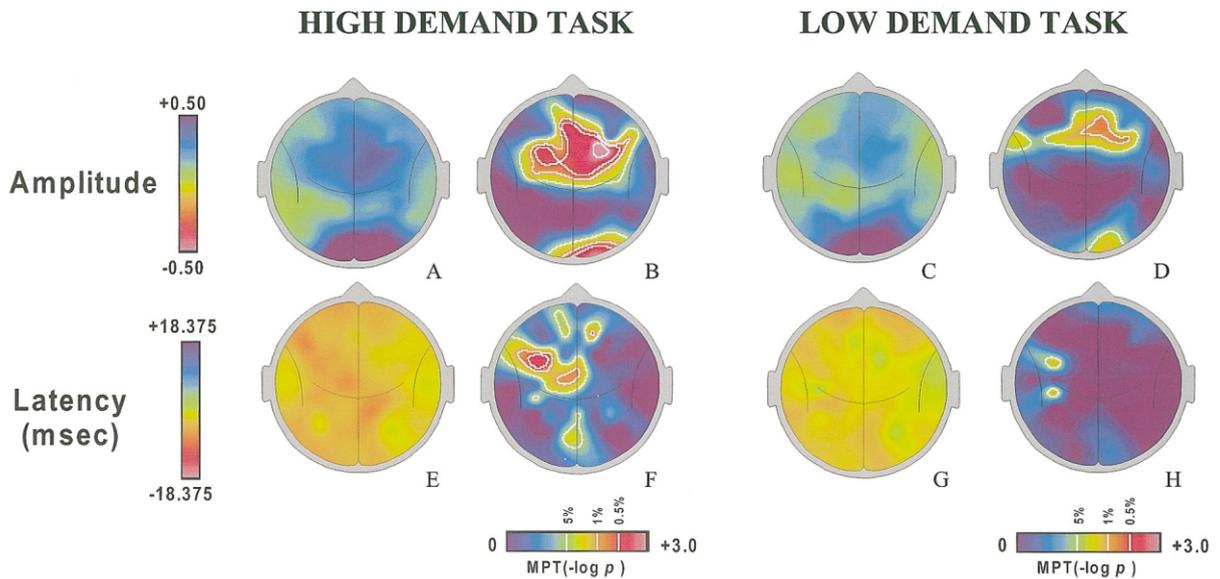


Fig. 6. Topographic map on left illustrates changes in SSVEP relative amplitude, 1.0 s after the appearance of the target material for the HD task. Warmer colors indicate regions where SSVEP relative amplitude is reduced compared to the external control and cooler colors the opposite. The map on the right illustrates the statistical significance of the SSVEP relative amplitude changes, calculated from the MPT. Iso-probability contours indicate values of 1.3 corresponding to $P = 0.05$. Intake is associated with a relative amplitude reduction at occipito-parietal sites.

frequency of the attended square increased at occipito-parietal sites. We suggest that differences in the visual stimulus used in our studies

and those of Morgan et al. (1996) and Hillyard et al. (1997) may have contributed to the differing effects of visual attention on SSVEP amplitude. In our studies, the SSVEP is elicited by a spatially diffuse stimulus subtending horizontal and vertical angles of 160 and 90°, respectively. By contrast, Hillyard et al. (1997) used a small flickering square located 5.7° lateral to the central fixation point and subtending horizontal and vertical angles of 2° to elicit the SSVEP. This difference is important as the spatial structure of the visual stimulus has a critical effect on the characteristics of the SSVEP. Diffuse visual stimuli of the type used in our study elicit SSVEP with amplitude maxima at stimulus frequencies of approximately 10, 18 and 40 Hz (Regan, 1989). By contrast, visual stimuli with high spatial detail, for example an oscillating checkerboard, exhibit a single amplitude maximum at a check alternation frequency of 10 Hz. These differences in the SSVEP amplitude spectrum suggest that different visual processing systems are activated by either structured or diffuse visual stimuli. The source of these differences is still speculative, although differences in the way that structured and diffuse visual stimuli are processed may shed some light.

Amplitude and Latency Changes in Hold Component



Diffuse visual stimuli, of the type used in our studies, are more likely to activate the magnocellular visual system that preferentially responds to rapidly changing diffuse stimuli (Derrington and Lennie, 1984; Silberstein, 1995a). By contrast, the small oscillating square used by Hillyard et al. (1997) is more likely to activate the parvocellular system that is known to mediate visual perception associated with fine detail (Merigan, 1991). The magnocellular and parvocellular regions possess different cortical projection patterns, with the magnocellular system projecting to frontal and central sites via projections from the pulvinar nucleus (Robinson and Petersen, 1990). The SSVEP amplitude decrease associated with visual vigilance may therefore be a property of the magnocellular system elicited by the diffuse stimuli we use. On the other hand, the amplitude increase associated with increased attention to small flickering squares may be more specific to the parvocellular system.

4.2. Hold component

The SSVEP relative amplitude and latency topography changed when subjects entered the hold component of the task. The strongest effect was seen in the HD task where SSVEP latency reductions were apparent at left prefrontal, central and parietal sites. We suggest that the pattern of SSVEP latency reduction in the hold component is consistent with the engagement of excitatory processes at left pre-frontal and central sites. The cause of the SSVEP latency prefrontal hemispheric asymmetry is unclear. It could reflect the adoption of a verbal strategy in the working memory task, although the shapes were selected to

reduce the chance of verbalization. Interestingly, the Smith et al. (1995) working memory study that used the same shapes also reported predominantly left hemisphere activation (left posterior parietal and left inferior temporal) in a PET functional brain imaging study.

While the SSVEP latency changes associated with the hold phase were most prominent at left prefrontal and central sites, the HD task SSVEP relative amplitude increase was more symmetrically distributed and most prominent at prefrontal, frontal and parieto-occipital sites. The difference in SSVEP relative amplitude and latency topography also suggests that the processes mediating the relative amplitude and latency changes are distinct. More generally, the results of this study have led us to reconsider the neurophysiological significance of the 13-Hz SSVEP relative amplitude. Previous visual vigilance studies demonstrated a reduced SSVEP amplitude at occipito-parietal sites during intervals of increased visual vigilance (Silberstein et al., 1990; Nield et al., 1998). This led us to suggest that reductions in SSVEP amplitude are associated with increases in regional brain activity in a similar fashion that EEG alpha activity is frequently considered a measure of reduced brain activity or 'idling' (see Pfurtscheller and Lopes da Silva, 1999). By contrast, our observation of a SSVEP amplitude increase at the prefrontal sites in a working memory task does not appear consistent with the notion that an increase in the SSVEP amplitude is simply a manifestation of reduced cortical activity. We suggest that the 13-Hz SSVEP amplitude may index the prominence of certain neural information processing modes. Specifically,

Fig. 7. Topographic maps illustrating the SSVEP amplitude and latency changes together with the statistical significance of those changes for the point in time 1 s into the hold component. Fig. 7A,C illustrates the changes in SSVEP amplitude for the HD and LD version of the task, while Fig. 7B,D illustrates the statistical significance of those changes. In Fig. 7A,C, reductions in SSVEP amplitude are indicated by warmer colors while SSVEP amplitude increases are indicated by cooler colors. Fig. 7B,D illustrates the distribution of the corresponding *P*-values derived from the MPT with warmer colors indicating regions of higher statistical significance (smaller *P*-values), iso-probability contours indicate values of 1.3 (outer contour), 2.0 and 2.3 corresponding to *P* = 0.05, 0.01 and 0.005, respectively. Fig. 7E,G illustrates changes in SSVEP latency for the HD and LD task, respectively, with reduced SSVEP latency indicated by warmer colors and increased SSVEP latency by cooler colors. Fig. 7F,H illustrates the corresponding distribution of statistical *P*-values for the SSVEP latency changes. The hold component is characterized by an increase in SSVEP relative amplitude at frontal and occipito parietal sites, and an SSVEP latency reduction that is most prominent at left pre-frontal sites. These effects are more prominent for the high demand task.

increases in the 13-Hz SSVEP amplitude are proposed to indicate a change in neural information processing characterized by a shift away from processing sensory information and an enhanced active storage ('hold') of internal representations. This active storage is proposed to involve the re-circulation of information through cortico-cortico loops and associated ILN thalamo-cortical loops.

4.3. Similarities between 13-Hz SSVEP and alpha EEG in memory tasks

We have previously suggested that the 13-Hz SSVEP and EEG alpha activity behave in a similar fashion during cognitive tasks. In particular, we observe an SSVEP relative amplitude reduction in vigilance tasks that is similar to the reductions in alpha EEG amplitude associated with cognitive and motor tasks (Pfurtscheller and Klimesch 1990). While this suggestion of a similarity between the SSVEP and alpha activity may appear at odds with our observation of an SSVEP relative amplitude increase during the hold component of the working memory task, a number of EEG memory studies have reported increases in EEG alpha activity during a memory 'hold' component. Ray and Cole (1985) demonstrated reductions in alpha when subject were required to attend to visual targets. By contrast, tasks that required the subjects attend to mental imagery were associated with enhanced alpha activity or alpha event-related synchronization (ERS). More recently, similar findings have been reported by a number of groups. Krause et al. (1996) reported alpha ERS during an auditory memory task while Tesche et al. (1995) observed increased alpha activity during mental imagery. Of particular interest is a report by Klimesch et al. (1999) demonstrating consistent increases in upper alpha activity (10.2–12.2 Hz) at frontal and temporal sites in an episodic short-memory task. Our observation of an increase in the SSVEP relative amplitude during the hold component of the working memory task thus, appears consistent with the behavior of alpha EEG, especially upper alpha, and we speculate that such a similarity suggests a common neurophysiological mechanism. Specifi-

cally, we propose that the upper alpha EEG and 13-Hz SSVEP relative amplitude increases both index increased loop gain in cortico-cortico and thalamo-cortico re-entrant loops associated with holding information actively or 'on-line'.

4.4. Re-entrant loops and working memory

Our proposal that working memory involves the re-circulation of information through cortico-cortico and thalamo-cortical loops utilizing cortical layer I is consistent with the suggestions of Vogt (1991) who proposed an 'event holding' function, similar to working memory, for layer I. Vogt (1991) cites studies indicating that lesions restricted to layer I in the rat visual cortex leave visual discrimination intact, but interfere with more complex perceptual tasks that require working memory (Levey and Jane, 1975). The relevance of Layer I in working memory tasks is also supported by studies in mutant mice with layer I abnormalities. Specifically, the BXSB mutant mouse is more likely to possess abnormal, ectopic, collections of cells in layer I. While this mouse strain exhibits normal learning when assessed with the Morris water-maze, it has poor spatial working memory when tested in a delayed match to sample task (Boehm et al., 1996; Walters et al., 1997).

The Intra-Laminar Nuclei (ILN) of the thalamus also project extensively to layer I while receiving cortical projections from layer V, and we suggest that both the cortico-cortico and ILN thalamo-cortico loops participate in the working memory function as both involve re-entry via layer I. This is consistent with the proposal of Purpura and Schiff (1997), who reviewed the function of the ILN and proposed a working memory function for it. More recently, Van der Werf et al. (2000) reviewed the neuropsychological deficits associated with human thalamic lesions and also suggested that executive function and working memory deficits were more likely to be a consequence of ILN lesions. The relevance of the ILN in working memory has also been supported by lesion studies in the rat, where ILN lesions have

been associated with working memory deficits in delayed match to sample tasks (Burk and Mair, 1998; Mair, 1994; Mair et al., 1998).

In summary, we propose that the SSVEP amplitude elicited by a diffuse visual flicker between 10 and 13 Hz indexes the resonance property of cortico–cortico and thalamo–cortico loops. Cognitive modes dominated by perceptual processes will be associated with a reduction in loop-gain and a reduction in the SSVEP amplitude. By contrast, cognitive modes that require information be held actively in working memory will be associated with increased loop gain and an increase in SSVEP amplitude.

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