A MEASURE OF CONSCIOUSNESS AND MEMORY DURING ISOFLURANE ADMINISTRATION: THE COHERENT FREQUENCY†

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SUMMARY

The coherent frequency (CF) of the auditory evoked response (AER) is derived using auditory clicks presented at frequencies in the range 5-47 Hz. CF and psychological performance were measured while seven subjects breathed isoflurane in doses increasing from 0% to 0.2%, 0.4% and 0.8% end-tidal concentration and then decreasing to 0%. With increasing doses of isoflurane, CF decreased and there was a decrease in within-list recognition (WLR) and category recognition (CR) scores. There was a correlation between changes in CF and WLR (P < 0.05) and between CF and category recognition (CR) (P < 0.05). A painful stimulus given in conjunction with 0.4% isoflurane caused an increase in CF, WLR and CR in some subjects. This did not reach statistical significance for the group as a whole, apart from the short word interval scores in the WLR which indicated an increase in attention (P < 0.01). Subjects did not respond with 0.8% isoflurane, either before or after painful stimulation. Reduction of end-tidal isoflurane from 0.8% to 0% caused an increase in CF and improved performance on the psychological tests. A category generation task on recovery showed no evidence of implicit learning of words presented in conjunction with 0.8% isoflurane. Memory testing after the trial showed a relationship between the CF obtained with isoflurane and subsequent memory: conscious awareness with explicit memory was associated with a median CF (25th-75th centile) of 32.8 (28.4-36.7) Hz; conscious awareness without explicit memory was associated with a CF 24.8 (21.5-30.6) Hz; absence of both responsiveness and memory was associated with a mean CF of 14.9 (14.2-17.3) Hz. There was a significant difference in CF associated with these different categories of memory (P < 0.02). We conclude that the coherent frequency of the AER reflects the likelihood of cognition during anaesthetic inhalation. (Br. J. Anaesth. 1993; 71: 633-641)

KEY WORDS


There is a need to produce an objective measure of depth of anaesthesia with which the anaesthetist can detect conscious awareness during light anaesthesia in patients with neuromuscular block. There is some confusion about what is meant by the term "depth of anaesthesia". The majority of papers on this subject are concerned with the relationship between a dose of anaesthetic and either somatic movement or a measurement such as EEG, heart rate, frontal EMG or oesophageal contraction. However, all these studies give no direct information about cognitive function. In contrast, the present study has examined the changes in cognitive function produced with stepwise changes in isoflurane concentration and compared these changes with a new measurement of depth of anaesthesia derived from the auditory evoked response (AER).

There are two ways of producing the AER: the transient method and the steady state method. The middle latency part of the transient response refers to a series of one to three bipolar waves occurring in the first 100 ms after an abrupt auditory event. This middle latency response (MLR), also termed the "early cortical response", represents processing at the primary auditory cortex and is elicited using clicks presented at rates near 10 s⁻¹, although rates of as few as 1 s⁻¹ produce a larger MLR but take a very long period of signal averaging to produce a satisfactory waveform. The transient MLR has been studied extensively in awake and anaesthetised patients and it looks promising as a method for measuring depth of anaesthesia [1]. However, there are two problems with the transient method: the prolonged time to produce the response (about 5 min) and difficulties in interpreting the waveforms so that conscious awareness can be inferred unequivocally from a particular waveform. In contrast to the transient method, the steady state method refers to electrophysiological activity in the EEG driven by a train of stimuli delivered at a sufficiently fast rate.
that responses evoked by successive stimuli overlap. The auditory steady state response is said to reach an amplitude maximum at rates of stimulation near 40 Hz [2]. In a personal communication, Robert Galambos suggested that the data presented in a series of papers [3–10] published from Northwick Park showed there was a dominant 40-Hz frequency before anaesthesia and this was similar to the response obtained more directly with the steady state method. All these studies [3–10] had shown that general anaesthetics caused a prolongation of the middle latency waves which are thought to contribute to the steady state response (SSR) and, consequently, it was predicted that the 40-Hz value of the dominant frequency response would decrease with anaesthesia.

Thus we decided to examine Galambos’ suggestions by studying the AER when the auditory pathway was stimulated with a wide range of frequencies. At the same time, subjects inhaled a stepwise increasing, then decreasing, concentration of isoflurane. During each step, the subjects were asked also to perform tests of cognition and memory. We would thus be able to compare changes in the auditory evoked potential with psychological performance at different alveolar concentrations of anaesthetic.

SUBJECTS AND METHODS

After approval from the local medical Ethics Committee, seven anaesthetists agreed to take part in the study. The group consisted of six males and one female. None suffered from known hearing loss.

After cleaning the skin with Skinpure (Nihon Koden, Holstar Instruments, Sussex), we applied silver-silver chloride electrodes (Medicotest N-50-E, Cambac, Cambridge) to frontal and right mastoid regions with a right pre-auricular electrode as a neutral. Inter-electrode impedances were checked and maintained less than 4 kΩ. Clicks of 1 ms duration were fed to TDH 39 Headphones. The output was 65 dB greater than average hearing threshold at 6 Hz. The click generator was controlled by a CED 1401 interface and Spike 2 data acquisition software (Cambridge Electronic Design, Cambridge) running on an IBM-compatible 486 PC. The auditory stimulation sequence contained a range of 43 frequencies at 1-Hz intervals from 47 Hz to 5 Hz. The EEG amplifier had a gain of 125000 and a 1–2000 Hz bandwidth with 12 db octave⁻¹ roll off. The sample rate was 1 kHz. The CED 1401 and Spike 2 program collected and averaged 100 samples of EEG at each stimulating frequency. Artefact rejection was not applied. A Fast-Fourier transform (FFT) was then applied to the evoked response at each frequency within the Spike 2 program. This “sweep” of frequencies was presented to the subject at all nine steps of the experiment (table I).

Derivation of coherent frequency

We found that the power in the FFT of the evoked response at each frequency usually had three components: the fundamental frequency and the first and second harmonics. Occasionally, further harmonics appeared, but were of small amplitude. Analysis of these FFT showed that, at certain frequencies, the power of the fundamental was very large, with little or no power in the harmonics (fig. 1).

Frequencies showing this pattern were termed the “coherent frequency”. Frequencies on each side of it did not show this pattern, having large harmonic power. A mathematical manipulation to show up these coherent frequencies was applied so that, if:

\[ P_1 + P_2 > 0.3 P_1 \]

where \( P_1 \) is the power in the fundamental, and \( P_1 \) and \( P_2 \) are the power in the first and second harmonics, respectively, then a value of zero was applied to the \( P_1 \), otherwise \( P_1 \) was left with its original value. The data were then recalculated to obtain \( Q_1 \), the resultant power, using a formula which reflected the relative power in the fundamental compared with that in the harmonics and the absolute power in the fundamental. Thus:

\[ Q_1 = \frac{P_1}{P_1 + P_2} \times P_1 \]

Table 1: Experimental design for the study

<table>
<thead>
<tr>
<th>Trial step</th>
<th>Concentration of isoflurane in oxygen (%)</th>
<th>Electrical stimulation to cause arousal</th>
<th>Coherent frequency</th>
<th>Within list recognition (explicit memory)</th>
<th>Categorization (cognitive function)</th>
<th>Word repetition (implicit memory)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Air</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>0.2</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>0.4</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>0.4</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>0.8</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>0.8</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>0.2</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>Air</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>(10 min after isoflurane)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Air</td>
<td></td>
<td>Yes</td>
<td>Category recognition for the above stimuli</td>
<td>Category generation for the above stimuli</td>
<td></td>
</tr>
</tbody>
</table>

With the above stimuli, we would be able to compare changes in the auditory steady state response (SSR) and, consequently, it was predicted that the 40-Hz value of the dominant frequency response would decrease with anaesthesia.
CONSCIOUSNESS, MEMORY AND COHERENT FREQUENCY OF THE AER

Fourier analysis of the auditory evoked potential

Derived coherent frequency

0.04
0.03
0.02
0.01
0.04
0.03
0.02
0.01

0 10 20 30 40 50
0 10 20 30 40 50

Air

Air

0.4% Isoflurane

0.4% Isoflurane

0.01
0.02
0.03
0.04

0 10 20 30 40 50
0 10 20 30 40 50

Fig. 1. Derivation of the coherent frequency for one subject. The panels on the left show the raw data plotted with the subject breathing air and then at an end-tidal isoflurane concentration of 0.4%. X axis = stimulating frequencies; Y axis = power of the resultant signal (i.e. the fourier analysis of the signal averaged EEG). The power of the fundamental is shown as a black line, whilst the 1st and 2nd harmonics are represented by open circles and a dotted line, respectively. The right hand panels show the data after the fundamental and the harmonics were transformed to obtain the coherent frequency as described in the text.

This procedure was repeated for all 43 observations and then the resultant power plotted against stimulating frequency.

Psychological tests

To validate any method of monitoring depth of anaesthesia, an independent measure of cognitive function is required. We therefore decided to examine cognitive function when volunteers breathed sub-MAC doses of isoflurane, and to test their memory function afterwards. Two tests of cognitive function were used:

1. A within-list recognition (WLR) test was used to assess working memory [11]. In this test, a list of words was read out by the observer and the subject’s task was to respond to repeated words. The number of intervening items between the first and second presentations of a target word varied, hence the retention interval also varied. It was assumed that performance on this task would decline as cognitive performance was compromised by increasing doses of the anaesthetic. For the WLR task, 16 lists of 23 words each served as stimuli. Each list comprised seven “target” words, each of which was repeated once, and nine “distractor” words. The target words were repeated after intervals of 0, 1, 2, 4, 8 or 16 intervening words (table II).

Two different lists were presented at each step of the experiment, apart from those steps at which the subject had an end-tidal isoflurane concentration of 0.8% and there was no response to verbal commands (table I). The lists were read aloud by the experimenter at a rate of one word every 2 s. The subject’s task was to respond to repeated words by raising the right thumb. The experimenter recorded the repetitions which were identified correctly.

2. A categorization test was used to assess general linguistic processing and attention. The subject’s task was to respond to each presented exemplar of a particular category and to ignore interpolated exemplars of other categories. Relatively well-defined categories were chosen (e.g. colours) and familiar exemplars were used (e.g. green, blue). We also assumed that learning at the time of stimulus presentation would be reflected in subsequent memory for that stimulus, hence on recovery from the anaesthetic we tested recognition (explicit) memory for the target category exemplars.

Thus immediately after the second list of each WLR test, the subject was told that another list would be presented and that the task was to listen for the names of items belonging to a particular category, for example “metals”. The experimenter then read out 20 words, of which 10 were exemplars of the specified category and 10 were distractor items from other, dissimilar, categories. The subject responded to identified exemplars by raising the right thumb. On recovery from the anaesthetic, recognition memory was tested for category exemplars presented at each of three end-tidal concentrations of isoflurane: 0%, 0.2% and 0.4%. A forced-choice procedure was used in which, for each category, pairs of exemplars were read out and the subject was asked to identify or guess which exemplar in each pair had been presented during anaesthesia.

The issue of learning under anaesthesia was examined further by reading out, 10 times, 10 exemplars of another category (e.g. birds, flowers) whilst the subject was inhaling 0.8% isoflurane—five times before the electrical stimulation and five times afterwards. On recovery, the subjects were asked if they could recall the category to which the exemplars belonged. If they failed, four categories were named and the subject was asked to choose or guess the one from which the exemplars had been taken. The subject was then told the correct category and asked to generate as many exemplars of that category as
TABLE II. An example of within list recognition set of words. The numerals refer to the number of other words intervening before the repetition. There are deliberately two sets of "0" words (words repeated with no gap) to test that the attention of the subject has been maintained through the list.

<table>
<thead>
<tr>
<th>Word list</th>
<th>Number of words between repetitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ability</td>
<td></td>
</tr>
<tr>
<td>Flavour</td>
<td>0</td>
</tr>
<tr>
<td>Flavour</td>
<td></td>
</tr>
<tr>
<td>Dignity</td>
<td></td>
</tr>
<tr>
<td>Demonstration</td>
<td></td>
</tr>
<tr>
<td>Member</td>
<td></td>
</tr>
<tr>
<td>Suggestion</td>
<td></td>
</tr>
<tr>
<td>Character</td>
<td></td>
</tr>
<tr>
<td>Suggestion</td>
<td>1</td>
</tr>
<tr>
<td>Segment</td>
<td></td>
</tr>
<tr>
<td>Expedition</td>
<td></td>
</tr>
<tr>
<td>Quantity</td>
<td></td>
</tr>
<tr>
<td>Overtone</td>
<td></td>
</tr>
<tr>
<td>Expedition</td>
<td>2</td>
</tr>
<tr>
<td>Segment</td>
<td>4</td>
</tr>
<tr>
<td>Bayonet</td>
<td></td>
</tr>
<tr>
<td>Character</td>
<td>8</td>
</tr>
<tr>
<td>Liberty</td>
<td></td>
</tr>
<tr>
<td>Liberty</td>
<td>0</td>
</tr>
<tr>
<td>Attempt</td>
<td></td>
</tr>
<tr>
<td>Dignity</td>
<td></td>
</tr>
<tr>
<td>Solution</td>
<td>16</td>
</tr>
<tr>
<td>Salvation</td>
<td></td>
</tr>
</tbody>
</table>

possible in 1 min. The number of exemplars generated from the presented category was compared with the number generated from a matched list of exemplars which had not been presented. This latter test examined implicit memory [12], which is reflected in a clear influence of a prior stimulus on behaviour, even though the subject was unable to recall or recognize that item as having been presented. Recognition memory (explicit memory) for the presented exemplars was tested also, using the forced-choice procedure described above. A note was made at each stage if the subject responded purposefully to any verbal command or stimulation. After the trial, the subject was asked also about recall of events or pain at any of the steps.

Procedure

After an overnight fast, the subject lay on a tilting bed. A 23-gauge cannula was inserted in the dorsum of the left hand. A Penlon anaesthetic machine was used to supply the isoflurane in oxygen. A Lack circuit attached to a mouthpiece was used to administer the gases to the subject, who wore a nose-clip. The subject inhaled isoflurane and the vaporizer concentration measured by a Bruel and Kjaer type 1304 anaesthetic gas monitor. When a stable end-tidal concentration was reached, the subject breathed the isoflurane for another 10 min before any measurements were performed. Monitoring also included pulse oximetry and heart rate. One anaesthetist with no other responsibilities was always assigned to monitor the subject.

EEG recordings and psychological tests were performed with the subjects breathing air and then isoflurane was administered in a stepwise fashion at concentrations listed in Table I. At end-tidal isoflurane concentrations of 0.4 % and 0.8 % (steps 3 and 6 in Table I), a peripheral nerve stimulator was used to apply a 60-mA tetanic stimulus to the left ulnar nerve for 5 s, followed by a single 200-ms pulse every 1 s until the end of the stage. This was to cause and maintain arousal [13]. The psychological tests were given immediately after the tetanic stimulus and they were then followed by a recording of the EEG.

Statistics

The evoked potential data were analysed by Spike 2. The analysis of the psychological data was performed with the program Statview 4 (Abacus Concepts Inc, CA) on an Apple Macintosh computer. Data were analysed using non-parametric tests, namely Wilcoxon rank signed test, Friedmann's test for repeated measures, Mann–Whitney U and Spearman's rank correlation. Significance was assessed as P < 0.05.

RESULTS

Coherent frequency

Figure 1 shows the transformation of the raw data to obtain the coherent frequency. The effect of isoflurane is also illustrated. If more than one peak appeared in the transformed data (which often happened with arousal), they tended to cluster and so an average CF was calculated by taking an amplitude weighted average of the coherent frequencies present for that particular sweep (fig. 1).

CF through the trial for all seven subjects are shown in figure 2. There was a variation in the initial CF, although they were all less than 41 Hz and greater than 28 Hz. Repeated measurements in the same subjects showed little variation. The CF at 0.4 % and 0.8 % were significantly different from those on air at the start of the trial (P < 0.02, Wilcoxon rank signed pair). Painful electrical stimulation of the subjects whilst breathing 0.4 % end-tidal isoflurane caused an increase in the CF in three
Fig. 3. Within list recognition (WLR) score (mean, SEM): A increasing end-tidal isoflurane concentration and the effect of painful stimulation; B with decreasing end-tidal isoflurane concentration. The data are shown as means with standard errors. ** Significant improvement in attending to the test between the short interval scores with 0.4% isoflurane and 0.4% isoflurane with painful stimulation (P < 0.01, Wilcoxon signed rank test). □ = Air; ○ = 0.2% isoflurane; ◂= 0.4% isoflurane; ● = 0.4% isoflurane + painful stimulation; ▼ = air (recovery); ▲ = 0.2% isoflurane (recovery).

Fig. 4. Percentage correct scores for the overall within list recognition task during each step of the trial. See text for details. (These are box plots as described for figure 2.) Stages as in figure 2.

of the seven subjects, no change in two and a small decrease (2 and 6 Hz) in two subjects. This was despite obvious arousal in six of the seven subjects. Possible reasons for this result are discussed below. One subject became excited after 0.4% isoflurane (step 4) and no recordings were possible at steps 5 and 6. Subsequent recordings were possible from step 7 onwards.

Psychological tests

Within list recognition (fig. 3.) With the subject breathing air there was a decline in performance with increasing word interval. Administration of 0.2% and 0.4% end-tidal isoflurane caused a dramatic deterioration in performance, whereas painful stimulation produced an improvement in performance on the test. This reached significance only with the short word intervals (that is 0-, 1- and 2-word intervals score summed together) (P < 0.01 (Wilcoxon signed rank)). Even so, two of seven subjects were achieving some correct responses at the 16-word interval with stimulation in conjunction with 0.4% end-tidal isoflurane. It was noted that, although stimulation produced arousal, there was no complaint of recall of pain from any subject, although two out of seven subjects could remember receiving the tetanic stimulus (only one of these two subjects performed correctly at the 16-word interval). Performance at 0.2% end-tidal isoflurane on recovery and during air breathing appeared to be worse than at the start of the test (compare the two panels in figure 3), but this did not reach significance.

The results of the WLR for each word interval were averaged and plotted against trial step to obtain figure 4. The summed scores of long and short word intervals prevented the effect of stimulation reaching statistical significance, despite an improvement in five of seven subjects (P = 0.12). There was no response to the verbal word list or verbal command with 0.8% end-tidal isoflurane.

Categorization scores. These followed the same pattern as the WLR test, with a decline in performance with increasing concentration of isoflurane. Stimulation at 0.4% end-tidal isoflurane caused an improvement in performance for five individuals, but this did not reach significance for the group (P = 0.17, Wilcoxon rank signed test).

Category recognition (fig. 5). Memory for the categorization stimuli was assessed on recovery (when the subject had been breathing air for 25 min). Since subjects had to choose between two exemplars, only one of which had been presented previously, guessing would result in a score of 5 out of 10. There was a significant decrease in performance on this explicit memory test with the increase in concentration of end-tidal isoflurane from 0% to 0.8% (P = 0.013, Friedman). The performance in conjunction with 0.2% isoflurane without stimulation and 0.4% isoflurane with stimulation were not significantly different from each other. Recognition of the exemplars which had been presented in conjunction with 0.8% isoflurane was no greater than chance.

Word repetition. On recovery, the subjects were asked which category had been presented in conjunction with the greatest concentration of end-tidal isoflurane (0.8%). No subject answered correctly. Out of a choice of four possible categories, only two out of seven subjects answered correctly. The
subjects were then told which category had been used and asked to name, in 1 min, as many exemplars of this category as possible. They showed no evidence of implicit memory formation for the exemplars at 0.8 % end-tidal isoflurane (P > 0.05, Wilcoxon rank signed).

Correlation of the psychological tests with the coherent frequency

An analysis of the Spearman's correlations between the CF, WLR and CR and end-tidal isoflurane showed significant correlation between all variables (P < 0.05). An alternative analysis of the results is to correlate memory function with the CF obtained at that time of testing—for example, to group all the CF obtained when subjects showed no evidence of implicit memory. Three levels of psychological performance with an associated median CF (25th-75th centile) may be defined (fig. 6): 1 = conscious awareness (defined here as an appropriate response to a test or command during the trial) with explicit memory was associated with a median CF of 32.8 (28.4-36.7) Hz; 2 = conscious awareness without explicit memory was associated with CF 24.8 (21.5-30.6) Hz; 3 = no responsiveness with no implicit memory was present when CF was 14.85 (14.2-17.3) Hz. Levels 1 and 2 have CF which are significantly different from each other (P < 0.02, Mann-Whitney U). Similarly, levels 2 and 3 were significantly different from each other (P < 0.0001, Mann-Whitney U).

DISCUSSION

We have described derivation of the coherent frequency (CF) in the AER using a range of auditory clicks presented at frequencies in the range 5–47 Hz. There were six main findings of the study.

1. A reduction in CF and a decline in within list recognition (WLR) and category recognition (CR) performance as the end-tidal concentration of isoflurane was increased from 0% to 0.8%. These changes reversed as the end-tidal isoflurane was decreased to 0%.

2. Significant correlations between CF, WLR, CR and isoflurane concentration; a painful stimulus in conjunction with 0.4% end-tidal isoflurane caused an increase in CF, WLR and CR in some subjects, in addition to a significant increase in the short word interval scores in the WLR.

3. No response of any subject receiving 0.8 % end-tidal isoflurane, before or after painful stimulation.

4. A free category generation task showed no evidence of implicit memory formation in conjunction with 0.8 % isoflurane.

5. The CF was significantly greater when conscious awareness was accompanied by explicit memory than in subjects in whom there was conscious awareness without explicit memory.

6. The CF associated with lack of responsiveness and no implicit memory was significantly less than that associated with conscious awareness but without explicit memory.

Coherent frequency

Previous studies of the AER during anaesthesia have used 1000 samples or more of EEG at 6-Hz stimulating frequency [2]. This is because a good quality trace is essential in order to quantify the amplitude and latency of the early cortical (middle latency) waves. Recently, some groups have examined the method of updating a 1000 sample average, weighted with the most recently acquired data [14]. As we did not attempt to define a latency or amplitude, but only frequency content, 100 samples gave consistent CF values with a low variance between repeated measures and, in the pilot

![Diagram](http://bja.oxfordjournals.org/Downloadedfromhttp://bja.oxfordjournals.org/)
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Fourier analysis assumes that the waveform under examination can be described as a series of sine waves of different amplitudes and phases. If the signal to be analysed is a pure sine wave, then its FFT gives rise to a single frequency with no harmonic content; however, if the signal is not sinusoidal, then the harmonic content increases [15]. Galambos' description of the 40-Hz SSR seen in the awake subject was that of a sine wave [16] and on this basis, by stimulating at the "correct frequency" we expected to see little harmonic content. This proved to be the case with CF in the range 28-41 Hz with the subject breathing air. The variation in frequency between subjects breathing air has been reported previously [17]; it may be related to the individual level of arousal because, in our pilot studies, the subject falling asleep during the recordings was associated with a decrease in frequency. Galambos' analysis [personal communication to J.G.J.] of the Northwick Park middle latency data [5-10] showing that the "correct frequency" would decrease with anaesthesia implied that we would expect to see smaller values of CF as anaesthesia was deepened. This was again verified in our present study.

The variation in CF between subjects seen in this study, especially in conjunction with 0.4% isoflurane, may be attributable to a number of factors; it may simply reflect the variability in frequency seen with subjects breathing air [17]; the depressant effect on CF of a dose of isoflurane may vary between subjects; there may have been difficulty in maintaining a steady state isoflurane concentration; a degree of excitation occurred in some subjects with administration of isoflurane. As the Northwick Park studies included data from both volatile and i.v. anaesthetic agents, this suggested that the CF changes reported here may be seen also with other agents. The inter-subject variation and decrease in CF with anaesthesia suggest that using a 40-Hz stimulating frequency for all subjects for monitoring depth of anaesthesia, as suggested by Plourde [18] may not be appropriate. This is discussed below.

Painful stimulation of the ulnar nerve was associated with a small but statistically insignificant increase in CF for the group in conjunction with 0.4%, and no change in the CF with 0.8% end-tidal isoflurane, despite obvious changes in behaviour of the subject and performance on the psychological tests. This was probably caused by our experimental paradigm, in which the stimulation was followed immediately by the psychological tests and then subsequently by the measure of the CF. We felt the subjects had drifted into "deeper" anaesthesia again by the time the EEG was recorded. After completing the present study, one of the subjects was retested with the electrical stimulation during continuous EEG measurements, but without the psychological tests. This revealed that, in conjunction with 0.8% isoflurane, the initial tetanic stimulation caused a marked increase in CF, from 10 to 15 Hz, but the subsequent 1-Hz stimulation was insufficient to maintain arousal and the next recording showed a CF of 10 Hz. This problem of selecting a sustained stimulus to represent surgical arousal will be more easily addressed in a study undertaken during a surgical operation.

**Psychological tests**

There was a decline in cognitive function with increasing dose of isoflurane, as shown by the WLR and CR results. Six of the seven subjects continued to respond when receiving 0.2%, and four with 0.4% isoflurane. The CF recorded at times when there was no explicit recall of events afterwards were significantly different from those recorded in other periods when the subjects showed no explicit memory for events. Painful stimulation caused an increase in overall performance in individuals with both tests, but this was not significant for the group as a whole. A more detailed analysis of the WLR test revealed an increase in performance at the short word interval scores. This would imply an effect on attention and short-term or working memory, but not on long-term memory. The scores for longer word intervals represent performance with increasing task difficulty and scores did not increase significantly for the group as a whole with stimulation in conjunction with 0.4% isoflurane, although two individuals began to respond correctly with painful stimulation. These results confirm that the overall state of arousal (and cognitive processing) of a subject is determined by the balance between the depressant effects of anaesthetics and the stimulation the subject receives. The implications for anaesthetic practice are obvious: that a previously unresponsive patient may become responsive with surgical stimulation, and care must be taken to avoid arousal to state of conscious awareness, especially if the patient is paralysed.

**Post trial recall**

The post-experiment category recognition tests revealed that there was a significant decline in explicit recall with increasing dose of isoflurane. These results confirm previous work [19-22] (fig. 6). There was no evidence of implicit memory formation in conjunction with 0.8% isoflurane. There are a number of possible explanations for this latter result: the words used were not salient enough [23]—although other authors have found evidence of implicit memory using this type of stimulus [24]; the number of word repeats consisted of only 10 repetitions, but there is some evidence that more presentations may allow learning to take place [25]; and there was not enough arousal even with ulnar nerve stimulation, implying that when implicit memory formation is found with greater concentrations of isoflurane, it may be because the surgical stimulation was enough to reverse the depressant effects of the anaesthetic. Finally, the WLR and CR tests preceding and following the 10 critical repetitions may have interfered with the implicit memory trace or its retrieval.

**Comparison of the 10-Hz transient MLR and the 40-Hz SSR with the CF**

Previous studies using the 40-Hz SSR showed that the amplitude of the EEG response is markedly

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*By guest on November 4, 2016*
reduced with anaesthesia at a time when there is loss of responsiveness of the patient to a button-pressing task. The reappearance of the 40-Hz SSR coincided with the patient beginning to respond to the button-pressing task [26, 27]. However, a recent study showed that implicit memory formation can still be demonstrated when the 40-Hz SSR is attenuated [28]. The result may be explained by the original suggestion of Galambos [R. Galambos, personal communication to J. G. J.] that, with lengthening of the MLR with anaesthesia, the 40-Hz stimulating frequency may no longer be appropriate. Thus a large reduction in the amplitude of the 40-Hz SSR with anaesthesia may not simply reflect reduction in attention or vigilance, but also a reduction in the coherent frequency of the brain. Another study comparing the 40-Hz SSR and the MLR showed that, whilst the latter was affected in a dose-dependent manner by the anaesthetic, the 40-Hz SSR was dramatically and maximally reduced during enflurane anaesthesia, irrespective of the concentration given [29].

In summary, the 40-Hz SSR is probably too sensitive a variable to measure information processing. Madler and colleagues [30], using a frequency analysis of the middle latency waves, showed a decrease in the dominant frequency from 40 Hz to about 10 Hz with concentrations of isoflurane increasing from 0% to 1.2%. Thus the variable frequency stimulating paradigm which generates the coherent frequency used in our study may be more appropriate.

**Relationship between the coherent frequency, psychological performance and post-trial memory**

The correlation of specific frequencies with psychological performance should be treated with some caution—as we have no evidence (or, indeed, test) of implicit memory in other conditions, we cannot exclude the possibility that our test is simply insensitive. Furthermore only seven subjects have been studied using this paradigm and it would be necessary to study a greater number of subjects to determine the clinical relevance of the findings. However, the coherent frequency/psychological performance correlation confirms recent studies which examined the presence or absence of the middle latency waves along with tests of implicit and explicit memory during anaesthesia [31]. With both the isoflurane and propofol techniques, no post-anaesthetic explicit or implicit memory could be demonstrated. Furthermore, the AER showed that the middle latency waves were abolished and a Fourier analysis revealed a frequency of about 10–15 Hz. However, with the benzodiazepine-fentanyl technique, an implicit memory task showed evidence of learning in this group, along with preservation of the middle latency and a Fourier analysis showing a frequency of about 40 Hz. In another study, signs of movement during operation were correlated with the re-appearance of the MLR and a dominant power spectrum frequency of approximately 40 Hz. Conversely, a supressed MLR, with a low spectrum frequency of 10–20 Hz, was not associated with movement [32]. These frequencies in both studies are similar to those seen in figure 6.

In summary, the coherent frequency was derived from the AER after Fourier transform. The coherent frequency, along with psychological tests, showed consistent changes with anaesthetic administration and stimulation. We suggest also that a relationship between responsiveness during the trial, post-trial memory and a particular range of coherent frequency may exist.

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**REFERENCES**

CONSCIOUSNESS, MEMORY AND COHERENT FREQUENCY OF THE AER 641


