

HARMONIC COMPOSITION AND TOPOGRAPHIC DISTRIBUTION OF RESPONSES TO SINE WAVE MODULATED LIGHT (SML), THEIR REPRODUCIBILITY AND THEIR INTERHEMISPHERIC RELATIONSHIP

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Since Van der Tweel *et al.* (1958) introduced sine wave modulated light (SML) as a stimulus for evoking visual responses, the method has been applied by various investigators, who used it for the study of responses recorded from the scalp in normal men (Van der Tweel and Verduyn Lunel 1965; Spekreyse 1966; Regan 1969) and recorded by means of intracerebral electrodes in patients (Kamp *et al.* 1960) and animals (Lopes da Silva 1970). The reasons for using the method need not be recapitulated here (see Van der Tweel *et al.* 1958; Kamphuisen 1969). The latter studied the significance of symmetry and asymmetry of the occipital scalp responses in normal subjects and patients. He observed that the responses had rather complex wave forms, which hampered evaluation considerably and limited clinical interpretation.

If, however, the SML evoked responses are considered as being composed of only a few harmonic components, a sizeable data reduction can be obtained to render the method useful for clinical purposes.

The aim of the present investigation was to obtain information about the harmonic composition of the responses to SML and their variability at different symmetrical scalp areas in normal human individuals. Moreover, this provided the possibility of determining the inter-hemispheric amplitude and phase relationship for each harmonic component.

Comparing the amplitudes of SML evoked potentials at symmetrical electrode positions on the scalp, Regan and Heron (1969) could show

considerable amplitude differences in a patient with a hemianopic field defect with macular sparing. These differences were more pronounced with sine wave modulated blank field stimulation than with sinusoidally modulated pattern stimulation. Moreover, with the latter form of stimulation, Halliday and Michael (1970), Michael and Halliday (1971) and Jeffreys and Axford (1972) showed the influence of the retinal site of stimulation on the evoked potential topography. Although this has not been investigated for blank field sine wave stimulation, in this case also it may lead to arbitrary topographical interpretations when whole field stimulation is used. Therefore, in using blank field sine wave stimulation, comparing responses at symmetrical electrode positions may have the advantages, first, to reveal the largest amplitude differences in cases of visual field defect and, secondly, to cancel out effects of the retinal site of stimulation on the cortical responses, since homologous structures in both hemispheres are equally influenced.

METHODS

Investigations were carried out in a group of 9 normal individuals (5 females, 4 males), consisting of students and personnel of the EEG department. Their ages ranged from 18 to 58 years; 8 were right handed, 1 was left handed.

1. Electrodes

They consisted of conventional Ag-AgCl cups (1.0 cm) fixed to the scalp with collodion

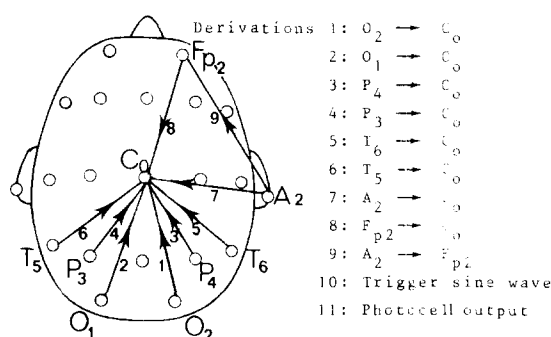


Fig. 1. Schematic representation of the derivations.

and placed according to the 10–20 system. Generally, derivations were used with C_0 as common reference electrode (Fig. 1), because this point is relatively distant from the frontal region and is little influenced by retinal potentials and by the EMG of frontal muscles. To check to what extent C_0 could be regarded as an “indifferent” reference, the derivations $F_{p2} \rightarrow C_0$ and $F_{p2} \rightarrow A_2$ were recorded simultaneously. It was assumed that the probability that electrodes F_{p2} and C_0 and A_2 were equally influenced by the evoked responses and were equipotential was negligible. Thus, whenever these derivations did not show responses to SML, electrode C_0 was considered to be “relatively indifferent” and the records were used for further analysis. In some instances responses were detected at C_0 and these trials were discarded.

2. Recording

Records were made from the homologous areas over the right and left occipital (O_2 , O_1), parietal (P_4 , P_3) and temporal (T_6 , T_5) regions (Fig. 1) on a 16-channel EEG apparatus (band pass 0.3–70 c/sec). In addition, the output of a photocell “looking” at the light source and the output of the sine wave generator were recorded. The EEG apparatus was connected to a 14-channel tape-recorder (0–500 c/sec) on which 9 EEG and 2 calibration signals were stored.

3. Stimulation

The SML was supplied by 6 fluorescent tubes covered by an opaque glass screen and wired in parallel. Their luminosity was modulated by a sine wave generator. The glass screen had a surface of 60×60 cm and produced diffuse

illumination with a harmonic distortion of less than 0.6%. The subject lay on a couch and was asked to look at the screen, 25 cm above the nasion, and not to fix his gaze. The average light intensity at the eyes was 750 lux and was kept constant between trials. A trial usually consisted of a period lasting approximately 25 sec during which SML stimulation was applied. Two modulation frequencies were used; 10 c/sec, *i.e.*, within the alpha frequency band; and 16 c/sec, *i.e.*, outside the alpha band.

Only one modulation depth was used, namely 30%, chosen to obtain response amplitudes which were not too small, and to avoid saturation phenomena (Van der Tweel and Verduyn Lunel 1965). In all subjects at least 4 trials were performed during which the stimulation parameters were kept constant.

4. Analysis

Two methods of analysis were used:

a. *Averaging.* The responses were averaged by means of a CAT 400B (Mnemotron). One channel was occupied by a reference signal of known amplitude, consisting of the output of a photocell placed inside the light source. This signal was summed simultaneously with the EEG and thus served as amplitude calibration. The outputs of the 4 channels were recorded on an X–Y plotter.

If the evoked potentials were composed exclusively of sine waves at the same frequency as the stimulus, the averaging method would have been adequate for obtaining quantitative information on their amplitudes. Since, however, they were generally more complex, the averaged curves were not suitable for measuring the amplitudes of the various response components with precision. For this reason, we performed a harmonic analysis of the evoked responses.

b. *Harmonic analysis.* The EEG records and calibration signals stored on the tape-recorder were played back into a digital computer (type CDC-1700, sampling frequency 125/sec). Before analog–digital conversion the signals passed through a high frequency filter of 50 c/sec (24 dB/octave), allowing 5 harmonics at 10 c/sec and 3 harmonics at 16 c/sec to be considered. The signals were then submitted to a discrete Fourier analysis, as described by Lopes da Silva (1970).

The computer was programmed to start 5 sec

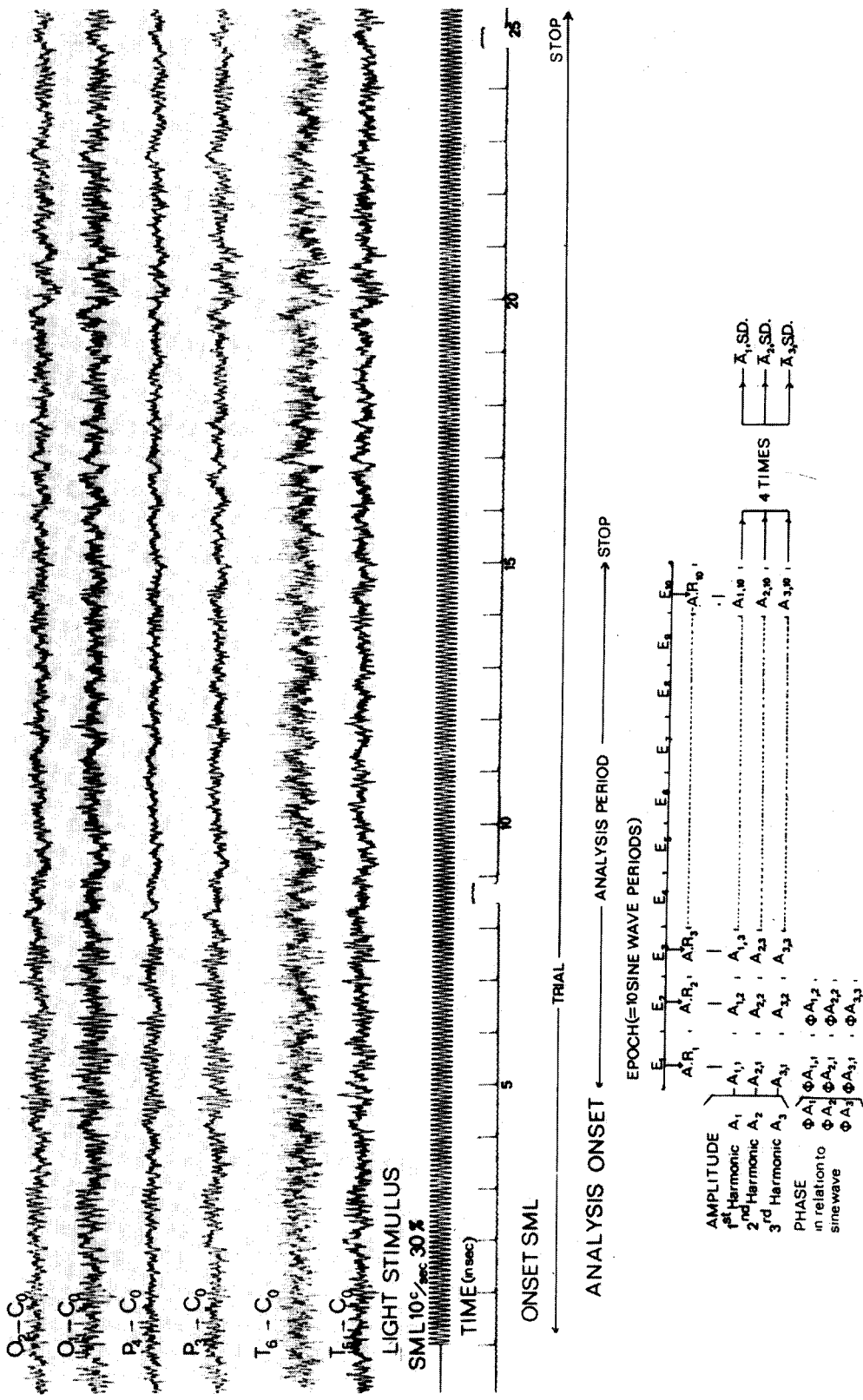


Fig. 2. From top to bottom, 6 scalp derivations (see Fig. 1) (derivations 7 and 8 deleted); photocell; time in seconds; duration of an analysis period. 5 sec after SML onset the EEG derivations and the photocell signal (trace 7) were divided into 10 epochs, each lasting 10 consecutive sine wave periods (at 10 c/sec an epoch lasts 1.0 sec). Bottom traces indicate epochs (E₁ to E₁₀), average SML evoked responses (A₁ to A₁₀), amplitudes of the harmonics (A_{1,1}, A_{2,1} and A_{3,1} to A_{1,10}, A_{2,10} and A_{3,10}), their averages (\bar{A}_1 , \bar{A}_2 and \bar{A}_3) with standard deviations (S.D.) over 4 trials. Average phase relation between harmonics and the stimulating sine wave are also presented (ϕA_1 , ϕA_2 and ϕA_3).

after the onset of SML and to select from each trial with SML stimulation 10 sequential epochs, each consisting of 10 cycles of sine wave stimulation (see Fig. 2). Thus, at the stimulation frequency of 10 c/sec an epoch lasted 1.000 sec ($10 \times \frac{1}{10}$) and at 16 c/sec, 0.625 sec ($10 \times \frac{1}{16}$).

For each epoch the computer determined averages of response components evoked by 10 consecutive cycles of sine wave stimulation. Besides the responses themselves a considerable amount of background activity, *e.g.*, alpha rhythm, was included; its amount was revealed by the variability, *i.e.*, the standard deviation. Computations were made: (1) of the amplitudes (in microvolts) of the 1st, 2nd and 3rd harmonics; and (2) of the phase differences (in degrees)

between the stimulating sine wave and the 1st, 2nd and 3rd harmonic components. Furthermore, the power of the first three harmonic components (P_1 , P_2 and P_3) was computed as well as the power of the average evoked response (P_{av}). The quantity $P_{av} - (P_1 + P_2 + P_3) \times 100/P_{av}$ was called Rest Power.

The reasons for averaging only 10 relatively short epochs were that (1) epochs were short enough to assume that the state of alertness and motivation of the subjects remained constant and did not influence the stationarity of the signals; and (2) the entire procedure was short enough to make it usable in a clinical context. Obviously the small number of cycles within each epoch entailed rather poor signal-to-noise ratios.

TABLE I

Average amplitudes (A_1) with standard deviations (s.d.) and variation coefficients (%) of first harmonics (in μV) of the SML evoked occipital, parietal and temporal responses (right and left) of 9 normal subjects. Stimulation frequencies: 10 and 16 c/sec. Values at 10 c/sec that are significantly larger than corresponding values at 16 c/sec and *vice versa* are in bold type. Variation coefficient values (%) per stimulation frequency per scalp area marked with * are significantly different from the other values.

SML input frequency	Subjects	Modulation depth: 30%																	
		Occipital						Parietal						Temporal					
		Right			Left			Right			Left			Right			Left		
		\bar{A}_1	s.d.	%	\bar{A}_1	s.d.	%	\bar{A}_1	s.d.	%	\bar{A}_1	s.d.	%	\bar{A}_1	s.d.	%	\bar{A}_1	s.d.	%
10 c/sec	S 1	17.5	7.8	45	26.8	13.6	51	12.6	5.6	44	10.3	5.5	53	13.9	6.6	47	9.9	5.4	55
	S 2	26.1	12.7	47	27.9	12.7	46	14.3	8.8	62	13.9	6.9	50	15.1	8.8	56	16.9	9.1	54
	S 3	9.6	6.6	69*	7.6	4.1	53	7.1	5.4	76*	4.6	2.0	43	9.4	5.2	55	6.5	2.3	35*
	S 4	21.0	9.1	43	14.4	8.3	58	9.4	5.3	56	6.1	3.5	57	12.3	3.9	32*	9.3	3.7	40
	S 5	2.0	1.0	50	2.9	1.7	59	1.1	0.6	55	1.3	0.9	69*	2.0	1.0	50	1.3	0.9	69*
	S 6	4.2	1.2	29*	5.9	1.7	27*	2.2	0.7	32*	2.6	0.9	35*	4.3	1.2	28*	3.6	1.3	36*
	S 7	4.6	3.0	65	5.9	3.4	58	3.0	2.2	73*	3.2	2.2	69*	5.0	3.3	66	4.1	2.5	61
	S 8	6.1	4.7	77*	10.7	6.0	56	3.8	2.7	71*	5.8	3.8	66	5.3	4.2	79*	4.7	2.9	62
	S 9	7.1	3.1	44	10.4	4.4	42	5.4	2.3	43	6.8	2.9	43	5.8	3.1	53	4.0	2.2	55
	Mean	10.9			12.5			6.5			6.1			8.1			6.7		
	S.D.	8.5			9.1			4.7			3.9			4.7			4.7		
16 c/sec	S 1	4.8	3.2	67*	10.2	5.2	51	4.4	2.3	52	4.5	2.6	58	7.6	3.8	50	6.8	3.6	53
	S 2	8.5	3.5	41	8.9	4.3	48	4.7	2.9	62	4.4	2.2	50	6.3	4.5	71*	6.8	3.8	56
	S 3	4.4	1.4	32*	2.6	1.3	50	2.5	1.2	48	1.5	0.7	47	2.9	1.4	46	2.2	0.8	36
	S 4	4.3	2.4	56	4.3	1.9	44	2.2	1.0	45	1.8	0.9	50	3.4	1.5	44	2.6	1.1	42
	S 5	4.5	1.3	29	4.9	1.9	39	2.3	0.8	35*	2.4	1.0	42	3.6	1.3	36	2.3	1.1	48
	S 6	2.1	1.1	52	3.5	1.6	46	1.2	0.8	67*	1.5	0.8	53	2.3	1.3	56	1.7	0.9	53
	S 7	4.1	2.5	61*	4.8	2.6	54	1.7	1.0	59	1.8	0.9	50	4.7	2.1	45	3.3	1.2	36
	S 8	15.6	2.5	16*	21.5	3.7	17*	9.0	1.5	16*	9.5	1.7	18*	7.7	2.1	27*	6.1	1.7	28*
	S 9	3.5	1.4	40	3.9	1.7	44	2.1	1.0	48	2.6	1.0	38	4.1	1.7	41	2.5	1.2	46
	Mean	5.7			7.3			3.4			3.3			4.7			3.8		
	S.D.	4.0			5.9			2.4			2.6			2.0			2.1		

In each subject 4 trials were performed at 10 c/sec and at 16 c/sec; therefore, $4 \times 10 = 40$ epochs were available per stimulation frequency, providing 40 amplitude values for each of the response components. The means, standard deviations and variation coefficients of these 40 values were computed.

From the phase differences between the stimulating sine wave and the harmonic components, the right-left phase difference of each of the harmonic components was determined at homologous scalp areas.

RESULTS

The data obtained by harmonic analysis in earlier experiments (Van der Tweel and Verduyn Lunel 1965; Donker 1972) as well as in the present series showed that the responses mainly consisted

of fundamental—called below 1st harmonic—and 2nd harmonics. Third harmonics were negligible. Since the Rest Power, with a few exceptions, was always smaller than 10% of the Pav, the contribution of higher harmonics was considered to be negligible. Therefore only the characteristics of the 1st and 2nd harmonics will be discussed. Their mean amplitudes and their variation coefficients, for all subjects, at all recorded areas and for both stimulation frequencies are presented in Table I (1st harmonic) and II (2nd harmonic). From these data relations have been studied between: amplitudes of the 1st (A_1) and the 2nd (A_2) harmonics and stimulation frequency (1a); amplitudes of harmonics and localization (1b); harmonic content of the responses and stimulation frequency (2a); and harmonic content and localization (2b).

TABLE II

Second harmonic component (A_2). Explanation see Table I.

SML input frequency	Subjects	Modulation depth: 30%																	
		Occipital						Parietal						Temporal					
		Right			Left			Right			Left			Right			Left		
		\bar{A}_2	s.d.	%	\bar{A}_2	s.d.	%	\bar{A}_2	s.d.	%	\bar{A}_2	s.d.	%	\bar{A}_2	s.d.	%	\bar{A}_2	s.d.	%
10 c/sec	S 1	4.7	2.5	53*	7.4	2.8	38	4.2	2.5	60	4.0	2.4	60	5.0	3.0	60*	4.0	2.4	60
	S 2	6.9	3.0	34	8.2	3.4	41	5.6	2.1	38	4.0	1.9	48	4.8	2.9	46	5.2	1.8	35
	S 3	3.0	1.3	43	3.7	1.4	38	1.8	1.0	56	1.7	0.7	41	2.4	1.1	45	1.5	0.7	47
	S 4	4.0	1.9	48	3.2	1.9	59*	1.4	0.8	57	1.4	0.8	57	2.0	0.9	43	1.8	0.8	44
	S 5	2.7	1.4	52	3.5	1.6	46	2.1	1.1	52	1.9	1.0	53	3.5	1.5	31*	1.8	0.8	33*
	S 6	4.7	1.0	21*	4.8	1.1	23*	2.6	0.7	27*	2.3	0.8	35*	3.2	1.0	58	1.9	0.7	37
	S 7	7.1	2.0	28*	9.6	2.2	22*	2.1	1.1	52	2.4	1.0	42	3.3	1.9	47	2.4	1.1	46
	S 8	5.1	1.6	31	5.5	1.9	35	2.5	1.0	40	1.9	1.0	53	4.5	2.1	48	2.2	1.2	55
	S 9	1.9	0.8	42	2.6	1.2	46	1.1	0.6	55	1.3	0.6	46	3.1	1.5	29*	1.5	0.9	60
	Mean	5.0			4.5			2.9			2.3			3.5			2.5		
	S.D.	1.6			2.5			0.9			1.0			1.0			1.3		
16 c/sec	S 1	2.9	1.6	55	2.6	1.6	62*	1.7	0.8	47	1.3	0.8	62*	2.3	1.4	60	1.8	1.1	61
	S 2	1.4	1.2	86*	2.0	1.1	55	1.7	1.0	58*	1.1	0.5	45	2.1	1.4	66*	1.8	1.0	55
	S 3	3.3	1.1	33*	7.1	2.8	39	5.5	1.5	27*	3.4	1.3	38	6.5	2.4	37	2.8	1.3	46
	S 4	1.8	0.9	50	1.7	0.8	47	1.1	0.5	45	0.8	0.4	50	1.0	0.6	60	1.0	0.4	40
	S 5	2.2	0.8	36	3.2	1.1	34	1.3	0.5	38	1.8	0.7	38	1.9	1.0	52	1.8	1.0	55
	S 6	6.8	0.7	10*	6.6	0.8	12*	2.5	0.4	16*	2.2	0.4	18*	3.1	0.7	23*	1.8	0.6	33*
	S 7	1.4	0.6	43	1.2	0.7	58	0.9	0.4	44	0.6	0.3	50	1.4	0.7	50	0.7	0.5	71*
	S 8	2.9	1.1	38	4.5	1.4	26*	1.7	0.7	41	2.0	0.7	35	2.0	0.8	40	1.6	0.7	44
	S 9	1.4	0.8	57	2.5	1.4	56	1.2	0.6	50	1.9	0.9	47	2.3	1.2	52	1.3	0.7	54
	Mean	2.7			3.5			1.9			1.7			2.5			1.6		
	S.D.	1.7			2.1			1.4			0.9			1.6			0.6		

The data obtained on standard deviations and variation coefficients have been used for studying the variability of the response components, mainly inter- and intra-individual variability, taking into account the influence of the stimulation frequency and the localization (2c).

1. Amplitude

a. Amplitude of 1st and 2nd harmonics (A_1 and A_2) and stimulation frequency

In 7 of the 9 subjects, in all areas, on both sides of the scalp the A_1 values (Table I) were larger at 10 c/sec than at 16 c/sec. By means of Student's t test for independent samples in these 7 subjects, except 1 (S 7), the hypothesis could be rejected ($\alpha=0.05$, two-sided) that A_1 values obtained at 10 c/sec and at 16 c/sec were identical. This meant that in 6 out of 9 subjects in all areas the A_1 values were larger at 10 c/sec than at 16

c/sec. In 2 subjects (S 5 and S 8) the A_1 values at 10 c/sec were significantly smaller ($\alpha=0.05$) than those at 16 c/sec.

For the A_2 values (Table II) it was found that in 4 subjects, in all scalp areas, these values were significantly larger at 10 c/sec than at 16 c/sec ($\alpha=0.05$). In one subject (S 3) the A_2 values at 10 c/sec were significantly smaller than at 16 c/sec in all areas except the right occipital.

In most scalp areas of the other subjects no significant differences were encountered between stimulation frequencies. In Tables I and II the values of A_1 and A_2 which are significantly larger at 10 c/sec than the corresponding values at 16 c/sec, and *vice versa*, are set in bold type for each subject.

b. Amplitude of 1st and 2nd harmonics (A_1 and A_2) and localization

First the A_1 and A_2 values, obtained in each

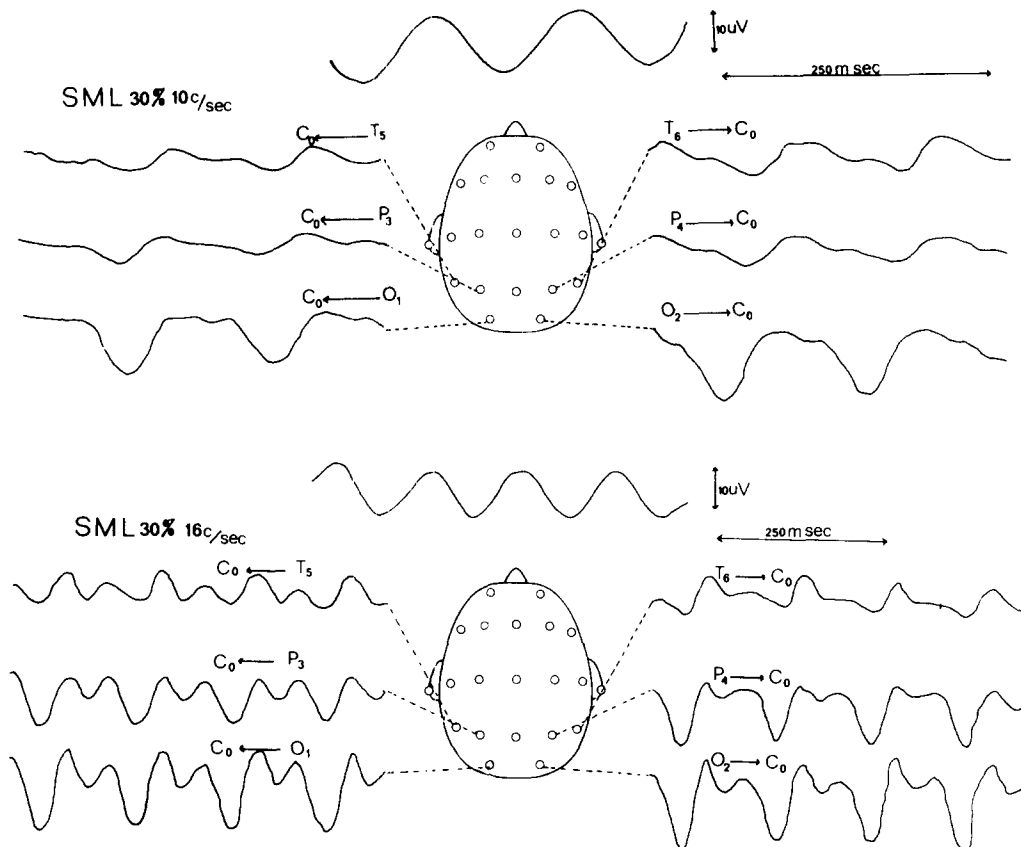


Fig. 3. Example of topographical distribution of average responses to SML recorded from symmetrical right and left areas. Stimulation frequencies: 10 and 16 c/sec. Modulation depth: 30%. Note wave form distortion varying with stimulation frequency and localization. (Analysis time 250 msec, $N=100$)

subject at both stimulation frequencies, were compared between the occipital, parietal and temporal areas on the right and left sides. By means of the t test for dependent samples ($\alpha=0.05$, two-sided) the whole group of 9 subjects was tested for statistically significant amplitude differences between the compared areas, and an influence of the side on the topographical distribution was investigated.

Secondly, whether significant amplitude differences of 1st and 2nd harmonics existed between homologous right and left scalp areas was tested.

The first comparison revealed that on the left side of the scalp similar topographical distributions of the amplitudes of both harmonics existed for both stimulation frequencies. In the occipital area both harmonics had significantly larger amplitudes than in the parietal and the temporal areas, while no significant amplitude differences existed between temporal and parietal areas. On the right side only the harmonic component A_1 presented similar distributions at 10 c/sec and at 16 c/sec. It was found that the A_1 amplitudes in the occipital and in temporal areas were significantly larger than in the parietal area, whereas no significant difference occurred between the occipital and temporal areas. The amplitudes of the harmonic component A_2 presented no consistent distribution on the right side of the scalp at both stimulation frequencies (Fig. 4).

As regards the amplitudes of the harmonics A_1 and A_2 in homologous areas, it was found that in the right temporal area they were significantly larger than in the left.

No significant differences of A_1 and A_2 were found between right and left parietal and occipital

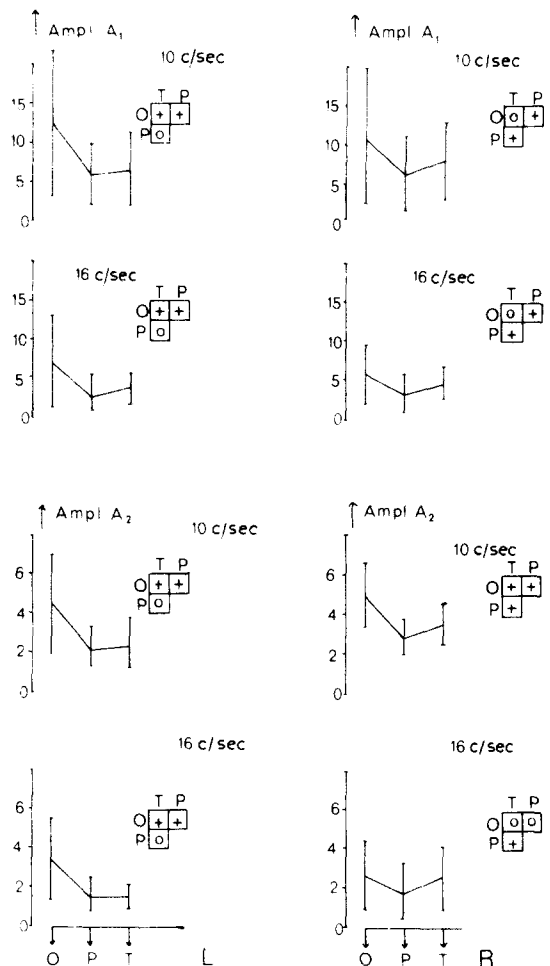


Fig. 4. Means of 1st (A_1) and 2nd (A_2) harmonic amplitudes at occipital (O), parietal (P) and temporal (T) areas (9 subjects, 4 trials) with standard deviations (vertical bars). Stimulation frequencies: 10 and 16 c/sec. R, right. L, left. To the right of each curve the significance of differences between scalp areas is shown: + = significant; 0 = not significant (t test for dependent samples; $\alpha=0.05$).

the first harmonics. Generally, this ratio was < 1 , meaning that the contribution of the second harmonic was smaller than that of the first.

a. The influence of both stimulation frequencies on the harmonic composition of the evoked responses did not show any consistent pattern. For the whole group it appeared that in 4 subjects the ratios at 10 c/sec were smaller than at 16 c/sec, that in 3 subjects they were larger and that in 2 subjects they did not clearly differ.

b. The A_2/A_1 ratio showed small differences between the areas investigated in 7 subjects. Comparison of the ratios between symmetrical

2. Harmonic content

The averages obtained showed that different forms of SML evoked responses could be distinguished. The wave form varied with stimulation frequency and with localization (Fig. 3). Pure sine wave forms were rarely encountered.

The wave form is, of course, determined by the harmonic content of the evoked potential, which may be presented as the ratio (A_2/A_1) between the mean amplitudes of the second and

right and left areas of the same subject revealed no obvious differences at 10 c/sec. At 16 c/sec this was also found except in the occipital areas of 2 subjects. One presented a ratio 3.5 times larger on the left than on the right, whereas the other presented a ratio approximately twice as large on the right as on the left.

c. Between homologous areas in different subjects clear differences could exist in the A_2/A_1 ratio. Most of them had values between 0.2 and 0.6; however, some of them presented values up to 2.2.

3. Variability of response components

An indication of the variability in amplitude of the harmonics was obtained by calculating the standard deviations and the variation coefficients, *i.e.*, the standard deviations expressed in percentages of the mean. The latter are summarized in Tables I (A_1) and II (A_2).

The following aspects of amplitude variability were studied: The inter-individual variability, *i.e.*, between amplitudes obtained at comparable areas in different subjects (3a). The intra-individual regional variability, *i.e.*, the variability at one area in the same subject. A subgroup of this kind of variability was considered (3b). The intra-individual interhemispheric variability, *i.e.*, the variability of differences in amplitude, obtained from homologous left and right areas in the same subject (3c).

a. Inter-individual variability

To obtain insight into this form of variability the variation coefficients of the A_1 and A_2 values, obtained in each scalp area, were compared between the 9 individuals. This comparison revealed that considerable differences existed between subjects, as can be seen in Table I and II. Testing the significance of these differences per scalp area, it was found that in only a few cases the hypothesis (confidence level 2%) could be rejected that the obtained values were identical (values with * in Tables I and II). There was, however, no consistency as to this aspect in relation to the different scalp areas and the stimulation frequencies. Moreover, in the calculation it was assumed that the 40 amplitudes from which the variation coefficient was computed were independent, which is probably not true. Therefore these significances were con-

sidered to be of little importance.

b. Intra-individual variability

The variation coefficients of the A_1 and A_2 values presented in Tables I and II show that a considerable amplitude variability existed at both stimulation frequencies at the same scalp area of each subject.

Generally, the variation coefficients at one stimulation frequency in one subject tended to be similar in all areas (*e.g.*, Table I, S 6 at 10 c/sec and S 9 at 16 c/sec; Table II, S 2 at 10 c/sec and S 9 at 16 c/sec). Comparison of the variation coefficients between homologous right and left areas of a subject revealed that comparatively small differences existed. With a few exceptions this held for both harmonics at both stimulation frequencies and at all areas of each subject. By means of the sign test (confidence level 1%) no significant differences were found between right and left variation coefficients at homologous scalp areas. This held for the variation coefficients of both harmonics and both stimulation frequencies.

c. Interhemispheric intra-individual variability

As the interhemispheric variability may be important from a diagnostic point of view this aspect was further investigated. At first, the interhemispheric amplitude relationship of the first and second harmonics was determined. For this purpose the A_1 and A_2 values obtained at each epoch were compared between homologous areas. Fig. 5 (*A, B*) shows an example of the interhemispheric relationship of the A_1 values in the occipital areas for two individuals (S 1, subject with small amplitude relation, and S 2, subject with large amplitude relation). By means of Kendall's rank correlation test their correlation (r_K) was determined. Table III presents the correlation coefficients computed for the A_1 and A_2 values at the occipital, parietal and temporal areas of all subjects at both stimulation frequencies. These correlations presented the following characteristics: (a) In each subject the right-left amplitude correlation expressed in r_K was larger in the occipital than in the temporal area. (b) The r_K obtained for the occipital, parietal and temporal areas had different values from subject to subject. (c) Since at a confidence level of 1% in our cases the minimum value of r_K was 0.28 it can be said that in 7 out of the 9 subjects (especi-

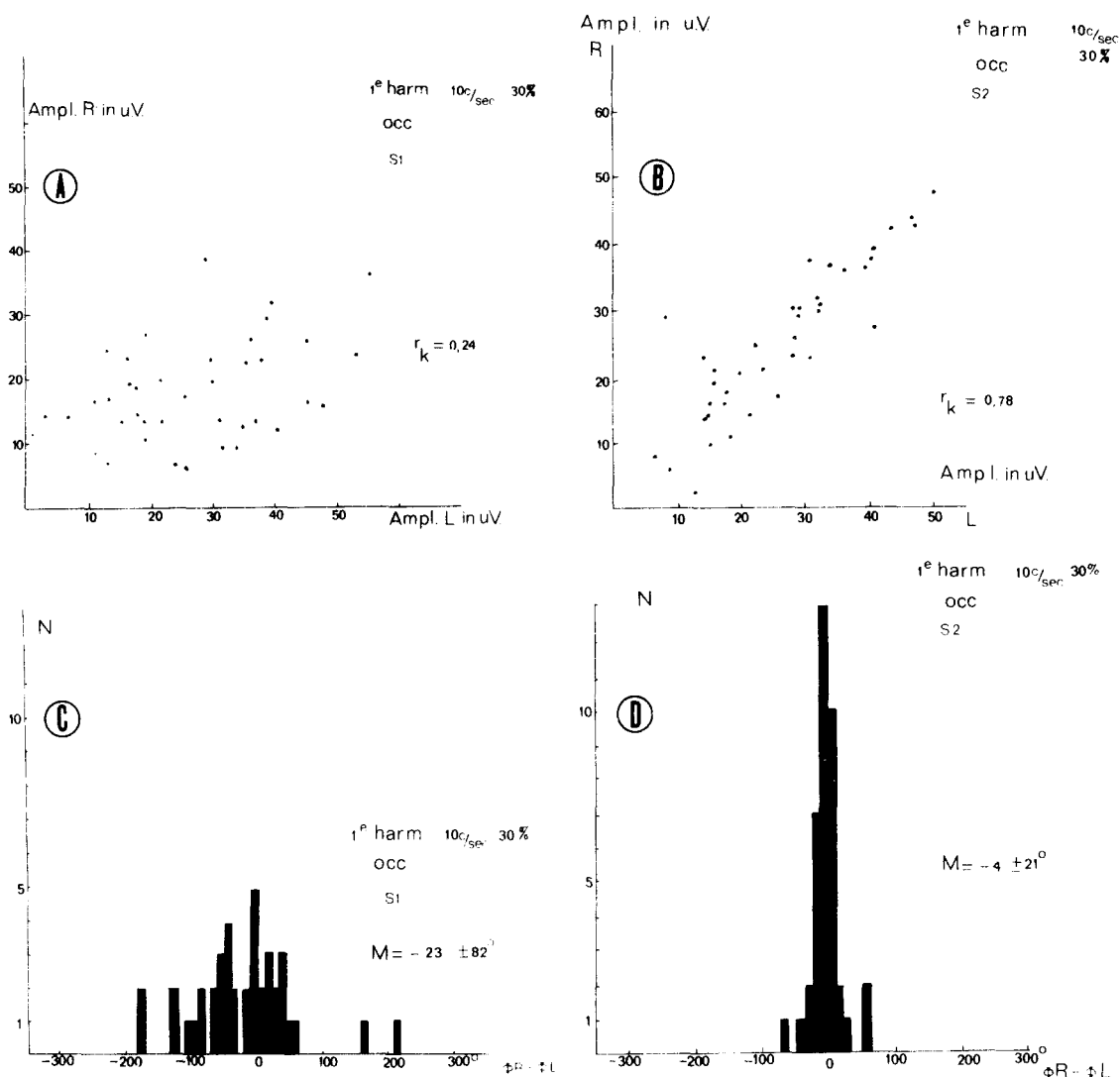


Fig. 5. A, B: Amplitude correlation of simultaneously recorded occipital right and left 1st harmonics (2 subjects: S1, S2). Ordinates: amplitudes of right harmonic components A_1 in μV . Abscissae: amplitudes of simultaneous left harmonic component A_1 in μV . r_k , rank-correlation coefficient of Kendall. C, D: Distribution of phase differences of simultaneous right and left harmonics A_1 from same subjects. Ordinates: number of differences (N). Abscissae: phase differences between bilateral harmonics A_1 . Mean phase difference and standard distribution are indicated for each histogram.

ally in the occipital area) a clear positive amplitude correlation existed. This held for the A_1 values and to a lesser degree also for the A_2 values.

That this right-left correlation has an important influence upon the variability of the differences between simultaneous amplitudes in homologous areas follows from the statistical statement that the variance (S^2) of the differences

of 2 pairs of variables is dependent on the variances of each separate pair and their mutual correlation, *i.e.*, in our cases the variance of the amplitude differences of the right and left harmonics (S^2_{diff}) depends on the variance of the harmonic component of each side (S^2_{ri} and S^2_{le}) and on their mutual correlation:

$$S^2_{diff} = S^2_{ri} + S^2_{le} - 2 \cdot R \cdot S_{ri} \cdot S_{le}.$$

TABLE III

Rank correlation coefficients (r_K) for the amplitudes of simultaneous right and left 1st (A_1) and 2nd (A_2) harmonic components in occipital, parietal and temporal areas in 9 normal individuals. Stimulation frequencies: 10 and 16 c/sec. Modulation depth: 30%. r_K values in bold type are those at which the hypothesis H_0 (no correlation) may be rejected ($\alpha: 0.05$), values in italics those at which it may be rejected for $\alpha=0.01$.

Subjects	10 c/sec 30 %						16 c/sec 30 %					
	Occipital		Parietal		Temporal		Occipital		Parietal		Temporal	
	A_1	A_2	A_1	A_2	A_1	A_2	A_1	A_2	A_1	A_2	A_1	A_2
S 1	0.24	0.14	0.34	0.12	0.02	0.07	0.07	0.14	0.36	0.41	0.39	0.48
S 2	0.78	0.69	0.67	0.34	0.47	0.08	0.57	0.36	0.24	0.25	0.21	0.22
S 3	0.24	0.46	0.05	0.05	0.17	0.09	0.29	0.39	0.10	0.57	0.14	0.58
S 4	0.47	0.53	0.40	0.16	0.26	0.13	0.50	0.50	0.32	0.43	0.19	0.44
S 5	0.60	0.53	0.24	0.35	0.33	0.43	0.60	0.51	0.07	0.32	0.06	0.28
S 6	0.64	0.52	0.31	0.28	0.28	0.13	0.37	0.55	-0.17	0.27	-0.02	0.05
S 7	0.61	0.56	0.13	0.15	0.29	0.17	0.53	0.47	0.24	0.13	0.36	0.28
S 8	0.68	0.34	0.54	0.30	0.39	0.34	0.62	0.67	0.60	0.46	0.48	0.22
S 9	0.75	0.55	0.65	0.20	0.63	0.36	0.50	0.53	0.28	0.48	0.26	0.12

In cases in which a maximal positive correlation exists, *i.e.*, in cases in which R is equal to +1, the variance of the differences (S^2_{diff}) is equal to the sum of each of the variances ($S^2_{ri} + S^2_{lef}$) diminished by twice the square root of their product ($2 \cdot +1 \cdot \sqrt{S^2_{ri} \cdot S^2_{le}}$). From this it follows that in those cases the variance of the differences (S^2_{diff}) becomes smaller than each of the variances S^2_{ri} and S^2_{le} .

Regarding the correlation coefficients obtained in the occipital scalp areas it becomes clear that the interhemispheric variability in these areas tended to be smaller than each of the variances on the right and left, *i.e.*, than each of the intra-individual variabilities.

4. Phase relations

Besides the interhemispheric amplitude correlations the interhemispheric phase relations between simultaneous right and left harmonic components were computed. Examples of these computations obtained for the 1st harmonic A_1 at the occipital scalp areas of 2 subjects (S1 and S2) are shown in Fig. 5 (C and D). It can be seen that between subjects differences of right-left phase relationship existed; this held for the 1st as well as for the 2nd harmonic.

Since the data of the right-left phase difference histograms and the right-left amplitude diagrams of Fig. 5 (A-D) are from the same sub-

jects and the same analysis periods, it is clear that a close relation existed between the interhemispheric phase relation and the interhemispheric amplitude correlation of the harmonics. The right-left amplitude correlation (r_K) of both harmonics was large in the subject with a small phase distribution and small in the subject with a large phase distribution. In other words the degree of right-left amplitude correlation, *i.e.*, the degree of coupling of the 1st and 2nd harmonics between the two hemispheres could be considered as an expression of the degree of right-left synchrony of each of the harmonics.

Comparison of the amplitude correlation (r_K) with the standard deviation (S) of the mean right-left phase differences for both harmonics in the occipital areas of the 9 subjects revealed that for the 1st harmonic (A_1) at both stimulation frequencies a correlation existed between the two parameters; this correlation was not clear for the 2nd harmonic (Fig. 6).

DISCUSSION

In accordance with Van der Tweel *et al.* (1958) and Van der Tweel and Verduyn Lunel (1965) our investigation has shown that responses to SML generally have complex wave forms, though occasionally nearly sinusoidal responses are encountered. The wave forms usually differ

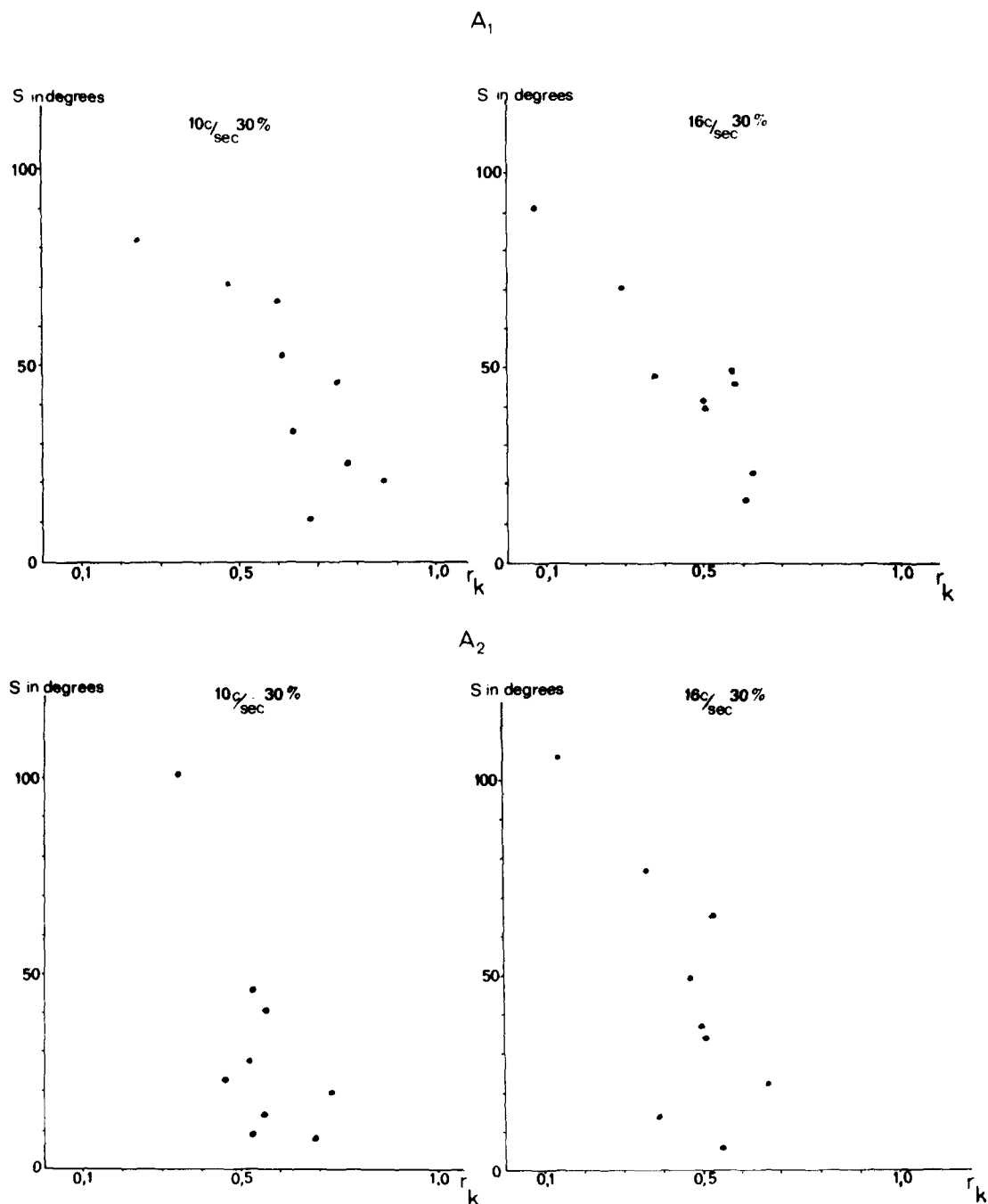


Fig. 6. Correlation between amplitude relation (r_k) and phase difference distribution (S) of bilateral simultaneous harmonics A_1 and A_2 , computed for the occipital area of 9 individuals. Note that harmonic A_1 presents a high correlation between both parameters (r_k and S), and that harmonic A_2 does not clearly present such correlation.

when recorded at different areas of the scalp, *i.e.*, occipital, temporal and parietal; they may even be different in homologous bilateral areas. The wave forms, moreover, differ with stimula-

tion frequency. This observation confirms the opinion of other authors that the visual system contains non-linear elements. Because of the complexity of the response wave forms they

were submitted to discrete Fourier analysis, which revealed that the responses were mainly composed of a 1st and a 2nd harmonic.

Concerning the amplitude distribution of the components, generally they are largest for all parameters over the occipital areas and smallest over the parietal areas. In our group of normal individuals this was a very consistent feature on the left side of the scalp. The asymmetry of the amplitudes of both harmonics A_1 and A_2 in the temporal areas may be related to the fact that 8 out of our 9 normal subjects were right handed. Since only those trials have been taken into consideration which had negligible responses at the vertex, the amplitudes of the responses recorded over the occipital, parietal and temporal areas are specific for the areas concerned. As far as the influence of the stimulation frequency is concerned, generally the harmonic components have larger amplitudes at 10 c/sec than at 16 c/sec. This was less conspicuous for the 2nd component than for the first, and less consistent in the temporal and parietal areas than in the occipital areas.

The responses are mainly composed of 1st and 2nd harmonic components. With a few notable exceptions the 1st harmonics are larger than the 2nd ones. This agrees with the observations of Van der Tweel and Verduyn Lunel (1965) and Spekreyse (1966) who, at stimulation frequencies between 9 and 18 c/sec, obtained responses that predominantly contained fundamental components. Contrary to our expectation that 2nd harmonic components might preponderate in the temporal areas no consistent regional differences were observed. It is important that the harmonic contents of the responses were comparatively similar in homologous bilateral areas.

The intra-individual amplitude variability of the responses is considerable. This applies to the amplitudes of both harmonic components for all subjects in all areas at both stimulation frequencies; it is illustrated by the large values of the variation coefficients in Tables I and II (%). The regional intra-individual amplitude variability was more pronounced in one subject than in another. In each of the subjects the values of the variation coefficients tended to have similar values, *i.e.*, low, median or high. Many

investigators have found that responses to light flashes are less variable in one subject than between subjects or that the intra-individual variability is smaller than the inter-individual variability. This is not confirmed for the responses to SML.

As regards the intra-individual interhemispheric amplitude variability our findings indicate that this kind of variability was small in the 7 subjects in whom a strong interhemispheric coupling between simultaneous right and left response components existed. Moreover, interhemispheric amplitude coupling is correlated with interhemispheric synchrony. This observation is of importance in connection with the problem of interhemispheric synchronization of "spontaneous" activities such as alpha activity, discussed since the beginning of electroencephalography (Adrian and Yamagiwa 1935; Aird and Garoutte 1958; Bremer 1958; Green and Russell 1966; Hoovey *et al.* 1972; Martinius and Hoovey 1972). This might suggest that with the stimulation frequency of 10 c/sec the underlying alpha rhythm was stimulated and that the observed synchronization was due to interhemispheric synchronization of the alpha rhythm. However, at 16 c/sec the interhemispheric relationship of the response components presented the same characteristics and from this it may be concluded that this feature is not related to alpha activity. Therefore intra-individual interhemispheric amplitude variability of responses to SML is considered by us to have the best chance of leading to significant clinical information. Surprisingly, this aspect has been proved statistically for visual evoked responses to flashes only by few investigators (Buchsbaum and Fedio 1969; Faidherbe and Danthine 1971; Davis and Wada 1974).

From a clinical point of view it may be important that 2 subjects (S 1 and S 3) out of our group of 9 normal subjects presented interhemispheric amplitude and phase relationships deviating considerably from the others (see Table III). After the investigation it came to light that these 2 subjects had neurological complaints. The one suffered from migraine, the other from visual disturbances. None of the other subjects had similar complaints. In this connection it should be remarked that the entire investigation

has been repeated on a larger group of normal subjects. They were selected on the basis of absence of abnormalities on careful general, ophthalmological, otological, neurological and EEG investigations.

Finally, it should be remarked that the responses to SML can be described largely by the amplitude and phase relations of the 1st and 2nd harmonic components. This observation furnishes a considerable data reduction of the responses to SML, which makes these responses readily available to objective quantitative automatic analysis.

SUMMARY

1. Responses to sine wave modulated light (SML) were recorded bipolarly from the occipital, parietal and temporal scalp areas on the right and the left sides of 9 normal individuals. Their harmonic composition was determined by means of Fourier analysis.

2. The wave form of the responses was rather complex in relation to the stimulus and differed according to stimulation frequency and localization.

3. The components of the responses were principally the 1st and 2nd harmonics.

4. The amplitudes of the harmonics were usually largest over the occipital and smallest over the parietal scalp areas.

5. Considerable intra-individual amplitude variabilities of both harmonic component amplitudes existed in all areas of all individuals.

6. The interhemispheric amplitude correlations of 1st and 2nd harmonic components, simultaneously recorded in homologous occipital, parietal and temporal areas, were measured by means of Kendall's rank correlation test.

7. The interhemispheric synchrony of the harmonic components was measured by determining the phase differences between each of the response components in homologous right and left scalp areas.

8. In subjects with a high amplitude correlation a strong synchrony existed and *vice versa*.

9. It is suggested that the interhemispheric relationships between harmonic components of the responses to SML might be of importance for clinical application. This opinion is supported

by the fact that through SML evoked responses a considerable data reduction is obtained in comparison with the responses to light flashes.

RESUME

COMPOSITION HARMONIQUE ET DISTRIBUTION TOPOGRAPHIQUE DES RESPONSES A LA LUMIERE A MODULATION SINUSOÏDALE. REPRODUCTIBILITE ET RELATIONS INTERHEMISPHERIQUES

1. Les réponses à la lumière à modulation sinusoïdale ont été recueillies en bipolaire à partir des zones occipitales, pariétales et temporales du scalp, à droite et à gauche chez 9 sujets normaux. Leur composition harmonique a été déterminée par l'analyse de Fourier.

2. L'allure des formes d'ondes était assez complexe, compte tenu du stimulus, et variait selon la fréquence de stimulation et la localisation.

3. Le contenu harmonique des réponses était essentiellement le 1er et le 2e harmonique.

4. La distribution topographique des amplitudes des harmoniques a montré des amplitudes maximales en occipital et minimales en pariétal.

5. D'importantes variabilités intra-individuelles des amplitudes affectaient les 2 harmoniques, sur toutes les régions et chez tous les individus.

6. Les corrélations interhémisphériques entre amplitudes des composants pour les régions symétriques, occipitales, pariétales et temporales ont été déterminées par le test de corrélation de Kendall.

7. Le synchronisme interhémisphérique des harmoniques a été analysé grâce aux différences de phase entre chaque composante de zones homologues droite et gauche.

8. Des sujets présentant une forte corrélation d'amplitude ont aussi présenté un important synchronisme et *vice-versa*.

9. Il est suggéré que les relations interhémisphériques entre harmoniques de la réponse au stimulus sinusoïdal pourraient avoir un intérêt clinique: ces réponses représentent une nette réduction des données, par rapport à celles au flash.

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