LOCAL SIGN IN AUTONOMIC RESPONSES

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There is already an extensive literature on the vascular and sweating responses which are evoked in the limbs by experimental painful stimuli. As far as the present authors are aware, previous investigators are all agreed that these responses show no evidence of "local sign"; that is to say, a painful stimulus applied to one limb produces an equal response on each side of the body. This point has been studied by Sattler (1943), who also reviewed the previous literature. Sattler, using the Hardy-Wolff stimulator, was unable to find any evidence of local sign in the limbs, either in the vasomotor responses, studied plethysmographically, or in the sudomotor responses, as measured by changes in the skin resistance (psychogalvanic response). He concludes that there is no tendency towards the localization of these responses.

However, as Sattler himself states, there is abundant clinical evidence that localized vasoconstriction does occur in association with painful trauma. Further, Carmichael (1950) has shown that, in subjects with complete transverse spinal lesions, the reflex vasomotor responses to painful stimuli below the level of the lesion are much greater on the ipsilateral side. Similarly, recent work in America, in particular that of Korr (1949), points to segmental differences in sweating patterns in pathological conditions. Korr finds cutaneous areas of increased sweating which are segmentally related either to diseased viscera or to skeletal damage. It seems clear, therefore, that local reflex pathways do exist, and there is no *a priori* reason why their function should not be demonstrated in the healthy human subject. There is some reason to believe that, in the intact and conscious subject, autonomic responses to painful stimuli derive not only from local reflex activity at the spinal level, but also from higher centres whose function may correlate with the subjective experience of emotion. Investigators are generally agreed, for example, that the unfulfilled

threat of injury may produce a greater degree of vasoconstriction or sudomotor activity than the injury itself. If it is assumed that the autonomic response associated with emotion is in the nature of the diffuse "fight or flight reaction" described by Cannon, and is without lateral sign, then a painful stimulus may be sufficiently disturbing to arouse a diffuse "emotional" response involving widespread vasoconstriction and increased sweating, which will overlie the comparatively small spinal reflex. It is this spinal reflex which might be assumed to mediate local sign.

In order, therefore, to demonstrate local sign, it would appear necessary to reduce the autonomic disturbances brought about by psychological reaction to as low a level as possible. Thus it is preferable to use "test sophisticated" subjects able to adopt an attitude of indifference to painful stimuli. Further, it is possible that the nature of the painful stimulus can also affect the demonstration of local sign. A sharp cutaneous pain may produce a large psychological response without much local activity, whereas a "dull" pain, resulting from deep stimulation, may produce a smaller psychological response but more local reflex activity.

In the present paper it is shown that, if attention is given to the considerations mentioned above, it is possible to demonstrate local sign. That is to say, if a painful stimulus is applied to either limb, an autonomic response is obtained which is comparatively greater on the ipsilateral side.

During preliminary investigations into the value of the psychogalvanic response for studying variations in autonomic function, local sign appeared to be present, and it was decided to repeat these experiments in a form suitable for precise analysis. This was done in the case of three healthy adult subjects. It was thought advisable to confirm the results obtained with these three subjects in other, less sophisticated, subjects.

Accordingly, the records of certain patients who had undergone bilateral stimulation and recording were analysed. The only criterion in the selection of these records was that they should be suitable for analysis. That is to say, every experiment is reported in which the presence or absence of local sign can be tested by statistical analysis.

Finally, the experiment was repeated plethysmographically, thus verifying that local sign was not an artefact of the electrical method of recording and stimulation. This procedure also has the advantage of demonstrating local sign in vasomotor as opposed to sudomotor responses.

Methods

Method 1 : Skin Resistance Technique.—The response recorded was the fall in skin resistance which followed the stimulus described below. These responses were measured from both sides of the body simultaneously on independent A.C. circuits of the type described by David Grant (1946). The subject was seated comfortably with the arms on arm rests, thus maintaining as far as possible equal conditions of posture and relaxation for each limb. Plain copper electrodes of 13 mm. diameter were lightly attached by rubber retaining straps to the pulp of the tips of digits 2 and 4 of each hand. Changes in the electrical resistance between these electrodes were recorded simultaneously in each hand with mirror galvanometers reflecting a focused beam of light onto moving photographic paper. The apparatus was of the constant current type, and the use of 50 cycle A.C. reduced variability in the recorded responses resulting from polarization, and enabled plain copper electrodes to be used. The sensitivity of the apparatus was calibrated so that the skin resistance changes could be measured in ohms. A photographic record of respiration was made simultaneously by means of a focused beam of light reflected from a chip mirror attached to a rubber tambour. It was thus possible to take account of responses resulting from irregular deep respirations, rather than from the experimental stimuli.

It is not the purpose of this paper to discuss the physiology of skin resistance, but it should be mentioned that the changes which occur are generally admitted to reflect alterations in autonomic tone, and most workers agree that these changes probably indicate alterations in sweating activity (McCleary, 1950).

In method 1, the stimulus was a square wave from an Edison electrical stimulator. The stimulus was applied to the pulp of the little finger by means of a plain copper electrode of the type used for recording. Each hand was stimulated separately. A saline pad attached to the leg acted as an indifferent electrode earthing the subject to the stimulating apparatus. The duration of the stimulus was controlled mechanically and was constant at 400 m. sec. The pulse duration was 1 m. sec. and the pulse frequency was 100 cycles per sec. A shock artefact appears in the photographic record but it can be seen that this is complete within the latent period of the autonomic response (Fig. 4). The intensity of the

stimulus varied from subject to subject, but was usually at the minimum level which gave easily measurable responses. When the strength of the stimulus varied within one experimental session, the responses resulting from these different stimulus intensities were nevertheless used, as this source of variability is allowed for in the method of analysis. An equal number of stimuli was applied to each side of the body, and the stimuli on each side were evenly distributed over the time series. Further, responses were recorded on both possible circuit arrangements. That is to say, recordings were made of responses from the left hand on circuit A, and those from the right hand on circuit B; and responses from the left hand on circuit B, and those from the right hand on circuit A. The recording circuits could be changed with respect to the two hands by means of switches and without removing and replacing electrodes. The purpose of this procedure was to enable separate estimates to be made of variability in responses attributable to a difference in the two circuits, and variability attributable to different reactivity of the two sides of the body.

Three healthy adults and ten patients suffering from irrelevant neurological disorders served as subjects for the experiments using method 1.

Method 2 : Plethysmographic Technique.—The response recorded was the diminution in finger volume which followed the stimulus. The technique has been described previously by Bolton, Carmichael, and Stürup (1936). The subject was seated as for method 1, except that in order to attain the maximum vasodilatation the subject's legs were immersed in water kept at a temperature of 44° C. Glass plethysmographs were placed over the third digit of each hand, and sealed with zinc oxide paste, care being taken to ensure that no venous occlusion occurred. Changes in the volume of the finger were recorded optically on moving photographic paper through the medium of mirrors attached to tambours, which were connected to the glass plethysmographs by a closed air conducting system. Although an approximately equal volume of the finger was included in the plethysmograph on each side, no attempt was made to measure this volume exactly. Nor was the recording system calibrated volumetrically. However the sensitivity of the circuits was adjusted by moving the tambour relative to the focused beam of light and the recording screen, so that a deep inspiration produced approximately equal deflections of the two recording light beams. Respiration was recorded as in method 1.

In method 2 the stimulus was squeezing of the muscles at the back of the neck.

Two healthy adults, who also served as subjects in method 1, served as subjects in method 2.

The Design of the Experiment

Local sign is often apparent from a careful inspection of the raw data, but in order to demonstrate unequivocally the presence of local sign in autonomic responses, a method of analysis of results is required which will give the level of confidence at which local sign can be said to be present.

It is important that all other factors which could influence the results should be held constant. A degree of control which will define the contributions to the final result made by each experimental variable, and by interactions between these variables, is provided in the methods of analysis of variance. Accordingly, in the case of method 1, we employed a three factor analysis of variance with replication, and in the case of method 2, a two factor analysis with replication (Brownlee, 1949).

Method 1.—In the case of the skin resistance technique the factors isolated as sources of variability in the size of autonomic responses are: (a) the side of the body stimulated, left or right; (b) the circuit on which the response is recorded (the two circuits were changed with respect to the two hands at intervals during the experiment); (c) the side of the body, left or right, from which the response is recorded.

Estimates are also made of variability resulting from interaction between each pair of these factors, i.e., between (a) and (b); between (a) and (c); and between (b) and (c). If there is a significant interaction between factors (a) and (c), that is to say between the side of the body stimulated, left or right, and the side of the body, left or right, from which the response is recorded, as factors affecting the size of recorded responses, then local sign is significantly present. It is to be noted that other irrelevant variables such as a difference in the sensitivity of the two circuits, or a time series effect resulting from practice or from a change in the strength of the stimulus, are either independently assessed as sources of variability, or appear in the residual variance against which variance attributable to local sign is tested.

A requirement of this three factor method of analysis is that an equal number of recordings from each side of the body should be made on each circuit, and that an equal number of stimuli on each side of the body should be applied for the recording from each side on each circuit. This calls for a basic block of eight recorded responses, which may be replicated any number of times in any one experiment. In the experiments using method 1, the number of replications varied from two to 12. Whenever a change in the stimulating voltage occurred during one experiment, it occurred with a change in circuits or between one replication and another, but never in such a way that an artefactual interaction between any pair of the three main factors could be involved.

Method 2.—In the plethysmographic experiments, the recording circuits were not changed with respect to the two hands, and so variability resulting from differences in reactivity of the two sides of the body, and variability resulting from differences in the sensitivity of the recording circuits, could not be separated. However, these two sources of variability are together a constant factor which is extracted by the method of analysis, and could not produce artefactual local sign. A two-factor analysis with replication was therefore applied to the results obtained with the plethysmographic technique and the two factors isolated were the compound factor already

mentioned of the circuit on which the recording was made, and the side of the body from which the recording was obtained; and the side of the body stimulated, left or right.

A significant interaction between these two factors provides evidence of local sign in vasomotor responses. In a simple two factor analysis it is not possible to isolate this interaction, which would appear in the residual variance, but when the additional factor of replication is introduced this first order interaction can be isolated. Accordingly, in the plethysmographic experiment reported here the basic block of four recorded responses required by the two factor analysis has been replicated twelve times.

Results

Method 1.—An analysis of the responses of the three healthy subjects (M.A.C., A.E., and M.P.) for the skin resistance experiments showed local sign to be present, according to the criterion discussed above, at the 0.001, 0.01 and 0.05 levels of confidence respectively (Table I).

Of the 10 patients whose records were suitable for analysis by the three factor method, three showed local sign, one at the 0.001 level of confidence, one at the 0.01 level, and one at the 0.05 level (Table II). Of the remaining seven subjects in whom local sign was not present at a statistically significant level, inspection of the raw data shows the effect (relationship between the side stimulated and the side giving the larger response) to be in the direction required by the hypothesis of local sign in every case (Table II). It should be mentioned that in the case of those subjects who showed local sign to a statistically significant degree, the analysis of variance does not itself give any indication of the direction of the effect but inspection of the original data makes it clear that the direction of the effect is according to hypothesis.

Method 2.—Of the two experiments using the technique of plethysmography, one was a failure, since the maximum practicable vasodilatation resulted in recorded responses which were too small to be measured or compared. The other, however, yielded a highly significant result. A two factor analysis with replication carried out on the results from this subject showed local sign to be present at the 0.01 level of confidence (Table III). The interaction in question just misses the 0.001 level of significance.

The results of this experiment, and the results of the skin resistance experiment on subject M.A.C., are also presented graphically. In Figs. 1 and 2, the ordinate and abscissa represent the size of the response from the left and the right sides of the body respectively. An indication is thus given of the ratio of the responses from each side of the body

TABLE IA

LOCAL SIGN IN SKIN RESISTANCE CHANGES FOLLOWING PAINFUL STIMULI IN THREE HEALTHY SUBJECTS
(MEAN RESPONSES)

Side of Response				Left		Right		Number of Replications (N)
Side Stimulated	..	..		Left	Right	Left	Right	
Subject M.A.C.								
Circuit A	..	..	..	5.9	2.6	3.7	7.2	7
Circuit B	..	..	..	5.3	1.8	3.4	6.5	
Subject A.E.								
Circuit A	..	..	..	7.2	7.9	5.0	9.2	12
Circuit B	..	..	..	7.8	7.7	5.0	7.5	
Subject M.P.								
Circuit A	..	..	..	10.3	8.0	5.2	6.9	7
Circuit B	..	..	..	6.8	5.0	5.8	7.1	

The actual recorded responses are not shown. The figures shown above give the mean value in ohms $\times 10^3$ of the responses obtained following stimulation on each side of the body. Figures under (N) refer to the number of replications, and indicate the number of observations from which each mean was calculated. The individual responses in subject M.A.C. are presented graphically in Fig. 3.

TABLE IB

LOCAL SIGN IN SKIN RESISTANCE CHANGES FOLLOWING PAINFUL STIMULI IN THREE HEALTHY SUBJECTS

Subject	M.A.C.			A.E.			M.P.		
	Degrees of Freedom	Mean Squares	P	Degrees of Freedom	Mean Squares	P	Degrees of Freedom	Mean Squares	P
Circuit (C) ..	1	4.5714	—	1	2.1600	—	1	29.0016	—
Side of Response (R) ..	1	23.1429	—	1	21.8504	—	1	21.5106	—
Side Stimulated (S) ..	1	0.0257	—	1	79.2066	—	1	0.9516	—
C $\times$ R	1	0.2579	—	1	6.7204	—	1	47.3616	0.05
C $\times$ S	1	0.3151	—	1	10.1400	—	1	0.0045	—
S $\times$ R .. Local Sign	1	159.8064	0.001	1	55.5105	0.01	1	44.1087	0.05
C $\times$ R $\times$ S ..	1	0.0113	—	1	1.1704	—	1	0.5716	—
Replication Factor ..	6	24.8053	—	11	76.6558	—	6	36.7348	—
Residual	42	7.7728	—	77	7.5998	—	42	8.0952	—

The raw data for this analysis (three factor analysis with replication) are the responses whose means are shown in Table IA. No estimation has been made of the significance of the replication factor, but all other factors and interactions significant at the 0.05 level and above are shown in the column headed P. The significant interaction between the circuit factor and the side of the response in subject M.P. results from the two possible arrangements of the circuits with respect to the sides of the body being unevenly distributed over the time series.

by the position of each symbol relative to the co-ordinates. The side of stimulation is indicated for each pair of responses. The distribution of the responses shows clearly the influence of the side of stimulation on the relative size of responses from the left and right sides of the body. It can also be seen that the responses to a deep inspiration are intermediate between those to stimulation of the left side of the body and those to stimulation of the right. A series of actual recorded responses are reproduced in Figs. 3 and 4.

Discussion

In the five experiments on healthy subjects (three skin resistance experiments, and two plethysmographic experiments) the attempt has been made to minimize conditions which would be likely to mask local sign. At the same time a method of analysis was used that would give results which, if positive, would provide unequivocal evidence of local sign. This attempt has been successful in all but one of our experiments on healthy subjects (the plethysmographic experiment on subject M.P.). The failure in

TABLE II
LOCAL SIGN IN SKIN RESISTANCE CHANGES FOLLOWING PAINFUL STIMULI IN TEN HOSPITAL PATIENTS

Subject	Mean Response on Left		Mean Response on Right		Number of Replications (N)	Level of Significance of Local Sign
	Left Side Stimulated	Right Side Stimulated	Left Side Stimulated	Right Side Stimulated		
E.S.	14.9	11.8	7.9	9.6	7	0.001
J.B.	8.1	3.7	4.1	3.3	4	0.01
C.J.	18.1	16.6	12.6	15.6	5	0.05
H.W.	2.0	1.5	1.6	2.1	4	—
D.R.	3.7	3.0	3.8	4.4	4	—
F.C.	15.3	15.6	7.9	12.6	3	—
H.S.	1.4	1.8	0.2	1.3	2	—
E.R.	10.8	8.1	10.0	9.4	7	—
E.C.	19.1	14.2	20.9	19.9	3	0.2
S.T.	2.1	1.4	2.3	1.8	3	—

The analysis of variance was a three factor analysis with replication resembling in all respects that shown in Table I. The figures given are the mean values in ohms $\times 10^3$ of the responses from each subject. The number of observations from which the mean is calculated is given in the column headed (N).

The level of significance refers to the interaction between the factor for the side of the body stimulated and the factor for the side of the body from which the response is recorded. The level of significance is indicated for each subject in which local sign reaches the 0.2 level or above.

TABLE III
LOCAL SIGN IN VASOMOTOR RESPONSES TO PAINFUL STIMULI

Subject				A.E.			
Side of Response				Left		Right	
Side Stimulated				Left	Right	Left	Right
Replications	1	..	..	3.2	1.8	1.6	0.6
	2	..	..	3.5	1.4	3.2	1.8
	3	..	..	4.9	1.3	2.6	4.6
	4	..	..	3.2	2.7	1.9	5.2
	5	..	..	1.0	2.7	0.3	4.2
	6	..	..	3.9	1.2	1.0	1.3
	7	..	..	1.1	0.3	0.5	1.6
	8	..	..	1.2	1.1	1.0	2.4
	9	..	..	2.2	0.9	0.7	0.8
	10	..	..	2.2	0.9	2.3	2.9
	11	..	..	2.9	1.0	2.2	3.0
	12	..	..	3.0	1.5	2.8	3.3
Total Response				32.3	16.8	20.1	31.7
Mean Response				2.7	1.4	1.7	2.6
Source of Variance				Degrees of Freedom		Mean Squares	Level of Significance
Side of Response (R)				1		0.1519	—
Side Stimulated (S)				1		0.3169	—
R $\times$ S Local Sign				1		15.3002	0.01
Replication Factor				11		1.4335	
Residual				33		1.2270	

In this table the size of the responses measured in cm. on the record are given in full together with the analysis of variance (two factor analysis with replication).

FIG. 1.—Graphic representation of local sign in skin resistance changes (method 1) following painful stimuli. The autonomic responses represented here are the raw data on subject M.A.C. analysed in Table I. The circuit on which each response is recorded is not shown here but the side stimulated is indicated by a symbol, and the size of the response on each side of the body is shown by the position of the symbol in relation to the coordinates.

this case can be attributed to recorded responses too small for measurement and comparison, resulting from inadequate vasodilatation. In the case of our less sophisticated subjects, only three out of 10 experiments gave results unequivocally supporting the hypothesis of local sign.

Previous failures to demonstrate local sign in the sweating and vasomotor responses to painful stimuli, and our own difficulty in demonstrating the effect in hospital patients, seems largely due to the difficulty of controlling the subject's attitude. Our three healthy subjects had had previous experience of similar experimental situations and were, of all our subjects, almost certainly the least disturbed emotionally by the conditions of the investigation. It would seem important for the demonstration of local sign in autonomic responses, that the comparatively simple reflex response to pain should be overlaid or modified as little as possible by any diffuse autonomic activity, appearing as a concomitant of emotion. Thus the subject should not be startled

by or made apprehensive of the stimuli, and the stimuli themselves should not be near the limit of the subject's tolerance, although, of course, they must be sufficiently intense to produce measurable responses even after some habituation.

The nature of the stimulus used in this type of experiment calls for brief comment. During the preliminary investigations, several different types of stimuli were used. No local sign was apparent in the responses to pin-prick or to pinching a small fold of skin. It was noted also that in the case of these stimuli there was a sharp decrease in the intensity of the response with repetition of the stimulus. It is presumed that a response which habituates so readily is largely in the nature of a startle reaction. Local sign did appear to be present, however, when the stimulus was squeezing of a larger volume of tissue including muscle (biceps, lower edge of pectoralis major, and the muscles at the back of the neck). Moreover, responses to this type of stimulus showed comparatively little habituation. The superiority of this type of stimulation may be due simply to the greater area of tissue stimulated as opposed to any qualitative differences associated with the particular receptors involved.

FIG. 2.—Graphic representation of local sign in vasomotor responses recorded plethysmographically (in subject A.E.). The responses to painful stimuli represented here are the raw data of the analysis shown in Table III. The side stimulated is indicated by a symbol and the side of the response on each side of the body is shown by the position of the symbol in relation to the coordinates. Responses to deep inspirations are also shown.

FIG. 3.—Subject A.E. Plethysmographic recording of vasoconstriction in digit 3 of each hand. Response to (1) maximal inspiration, (2) stimulus on the right, (3) stimulus on the left. Recording systems adjusted so that the response to a deep breath gives approximately equal deflections on the two sides. Stimuli for responses (2) and (3): painful pressure on the posterior muscles of the neck at the level of the seventh cervical vertebra. Vasoconstriction is greater on the side stimulated. The arrows indicate increase in volume of the third finger of each hand (L.F.3 and R.F.3).

The results reported here were obtained only with stimuli which were painful. However, it is clear that other sensory modalities were involved (e.g., proprioceptive), and we have no definite evidence that the afferent fibres mediating the reflex were those subserving pain.

Summary

Autonomic responses to painful stimuli in the upper limbs have been studied, using skin resistance and plethysmographic techniques. It has been shown that, when the attitude of the subject can be suitably controlled, it is possible to demonstrate local differences in the autonomic responses to painful stimuli which are anatomically related to the site of stimulation.

Previous failures to detect this effect are discussed.

FIG. 4.—Subject M.A.C. Changes in skin resistance following electrical stimulation of the pulp of digit 5 of each hand. Each shock is marked by a large stimulus artefact. The first two shocks are on the right, and the third and fourth on the left. The fall in skin resistance is greater on the side stimulated. Stimulus, 70 volts in each case, pulse duration 1.0 m/s., frequency 100 c/s., duration 400 m/s. The arrows indicate direction of a rise in skin resistance, and also show the excursion corresponding to a change in resistance of 5,000 ohms.

We wish to record our thanks to Dr. E. A. Carmichael and Mr. O. L. Zangwill for their encouragement and helpful suggestions. We wish also to express our gratitude to the medical staff of the National Hospital for their courtesy in allowing us to examine patients under their care.

Mr. Piercy was supported in this work by a grant from the trustees of the Pinsent-Darwin Studentship in Mental Pathology, University of Cambridge.

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