MECHANISM OF THALAMOCORTICAL AUGMENTATION AND REPETITION

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In another paper two types of cortical activity elicited by stimulation of the sensory path have been described. Evidence was presented that these phenomena, the so-called augmented and repetitive sensory responses, share a single neuronal mechanism, but may, on the other hand, be segregated both from the simple "primary" sensory response and the generalized 8 to 12 per second "spontaneous" bursts (Dempsey and Morison, 1943). The present study was directed toward a more thorough investigation of the properties of the system responsible for the augmented and repeating effects.

METHODS. The methods employed were entirely similar to those employed in the preceding papers and need not be repeated.

RESULTS. Site of repetition and augmentation. Since repetition is not a feature of sensory responses recorded from the lemniscus (Dempsey and Morison, 1943), attention was directed to the thalamus and cortex. Adrian (1941) has demonstrated that the thalamus deprived of its cortex still exhibits repetitive responses. In the present investigation records taken from the thalamus before and after cutting of the internal capsule showed that the repetitive response of the thalamus, though still present after the procedure, was always depressed. In order to facilitate cutting of the capsule in this and other types of experiments, the ventricle was carefully unroofed before any observations were made, so that the cutting of the capsule could be carried out with a minimum of additional operative trauma. Since depression of the thalamic response might still be attributable to some nonspecific effects of the operation, however, the influence of the cortex on the thalamic response was tested in another way. Cortical repetition was enhanced by local application of acetylcholine (Chatfield and Dempsey, 1942). The thalamic repetitive response was enhanced pari passu (fig. 1).

The question still remained as to whether the cortex alone may exhibit repetitive or augmented sensory responses. In order to solve this question, stimulating electrodes were introduced into the capsule and the cortical responses recorded. Division of the capsular fibers caudal to the electrodes abolished both the repetitive and augmented (fig. 2) responses. Even though acetylcholine was applied to the cortex in the hope of compensating for the loss of an asynchronous thalamic bombardment (cf. its facilitating effect in intact animals above), the abolished repetitive response did not return.

The primary response induced by capsular stimulation invariably was smaller and its second and third component declined more rapidly with frequency before section of the thalamic radiations. As the augmenting response developed (fig. 2A), a decline in the primary response occurred. Figure 2B shows the larger
size and greater durability of the primary effect after section of the thalamic radiations.

At this point it may be recognized that capsular stimulation could presumably involve both dromic and antidromic activation of either corticopetal or corticofugal elements. Difficulties arising from antidromic stimulation have been so slight as to justify their complete neglect. Phenomena of short latency (0–1 msec.) and duration (1–2 msec.) did indeed occur both in the cortex and thalamus as a result of capsular stimulation (cf. Dempsey and Morison, 1943), but they had little effect upon the later augmented and repetitive responses. These early effects in the cortex were presumably due to direct activation of the thalamocortical fibers along with an undetermined amount of antidromic firing of corticopetal elements. At all events, it seems unlikely that a very large propor-

Fig. 1. Reinforcement of repetitive response by local application of prostigmine and acetylcholine to the cortex. Upper record, n. ventralis lateralis pars externa; lower record, radial cortical projection, surface bipolar recording. Paper speed, 10 mm. per second.

A. Immediate and repetitive effects in thalamus and cortex after single shock applied to the radial nerve.

B. After local application of prostigmine and acetylcholine to the cortex. The repetitive effect is enhanced in both cortex and thalamus.

C. After decortication by section of the internal capsular fibers. The thalamic repetitive effect, although still present, is greatly depressed.

tion of fibers carrying the augmented response to the cortex are activated directly by the electrodes in the capsule for the augmented response was typically very much larger than any early response to capsular stimulation. Indeed, from certain positions in the capsule virtually no cortical response other than the augmented one was detectable (cf. Dempsey and Morison, 1943).

Further evidence against attributing a significant role to direct activation of thalamocortical neurons is found in the observation that neither augmented nor repetitive responses could be produced in the cortex deprived of its thalamus. On the other hand, augmented and repetitive effects in the thalamus were easily elicited by capsular stimulation whether or not the cortex were present. The latency of the augmented response in the thalamus (2–3 msec.) was such that it preceded by an appropriate interval the corresponding cortical effect (3–5 msec.), an observation which lends cogency to the view that capsular stimulation exerts its effects on the cortex via the thalamus and not vice versa (fig. 3). Other
evidence which serves to establish the view even more satisfactorily may be found in the subsequent experiments.\(^1\)

**Rhythmic responses to high frequency stimulation.** Relatively rapid frequencies applied either to the capsule or an afferent nerve resulted in a marked reduction of both the cortical and thalamic responses, a phenomenon due apparently to the

![Fig. 2](image1)

A. Stimulus to the internal capsule. Primary and augmenting effects are present.

B. Same after section of the internal capsule posterior to the stimulating electrodes. The augmenting effect does not appear. The primary response is larger and does not decline so rapidly as in record A. Time signal, 250 cps.

Fig. 3. Simultaneous augmentation in thalamus and cortex during repetitive stimulation of the internal capsule. Left record, *n. centralis lateralis pars externa*. Right record, radial cortical projection, surface to deep electrodes. Time signals, 100 cps. Note that the latency is shorter in the thalamic response.

Fig. 4. Interaction between capsular and afferent nerve stimulation. Radial cortical projection, surface bipolar electrodes. Paper speed, 40 mm. per second.

A. Effect of 120 per sec. stimulation of radial nerve. Note irregular repetitive discharges.

B. Equilibrated response to 12 per sec. stimulation of an augmentor point in the internal capsule.

C. One hundred twenty per sec. stimulation of radial nerve between arrows. Note increased responses to the capsular stimuli, and that this effect outlasts the period of nerve stimulation.

Combined effects of fractionation and "fatigue." Superimposed upon the equilibrated series in many experiments a series of rhythmic waves of slow (8-12/sec.) frequency appeared both in the thalamus and cortex (figs. 4A and 5).

\(^1\) The analysis here and throughout this study has assumed that the growth of the augmented response is produced by increasing the number of active elements. Owing to the exigencies of space, the somewhat elaborate discussion necessary to justify this procedure is omitted.
Again the effects of both capsular, lemniscal and afferent nerve stimulation were similar, except that the former were easier to obtain and more marked in extent. The rhythmic waves occurred in the thalamus deprived of its cortex, but not in the cortex without the thalamus.

Interaction of afferent and capsular stimulation. It has been shown elsewhere that the simple sensory primary response elicited from afferent nerve stimulation is "blocked" by prior activation of the appropriate portion of n. ventralis lateralis pars externa or of the internal capsule (Dempsey and Morison, 1942). Similar experiments involving the augmented response revealed much more complex interactions. Complete block has never been unequivocally encountered, but various degrees of mutual facilitation or occlusion have been the rule. Facilitation was strikingly illustrated in some experiments by setting up a cortical response by capsular stimulation at a frequency high enough to result in marked equilibration. An added stimulation of an afferent nerve at rates so high that

![Fig. 5. Effect of high frequency stimulation of the internal capsule. Upper record, n. ventralis lateralis pars externa. Lower record, radial cortical projection, surface to deep recording. Paper speed, 15 mm. per sec. Stimulus frequency, 250 per sec. Note the development of oscillations in the records.](http://ajplegacy.physiology.org/)

Figure 5: Effect of high frequency stimulation of the internal capsule. Upper record, n. ventralis lateralis pars externa. Lower record, radial cortical projection, surface to deep recording. Paper speed, 15 mm. per sec. Stimulus frequency, 250 per sec. Note the development of oscillations in the records.

discrete responses to the individual volleys were undetectable yielded marked facilitation of the cortical response at the capsular frequency (fig. 4).

At slower frequencies the effects depended upon several factors including especially the time relations or phase angle between the two types of volleys. Less than linear or greater than linear addition of the effects were encountered in different conditions suggesting that the pool of thalamocortical neurons could be shared by the corticofugal and lemniscus fibers. Under conditions of marked equilibration or slight augmentation a large subliminal fringe was available to the other stimulus, and facilitation would result. With highly augmented or slightly equilibrated responses "occlusion" was revealed (i.e., less than linear addition).

Time course of augmentation. One of the most interesting features of the augmentation effect was its time course. Figure 6 shows the effect of a second stimulus at varying intervals after the first. It is clear that augmentation was minimal shortly after the first stimulus and rose, first rapidly then more slowly,
to reach a maximum at 100 to 120 msec. immediately before the appearance of the first repetitive wave. All augmentation was abolished during the repetitive wave, but reappeared immediately afterwards to rise to another, frequently higher, maximum before the next repetitive wave and so on (fig. 7). The presence of the repetitive response made it difficult to determine the total duration of the augmentation produced by the first shock because the repetitive waves might have contributed to or subtracted from it.

Fig. 6. Timing of the repetitive response by the second of two stimuli. Radial cortical projection, surface to deep electrodes. Paper speed, 20 mm. per second.
A. Immediate and repetitive effects of a single shock applied to the internal capsule.
B. Response to two shocks separated by an interval of 100 msec.

The first repetitive potential occurs at a constant time after the second stimulus, regardless of its phase relation to the first.

Fig. 7. Growth of augmentation during the interval between repetitive potentials. Radial cortical projection, surface bipolar electrodes. Paper speed, 20 mm. per second.
A. Immediate and repetitive responses to a single shock applied to the ventrolateral thalamic nucleus.
B. Block of augmentation when a second shock falls during the first repetitive potential.
C, D, E and F. Increase in augmentation as second shock falls later and later after the preceding repetitive potential.
G. Block of augmentation when second shock falls upon the second repetitive potential. Compare with B.
H. Augmentation when second shock falls after the second repetitive response. Compare with F.

Note that the repetitive effects are retimed by the second shock. The interval between the second shock and the next repetitive potential is constant, regardless of the phase at which the stimulus falls.

A somewhat similar waxing and waning of the responses of the optic cortex to the second of two stimuli has been discussed by Bartley (1936, fig. 3). In spite of the differences in cortical area, species, anesthesia and stimulating methods employed, the similarities between the two results suggest that a similar mechanism may be fundamental to both situations. It may be suggested that the second or slow response of Bartley and Bishop (1933) is analogous to the augmenting response identified here. As Bartley (1941) points out, the slow response is more intimately connected than is the earlier diphasic wave with spontaneous cortical activity, a point consistent with the augmenting effect of
Dempsey and Morison (1943, p. 291). On the other hand, it seems regularly to occur in the optic area in response to a single shock, whereas in the somatic sensory area it was more typically the result of repeated stimulation. This and other differences have led to rather different interpretations in the two cases, but it seems probable that as more information accumulates a single, general explanation may be possible.

In preparations without a repetitive response or in those in which it had been fatigued, augmentation as tested by two shocks usually recorded a maximum at 100 to 300 msec. and then slowly declined after the next second or two to normal, although in this condition the maximal possible effect was somewhat less than in the unfatigued preparation. Other facts which suggest that the early rising phase of augmentation is relatively uninfluenced by intercurrent discharges were brought out by the use of repetitive stimulation. At frequencies higher than that of the repetitive rhythm consecutive augmentation of the first several shocks was usually seen. Over a range of from 8 to 20 per second the curve relating height of the individual responses to time was relatively constant (cf. fig. 8) at least in its early phases. In other words, neither the slope of the rising phase nor the maximum height of augmentation was increased by increasing the number of stimuli per unit time. At optimal frequencies the total duration was, however, longer than that produced by a single shock. As frequency increased, however, the curves of augmentation began to decline earlier, suggesting "fatigue" and the appearance of progressive fractionation. At frequencies above about 30 per second complexities appeared in the early part of the curve, suggesting that refractoriness and fractionation were the dominant factors.

**Timing of the repetitive responses.** Perhaps the most interesting feature of the repetitive response is the regularity of its timing. In the course of a single experiment the frequency of the beats remained surprisingly constant even when various procedures had greatly altered the height of each individual beat or the duration of the train.

The application of acetylcholine to the cortex greatly enhanced the responses both in individual height and in total duration not only in the cortex but also in the thalamus. The frequency of the discharge, however, was essentially unchanged. Conversely, repeated production of the repetitive response at intervals of about 3 to 5 sec. greatly reduced the duration of the discharge and the height of the constituent waves without influencing their frequency. Indeed as each individual discharge petered out, the waves declined in size but changes in the interval between them were insignificant. Furthermore, although the repetitive response was always greater when produced by stimulation of the internal capsule than as a result of afferent nerve activation, the frequency in both cases was similar.

The following summary statement appears to be justified. The mechanism responsible for the repetitive response is timed by some subsidiary mechanism relatively inaccessible to the excitatory state upon which duration of after discharge or the height of the individual waves depends.
Another extraordinary feature of the mechanism was revealed when two single shocks were given at varying intervals. The experiment illustrated in figure 6 in which the stimulating electrodes were in n. ventralis lateralis pars externa was typical; similar results have been obtained by the stimulation of afferent nerve or capsule. The first stimulus set up the repetitive train. No matter when the second shock was given and irrespective of how small the response elicited, the interval between it and the next succeeding repetitive wave was constant, i.e., the timing of the remainder of the train was set by the second stimulus. The total duration of the train as measured from the first stimulus, however, was but slightly if at all increased by the addition of the second shock. In other words, a second shock could alter the timing of the series but did not contribute significantly to the duration of the excitatory state.

As the stimulus interval was decreased below 20 msec. the second shock became less efficient at taking over the timing, and irregularities appeared in the repetitive waves suggesting that the pool of thalamic neurons was split between the two stimuli, but beyond this limit the rule outlined above was strictly followed. Similar results were obtained if three or even four shocks were used; the last one always set the remainder of the rhythm. In the multiple shock experiment the train was usually somewhat shortened or even completely abolished.

An exception to the statement made above that a second shock did not contribute to the excitatory state responsible for repetition should be mentioned. A weak stimulus to the capsule would sometimes be followed by a repetitive response smaller and shorter than "maximal." Such responses were increased by the addition of a second shock at some reasonable later interval. The gradations between submaximal and maximal responses were not smooth, but tended to occur in steps. This fact which suggests that the elements controlling repetition are relatively few in number was reinforced by other observations. Many of the repetitive discharges tended to show constant irregularities in the constituent waves which suggested that they were made up of two or more units firing slightly out of phase. As the discharge disappeared, the height of the original waves tended to decline by steps and not by a continuous decline (cf. Dempsey and Morison, 1943, fig. 7A). The splitting of the pool between two stimuli arriving a short time apart mentioned in the preceding paragraph also reinforces the suggestion that the repetitive mechanism is made up of relatively few "all or none" units.

DISCUSSION. The experiments described in this and accompanying paper suggest that a system in addition to the simple lemniscus to internal capsule relay is present in the ventrolateral thalamus. It would appear that extensive afferents to this thalamic system are derived from the cerebral cortex and the medial lemniscus. Moreover, these afferents apparently do not end upon the ultimate thalamocortical neurons, but exert their effects through interneurons. Finally, this system of thalamic afferents, interneurons and efferent cells has certain properties, typified by a slowly rising excitatory state and by prolonged rhythmic activity, which are pertinent to a discussion of the possible anatomical and physiological organizations underlying the various phenomena.
In order to summarize the data and point up its implications, it may be helpful to consider a diagram (fig. 9). Clearly in such a complex system data can only be cited very tentatively as favoring one or another of the contested views in regard to the intimate nature of synaptic transmission, facilitation, e. e. s., c. i. s., or after discharge.

As Lorente de Nó (1939) has shown, many of the properties attributed by others to c. e. s. and "detonator" activity may be reduced to temporal and spatial patterns of activity in interneurons. Although the phenomena presented here can apparently be explained in these terms, such a diagram becomes very complex, and, as Lorente de No has pointed out, loses therefore much of its didactic value. A rigidly complete analysis in those terms has therefore not been attempted.

The key to the present system lies in the fact that the timing mechanism of the rhythm of the repetitive response bears a highly specialized relationship to the afferent fibers (either capsular or lemniscal) on the one hand, and to the
efferent or thalamocortical fibers on the other. The principal point of interest is that the entire system may be retimed by stimuli which may activate relatively few of the thalamocortical fibers (fig. 6). It seems desirable, therefore, to postulate at least one group of homologous interneurons \( I_n \) between afferents and efferents, which may be thought of as completely accessible to successive volleys arriving at intervals so short as to be within the unresponsive period of the thalamocortical pool \( T_n \). This group may be taken as symbolic of a much more complex interneuronal system, primarily concerned with control of the rhythm.

The fact that the rhythmic waves of the repetitive response could be resolved in favorable instances into a relatively small group of units which tended to appear or disappear in a relatively “all-or-none” manner has suggested the representation of the interneuronal system as composed of a few large cells receiving many corticothalamic and lemniscus afferents and relaying to a large number of thalamocortical efferents. The smoothly graded nature of the augmented response may then be attributed largely to recruitment in the large pool of the latter type, although facilitation at both \( I_n \) and \( T_n \) would of course be important with weak capsular stimuli or in the case of activation of afferent nerves (cf. p. 303). For conveniently analyzing recruitment at \( T_n \), stimuli maximal for \( I_n \) are therefore desirable, and the data detailed in figures 6 and 8 have been obtained with intensities such that temporal effects at \( I_n \) may be neglected. Started by a single volley, augmentation slowly rose for 100 to 300 msec. and then slowly disappeared. The rising phase and total amount of augmentation have further been shown to be relatively uninfluenced by additional volleys, although the duration of the effect may be prolonged by repetitive stimulation (fig. 8).

The excitatory state responsible for augmentation has, therefore, been represented as a self-re-exciting chain which is started by a single shock and continues to run for 2 to 3 seconds with a rate uninfluenced by successive volleys within that interval. Activity in this system may be thought of as progressively lowering the threshold of \( T_n \) so that more and more of them become available to the second volley arriving over \( I_n \). A strict interpretation of the concept of Lorente de Nó would apparently rule out such an accumulation and a more complicated system of delays would be necessary. On the other hand, the shape of the time curve and the lack of evidence for actual firing of \( T_n \) by the facilitating process alone suggest the c. e. s. postulated by Eccles (1936).

It is now possible to consider the characteristics of pool \( I_n \) which is made responsible for the rhythmic properties of the system. In addition to relaying impulses to pool \( T_n \) as outlined above, pool \( I_n \) is postulated as firing rhythmically under proper conditions. At present the whole problem of rhythmicity can only be discussed in vague terms, but the phenomena considered here are most readily understood if one assumes that the rhythmic firing of \( I_n \) is due to the interaction of an extrinsic excitatory effect represented by a collateral from the reverberating side chain already postulated to account for facilitation at \( T_n \), and a non-summatable recurring refractoriness or subnormality of constant
duration. The arrangements necessary for rhythmic activity are clearly more specialized and labile, however, than are those of the simple relay activity. In general more impulses must reach I_n to elicit the repetitive response and it is distinctly more affected by fatigue. No matter what the mechanism of rhythmicity, the accurate retiming of the system by a second shock raises an interesting point (figs. 6 and 7, p. 301). All the interneurons controlling T_n are affected by the interpolated shock whether or not T_n are fired thereby since no wave appears at the usual interval after the first stimulus. On the other hand, the entire pool fires repetitively at the usual interval as measured from the interpolated stimulus. The constancy of the interval between interpolated discharge and first repetitive wave differentiates the phenomenon from the retiming of rhythmic motor neuron discharge described by Eccles and Hoff (1931). In their instance the interval succeeding the interpolated discharge varied inversely with the length of the curtailed cycle, a situation which appears easily explicable on the basis of summation of subnormality or an interaction of N and P waves (Eccles, 1936). The present case, though superficially simpler, is actually more difficult to explain, and necessitates the non-summatability of the subnormal state postulated above, which just cancels the accumulated facilitation.

The fact that repetitive responses are more difficult to elicit by afferent nerve or lemniscal stimulation than from the capsule has led to the supposition that the lemniscus fibers relaying impulses from a particular afferent nerve are sparsely represented on the I_n cells. On the other hand, when properly facilitated (i.e., by application of acetylcholine and prostigmine to the cortex) a very large part of I_n becomes available. The inference is that any portion of the lemniscus though poorly represented on any particular part of I_n is distributed widely through the pool. Cross linkages between the interneurons I_n could also contribute to the spread of effects and are rendered quite probable by the synchronization of the waves in the repetitive response and the presumably similar rhythmic waves produced by high frequency stimulation. A mechanism for avalanche conduction and the more elaborate interpretations discussed by Marshall and Talbot (1941) is provided by either sort of connection. Clearly also an opportunity for the various forms of interaction between lemniscal and capsular stimulation outlined on page 300 is offered by the overlap of these two types of afferents on the I_n cells.

It is interesting to note that although interactions between capsular and afferent nerve stimulation reveal various states of facilitation as well as occlusion of the augmented response, the true primary (elements 1, 2, 3 of Dempsey and Morison, 1943) exhibits occlusion only (Dempsey and Morison, 1942). This and other evidence such as the independence of the primary response from spontaneous activity in any recognized corticothalamic circuits suggest that corticothalamic fibers are poorly represented on the neurons responsible for the relaying of the simple primary response.

Presumably the repetitive waves recorded in response to high frequency stimulation of either capsule or afferent nerve (p. 299) is due to a piling up of excitation at these interneurons. At these high rates responses of the I_n cells to the indi-
vidual volleys seem to be prevented probably by the postulated subnormality which allows only the much slower rhythmic waves to appear in response to an accumulated excitatory state.

In conclusion it may be worth while to turn for a moment to the problem of corticothalamic interaction. From the evidence presented (p. 297) it is clear that the principal mechanism underlying augmentation and repetitiveness lies in the thalamus. The fact that the rhythm of the repetitive response of the thalamus is unaltered by decortication (p. 298) emphasizes that the timing is localized in the thalamus and is not a property of the circuit as a whole. On the other hand, the cortex contributes importantly to the intensity of the response and to its duration, presumably by facilitation fed back to I_n and perhaps to T_n. Thus, though the circuit may not be strictly "reverberating," it may properly be referred to as mutually reinforcing. The relation of this system to an element of the spontaneous electrocorticogram and the fundamental experiments of Dusser de Barenne and McCulloch is discussed elsewhere (Dempsey and Morrison, 1943).

CONCLUSIONS

Investigation of the mechanism underlying the production of repetitive and augmenting sensory responses has revealed the following:

Decortication reduced but did not abolish the repetitive response recorded from the thalamus. Enhancement of the cortical response by local application of drugs increased the thalamic effect (fig. 1). Removal of the thalamus abolished the repetitive and augmented responses evoked by capsular stimulation. These and other experiments (cf. figs. 2, 3, 4, 5 and p. 300) show that extensive thalamic afferents are derived from the internal capsule as well as the medial lemniscus. It is concluded that in this system there is a mutual reinforcement of cortical and thalamic effects, but that the thalamus alone is necessary for the occurrence of repetitiveness and augmentation.

Augmentation induced by a conditioning shock, and revealed by a second test shock, extends over several hundred milliseconds (p. 301; figs. 6, 7 and 8). Furthermore, once the process is started, it proceeds at a rate which is not influenced by subsequent stimulation (fig. 8).

Repetitive sensory potentials induced by the conditioning shock destroy augmentation. Following the repetitive effect, the process of augmentation again builds up to a maximum just before the next repetitive response (fig. 7).

The timing of the repetitive rhythm bears a highly specialized relationship to the afferent stimuli. The rhythm is timed by the last stimulus, whether it falls during the repetitive train (fig. 7) or ahead of the first repetitive potential (fig. 6). Likewise, the rhythm is set by the last shock both when the number of thalamocortical elements fired is small (fig. 6 E, F and G) and large (fig. 6 B, C and D).

The data presented above imply certain properties of the thalamocortical system which are summarized (p. 303) and discussed with reference to a circuit diagram (fig. 9) whose elements are to be regarded as symbolizing such physiological phenomena as the excitatory state, detonator action and repetitiveness.
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