ASSOCIATION CORTEX RESPONSES DURING LOCALIZED COOLING OF NUCLEUS VENTRALIS POSTERO-LATERALIS

by

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A THESIS

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Introduction

Amassian (1954) was the first to describe cortical association evoked responses in the cat. Since that time, there has continued to be considerable interest in the characteristics of the response itself, the nature of the pathways contributing to activity in the association areas, and the similarities and differences which these types of responses exhibit in comparison with primary evoked activity. In general, sensory evoked activity recorded at the level of the cerebral cortex can be divided into two major types: primary and nonprimary. Primary responses can be recorded from the primary sensory receiving areas for the three major modalities (somatosensory, auditory, and visual) and are characterized by an initial short-latency phase followed by a more variable pattern of activity of longer duration.

Nonprimary responses (NPRs) in the cat have been subdivided into three types by Buser and Bignall (1967). Type I NPRs bear a close resemblance to primary responses, with only a slightly longer latency than the primary responses. An example of the Type I NPR would be the short latency response to photic stimulation in the lateral border of the suprasylvian gyrus (Area V_{ss}, according to Thompson, Johnson, & Hoopes, 1963). Similar to the primary responses, Type I NPRs in a given area can only be elicited by a single modality. Thus, V_{ss} is unresponsive to peripheral auditory or somatic stimulation (Thompson, Johnson, & Hoopes, 1963).

Type II NPRs, according to Buser and Bignall (1967), consist of a monophasic positive wave, with a latency considerably longer than that of

the corresponding wave of the primary response. In contrast to the relatively robust primary response and Type I NPR, the Type II NPR is depressed by barbiturates and enhanced by chloralose. Type II NPRs have been found in four major foci on the cerebral cortex (in cats): anterior marginal gyrus (termed "ALA" by Thompson, Johnson, & Hoopes [1963] who referred to the marginal gyrus as the lateral gyrus), anterior middle suprasylvian (AMSA), and posterior middle suprasylvian (PMSA) gyri and the pericruciate area (PCA). These areas are polysensory in nature with somatic, auditory, and visual Type II NPRs all recordable in a given locus. This finding has been well documented by various workers including Buser and Bignall (1967), Albe-Fessard and Besson (1973), Thompson, Johnson, and Hoopes (1963), and Thompson, Smith, and Bliss (1963). In the cat, these four cortical areas constitute what is referred to as the association cortex. Unless otherwise indicated, reference to "association" responses in this paper refer to Type II NPRs. The vast majority of the literature dealing with the association cortex has used the cat as the experimental preparation.

Buser and Bignall (1967) defined the Type III NPR as a response of variable amplitude and waveform and having very long latency. Type III NPRs can be recorded over much of the cortex (in cats). Relatively little is known about Type III NPRs.

Thompson, Johnson, and Hoopes (1963) have described further, using the cat, the characteristics of cortical association evoked responses to auditory, somatic, and visual stimulation. They reported that the association response waveform was the same in all cortical association

areas to all modalities of stimulation. In addition, Thompson, Smith, and Bliss (1963), also working with the cat, found that successive stimulation by any two modalities resulted in periods of unresponsiveness for the second of the two association responses, and this result was identical to the pattern of interaction seen when stimulating twice, using the same modality. Further, they found almost perfect correlations of response amplitude between any two association areas during repeated stimulation using any modality. Based on these findings, Thompson, Johnson, and Hoopes (1963) proposed that stimulation of the auditory, somatic or visual pathways activated a common central association system which projected in an undifferentiated and equivalent manner to the four cortical association areas.

Goldring, Sheptak, and Karahashi (1967) questioned whether the association response in the cat observed under chloralose anesthesia was locally generated in the cortex, or was the result of volume conduction from some more distant area. They studied the click-elicited, averaged evoked response in ALA and PMSA in chronically prepared cats. They found that click-elicited association responses, present when the animal was under chloralose anesthesia, disappeared when the animal was awake and unrestrained.

Thompson et al. (1969) questioned Goldring et al.'s (1967) findings on several grounds. First, it had been previously shown by Thompson and Shaw (1965) that the amplitude of the association evoked response in the awake cat was inversely proportional to the degree of behavioral arousal. No mention was made in the Goldring et al. (1967) article of the behav-

ioral state of the animal when they failed to obtain click-elicited association responses.

Thompson et al. (1969) compared averaged evoked and unit responses to somatic, auditory, and visual stimuli in PMSA in the cat. They hypothesized that a close correspondence between the temporal pattern of evoked cellular discharge and the gross evoked response indicated local generation (i.e., within PMSA) of the gross evoked response. Fox and O'Brien (1965) had previously demonstrated this correspondence in the primary visual system. Comparing the averaged evoked potential and the unit poststimulus histogram, Thompson et al. (1969) found that the periods of maximum probability of unit discharge tended to occur at, or just after, the peaks of the negative components of the evoked responses. Thompson et al. (1969) interpreted these data as indicating local generation (i.e. within PMSA) of the gross evoked association response.

Bental and Bihari (1963) studied single unit activity in the middle suprasylvian association area in response to auditory and visual stimuli in the cat. They found a high degree of convergence on single cells of input from auditory and visual stimuli. They found, in addition, that although visual stimulation was more effective than auditory stimulation in eliciting responses, when responses occurred to both types of stimuli the temporal patterns were similar. The finding of greater effectiveness on the part of visual stimuli tends to weaken the Thompson hypothesis concerning undifferentiated projection to the association areas. Dubner and Rutledge (1964) also studied single unit activity in AMSA in the cat. They confirmed and extended the results of Bental and

Bihari (1963) by finding a tendency for greater responsiveness to visual input than to auditory or somatic stimulation.

Schneider and Davis (1974) studied evoked potential responses in the anterior and posterior suprasylvian association areas in the cat. In particular, they examined interaction effects by presenting pairs of stimuli at varying interstimulus intervals (ISIs) and measuring the amplitude of the response to the second stimulus. They found that single modality stimulus pairs (e.g., visual-visual) yielded recovery curves (plotted as a function of ISI). However, if two stimuli from different modalities were presented (e.g., auditory-visual), then these recovery curves were different from those generated using single modality pairs. In general, Schneider and Davis (1974) found that mixed modality pairs resulted in greater recovery in amplitude with a shorter ISI than single modality pairing. These data conflicts directly with the interaction data reported by Thompson, Smith, and Bliss (1963) who found similar interaction effects for single modality and mixed modality pairs of stimuli.

Robertson et al. (1975) studied single unit activity in PMSA in response to auditory, visual, and somatic stimulation in the cat. This study examined some variables not controlled for in experiments cited previously. Specifically, differences in the anesthetized versus the awake but paralyzed animal were examined. In addition, the rate of presentation of stimuli was also found to be an important variable. Robertson et al. (1975) found that 82% of all neurons investigated responded to all three modalities of stimulation, but there were differences in the neurons in terms of probability of response to different stim-

ulus modalities. They found that in the chloralose anesthetized animal there was a greater tendency toward equipotency among the polysensory neurons than in the unanesthetized preparation. This was attributed to the lowered spontaneous discharge rate of single neurons observed in the chloralose anesthetized animal.

Robertson et al. (1975) found that neurons which were classified as unresponsive to a particular modality at a given stimulus presentation rate (ISI of 2 sec) exhibited much greater responsiveness at a longer ISI (4 sec). This finding is of particular importance in that previous studies which found a tendency for differential modality specific responsivity in association neurons used ISIs of less than optimal values (Dubner & Rutledge, 1964 - ISI of 2 sec; Bental & Bihari, 1963 - ISI of .2 sec).

Narikshvili, Timchenko, and Khadortseva (1967) examined the hypothesis of the equivalence of association areas in the cat. They systematically analyzed changes in gross evoked association responses following manipulation of both the interstimulus interval and the stimulus intensity. They found evidence supporting the hypothesis that the nonspecific thalamic system is responsible for the relay of activity to association cortex. However, in contrast to the findings of Thompson, Johnson, and Hoopes (1963) that there is stimulus equivalence in all association areas, Narikshvili et al. (1967) found stimulus modality differences among ALA, AMSA, and PMSA. Specifically, they found that for visual stimuli, the most responsive association area was ALA, while for auditory stimuli, the most responsive area was PMSA. For somatic stimuli,

both AMSA and PMSA were more responsive than ALA. This finding apparently conflicts with the results of Bental and Bihari (1963) and Dubner and Rutledge (1964), who found that AMSA was maximally responsive to visual stimulation. However, since Narikshvili et al. (1967) made their evaluation based on the most responsive cortical area and Dubner and Rutledge (1964) and Bental and Bihari (1963) made their evaluation based on the stimulus modality which resulted in the greatest activity in one particular association area, a direct comparison of the results is not possible.

Thalamic Control of Association Areas

There has been a great deal of interest in defining the subcortical systems responsible for activity in the association cortex. Thompson, Johnson, and Hoopes (1963) hypothesized that the nonspecific thalamic nuclei were responsible for projection of activity to association areas. Bignall (1967b) examined the effect of ablation of the mesencephalic reticular formation, nucleus centrum medianum, and midline nuclei on the association responses in PCA, ALA, and PMSA in the cat. In general, they found that, while immediately after bilateral ablation of these areas the association responses were abolished, there was considerable recovery of responses over time (1 to 5 hrs post-surgery). They felt that these data indicated a modulatory role for these nuclei, rather than a role as relay centers for the association responses.

O'Brien and Rosenblum (1975) studied the effect of localized cooling of the centromedian area of the thalamus on the shape of evoked potentials and the pattern of single unit activity in PCA in the cat.

Cooling of centromedian produced different changes in the shape of the evoked potential waveform for somatic and visual stimuli. This indicated a differential and not a nonspecific, projection system from the midline thalamus to the association areas.

O'Brien and Rosenblum (1974) also working with the cat, examined the effect of cryogenic blockade of the centromedian area of the thalamus on unit and evoked activity in PCA, in response to somatic and visual stimulation. They found that a cooling block of centromedian produced decreases both in evoked potential activity and in excitatory and inhibitory components of single cell responses. For somatic stimuli, the major effect of cooling was from 100 to 200 msec poststimulus, but the cooling effect for visual stimulation was not restricted to a particular poststimulus period.

Skinner and Lindsley (1971) studied the effect of a reversible cryogenic blockade of the inferior thalamic peduncle on visual and auditory evoked potentials in primary auditory cortex, primary visual cortex, PCA, and PMSA in the cat. They found that evoked potentials, in all cortical areas recorded from, in response to stimulation of the optic radiations, optic tracts, or cochlear nucleus, were enhanced in amplitude during the cryogenic blockade. They felt that these data indicated that the thalamocortical system mediated by the inferior thalamic peduncle maintains, in the normal state, tonic suppression of evoked potentials at the cortical level.

Chalupa, Anchel, and Lindsley (1973) studied the effect of cryogenic blockade of the pulvinar upon visually evoked responses in visual

cortex and PMSA in the cat. They found that cooling of the pulvinar reduced the peak-to-peak amplitude of both the early and late components of the visual evoked response in PMSA and only the late components in the visual cortex. They then studied the effect of cooling the suprasylvian gyrus on the evoked response in visual cortex. Using this procedure, they found that during cooling there was a reduction in amplitude of the late components of the evoked response (in general, "early" components referred to peaks up to 50 msec poststimulus, while "late" components referred to peaks 200 msec poststimulus and beyond). They interpreted their findings as suggesting that there is visual input from the pulvinar to PMSA. Further, input from PMSA to visual cortex appeared to account for a substantial amount of the "late" activity in visual cortex.

Huang and Lindsley (1973) mapped evoked responses to auditory, visual, and somatic stimuli in the pulvinar in the cat. They suggested that the pulvinar was a polysensory convergence area, similar to the centromedian nucleus.

Thus far, evidence has been presented concerning the role of nonspecific thalamic nuclei (centromedian) and the pulvinar in the origin of cortical association responses. The contribution of specific sensory relay nuclei to cortical association responses has also been studied. Vastola (1961) presented evidence for a direct projection from the lateral geniculate, contributing to the Type I visual NPR recorded in Area V_{ss}.

Bignall (1967a) studied photically evoked activity in areas AMSA, ALA, and PCA in the cat. He found evidence suggesting that a major

source of optic input to the association areas was a system of small fibers which paralleled the system of primary visual afferents to the lateral geniculate but projected separately from the lateral geniculate to the association areas.

Poliakova (1971) studied the contribution of the nucleus ventralis postero-lateralis (VPL), the primary somatosensory relay nucleus, to the early components of the association response in ALA and AMSA. Poliakova found that topical application of KCL to the primary somatosensory area (S1), which suppressed the primary response, did not affect the early components of the association response. This would indicate that these early components were not due to cortico-cortical connections. Local application of KCL in ALA and AMSA resulted in the disappearance of the early components of the association response while the primary response was relatively unaffected. Poliakova took this as further evidence that these early components were locally generated in the association cortex.

Following electrolytic lesioning of VPL, Poliakova (1971) found that both the early components of the response recorded in ALA and AMSA, and the primary response, recorded in S1, were eliminated. Based on these data, Poliakova proposed that activity in the association cortex was due primarily to two types of input. Early components of the association response were due to relay through the specific sensory relay nuclei and later components originated in the nonspecific thalamic system.

Cortico-Cortical Influences on Association Areas

Imbert, Bignall, and Buser (1966) studied the interconnections of various cortical areas in the cat. In order to eliminate the possibility of cortico-thalamo-cortical pathways confounding their analysis, they first ablated the thalamus and certain other subcortical structures. They then analyzed cortico-cortical interconnections by electrically stimulating the cortex in one area and mapping the evoked responses in selected areas across the rest of the cortex. Stimulation of the primary visual area produced responses throughout much of the cortex, with stimulation of the primary auditory and somatic areas having somewhat less of an effect.

In contrast, using Nauta silver degeneration techniques, Kawamura (1973) demonstrated specific interconnections among ALA, PCA, AMSA, and PMSA. Kawamura also found strong interconnections between primary visual cortex and association areas, as well as somewhat less strong connections between S1 and association areas. Cortical interconnections between the primary auditory area and the association areas were much less prominent than the primary visual- or somatosensory-association area interconnections.

Bignall, Singer, and Herman (1967) studied the interaction of cortical and peripheral inputs to association areas in PCA, ALA, and AMSA. Using electrical stimulation of primary visual, auditory, or somatosensory cortex, and peripheral light flash, paw shock, or click stimulation, they found a complex pattern of interactions when cortical stimulation was paired at varying intervals with a given peripheral stimulus. Thus,

while other workers have shown that the presence of the primary sensory areas is not necessary for the occurrence of association responses (e.g., Poliakova, 1971), the work of Bignall, Singer, and Herman (1967) indicates that the primary areas might function as modulators of activity in the association areas.

The data presented thus far indicate that the origin of the association response is not quite as simple as Thompson, Johnson, and Hoopes (1963) originally suggested. While there is strong evidence that the nonspecific thalamic nuclei contribute to certain components of the association response, cortical input from primary sensory areas also appears to affect the form of the association response. In addition, there is some evidence that sensory relay nuclei might contribute to early components of the association response (e.g., Poliakova, 1971).

Role of Vb Complex

Compared to studies investigating the role of the nonspecific thalamic system, there has been, in general, less work dealing with the contribution of the primary sensory relay nuclei to the generation of the association response. There has been a fair amount of work investigating the role of the lateral geniculate, but the role of the other primary relay nuclei (medial geniculate and ventrobasal complex [Vb]) has not been as carefully examined. It is therefore of interest to examine in more detail the anatomy and physiology of the ventrobasal complex in order to understand the means by which the somatosensory association response could be affected by activity in Vb, the primary somatosensory relay nuclei.

According to Crosby, Humphrey, and Lauer (1962), the Vb complex occupies the caudal half of the diencephalon, lying ventral and ventrolateral to the dorsomedial nucleus and the internal medullary lamina, ventral and ventromedial to the lateral nuclear group, dorsal to the zona incerta and internal to the external medullary lamina and the reticular nucleus. The Vb complex is commonly divided into a ventral posterolateral (VPL) portion and a ventral postero-medial (VPM) portion.

There is general agreement that the cells of the Vb complex respond to stimulation of somatosensory receptors. Welker (1973) has reviewed studies which indicate that receptors innervating epidermis, dermis, joint capsule, deep connective tissue of tendons and muscles, and intraoral mucosa are all capable of activating Vb neurons. Many of the major ascending somatic spinal pathways terminate in the Vb complex. The lemniscal system (in particular, the dorsal column system) and the spino-cervical tract both have terminations in Vb via the medial lemniscus (Crosby, Humphrey, & Lauer, 1962). At least part of the spinothalamic tract also synapses in Vb (Crosby, Humphrey, & Lauer, 1962). Cohen (1955), working with cats, reported that early activity in the Vb complex was apparently initiated by lemniscal input, containing both crossed and uncrossed components.

Albe-Fessard and Fessard (1963), in reviewing a series of studies conducted in their laboratory, concluded that input to the Vb complex and the nonspecific thalamic nuclei were due to separate spinal column patnways. Thus, they found that section of the dorsal columns did not modify the response of the centromedian-parafascicular complex,

but did considerably reduce the response in Vb. They concluded that nonspecific thalamic nuclei received somatic input primarily from the anterolateral pathways (spinothalamic). Thus, the nonspecific and primary sensory systems appear to be differentiated at the level of the spinal cord.

The gracile component of the medial lemniscus terminates in the dorsolateral portion of VPL, while the cuneate component synapses more ventromedially (Crosby, Humphrey, & Lauer, 1962). Crosby, Humphrey, and Lauer also reviewed studies which suggested that painful, thermal, and tactile stimulation of facial areas projected contralaterally over the ventral secondary ascending tract of the fifth cranial nerve to VPM, while finer tactile and proprioceptive impulses from the face projected bilaterally via the dorsal secondary ascending tract of the fifth cranial nerve. Input from taste receptors enter the CNS through the seventh, ninth, and tenth cranial nerves and eventually ascend with the fibers of the lemniscal system to terminate in the most medial portions of VPM (Crosby, Humphrey, & Lauer, 1962).

Somatotopic organization. In their review, Crosby, Humphrey, and Lauer (1962) noted a pattern of projection to the Vb complex in which afferent systems from the lower (or hind) extremities terminated more dorsolaterally, while those from the upper extremities synapsed in an intermediate position, and those from the face and mouth ended more ventromedially within the Vb complex.

The Vb complex is even more highly organized, in terms of thalamic representation of body surface, than the preceding statement indicates.

Mountcastle and Henneman (1949) systematically mapped the Vb complex of the cat for evoked responses to peripheral light mechanical stimulation. They found that excitation of tactile receptors produced a localized potential change in this region of the thalamus. They reported that the contralateral surface of the body was represented within the Vb complex as a figure of the animal, with tail pointed anterolaterally, face and mouth medially, the extremities inferiorly. In other words, this area of the thalamus exhibited the principle of somatotopic organization, with receptors in adjacent peripheral body regions projecting to adjacent regions in the thalamus (Welker, 1973).

This finding has not, however, been universally accepted. Thus, Cohen and Grundfest (1954) studied responses in the thalamus of the cat evoked by electrical stimulation of afferent pathways and mechanical stimulation of various skin areas. They found relatively little evidence for localization of responses within the Vb complex. They based this conclusion on data which indicated that there were ipsilateral, as well as contralateral, inputs to the Vb nucleus. In addition, they found that at a given recording point within the thalamus, responses were observed as a consequence of activation by several different afferent nerves or tactile stimulation of different skin areas. They felt that the reason for the difference in findings between their study and Mountcastle and Henneman's (1949) was due to different criteria for the interpretation of what constituted a thalamic response to peripheral excitation.

Gage and Gordon (1954) studied single unit activity in the Vb area

of both cats and monkeys. They confirmed, in general, the findings of Mountcastle and Henneman (1949) concerning the contralateral representation of tactile sense, but they also found that a substantial anatomical overlap occurred at the thalamic level between regions for face, forelimb, and hindlimb in both cat and monkey. Gage and Gordon (1954) made a detailed study of the hindlimb representation in the Vb complex of the cat using stimulation of the saphenous nerve as well as cutaneous stimulation. They found a substantial ipsilateral representation of the hindlimb in an area of the thalamus where there was also contralateral hindlimb representation. Thus, they partially confirmed some of Cohen and Grundfest's (1954) findings.

Harris (1970) studied responses to both natural and electrical stimulation of peripheral cutaneous structures for a sample of forepaw responsive neurons in the VPL of the cat. He found evidence indicating that VPL was organized (in addition to the principle of somatotopy) according to stimulus sensitivity (e.g., hair vs touch cells) and receptive field size. Thus, it would appear that the Vb complex is highly organized in terms of representation of peripheral somatic input. Welker (1973), in hypothesizing about the possible functional significance of this organization, suggested that somatotopy was the neural substrate preserving information about the absolute and relative position of peripheral somatic sensory stimuli. He suggested that this organization played an important role in the development of discriminative processes.

Efferent projections. Known efferent projections from the Vb complex terminate primarily in cerebral cortical areas, although Vb does

send projections to other areas as well, including the basal ganglia (Crosby, Humphrey, & Lauer, 1962). Projections to the cortex from Vb are strictly ipsilateral, i.e., fibers leaving Vb on one side of the brain enter the cortex on the same side. The most extensively investigated terminals for Vb projections are the primary somatosensory areas SI and SII. Both SI and SII receive input from Vb (Welker, 1973). There are three basic types of projections which an individual neuron can exhibit. The neuron can project either to SI or SII alone, or to both these areas via collaterals (Welker, 1973).

Jones and Powell (1969) conducted an extensive study of cortical projections of the ventroposterior nucleus of the thalamus by examining the extent of neocortical degeneration following lesions in specific regions of the ventroposterior nucleus. Their analysis agreed with the statements of Welker (1973) in that they found degeneration in SI and SII following lesioning of portions of the Vb complex (ventroposterior nucleus was defined as Vb complex + ventromedial nucleus). In addition, Jones and Powell (1969) found that projections of the Vb complex to SI and SII were topographically organized, in that a given portion of the Vb complex projected only to those regions of SI and SII which were related to the same part of the peripheral receptor system. Jones and Powell (1969) also found no evidence of contralateral projections from Vb to the neocortex.

Corticothalamic projections. Frigyesi, Rinvik, and Yahr (1973) discussed the pattern of projection from SI and SII to the thalamus. In reviewing studies mainly employing the anterograde degeneration techni-

que, they found clear evidence that both S1 and S11 send projections to the Vb complex and that these projections are organized in a somatotopic pattern. Welker (1973) reviewed studies which examined corticothalamic projections to Vb from S1 and S11 and concluded that homotopical corticothalamic connections had been found for foot, hand, and head projections. Based on the likelihood that corticothalamic axons elicited both excitatory and inhibitory actions via connections with both thalamocortical relay cells and interneurons, Welker (1973) postulated that this system provided for selective, differential facilitation and inhibition of transmission and coding of information through Vb.

Vb neuronal fine structure. Bava and associates have studied interactions between the VPL nuclei of both sides of the brain. Bava, Fadiga, and Manzoni (1968) examined excitatory reactions of single units in VPL following ablation of S1 and S11 in cats. Under these conditions, VPL neurons exhibited responses to stimulation of the contralateral VPL. Bava et al. (1968) speculated that the increased reactivity of the VPL nucleus to stimulation of the contralateral VPL was due to a reduction in inhibition of VPL. This reduction in inhibition could be produced by either a reduction in lemniscal input, or by degeneration of thalamocortical relay cells following ablation of S1 and S11. Bava et al. (1968) postulated that the thalamocortical relay cells produced inhibition of VPL via recurrent collaterals.

Bava, Fadiga, Manzoni, and Marricchiolo (1970) found that the VPL nuclei could exhibit inhibitory effects on their homologues. Following removal of S1 and S11 and sectioning of the corpus callosum, radiation

potentials were recorded from the cortical white matter (in the S1 location from which overlying grey matter had been removed) in response to activation of lemniscal input to the ipsilateral VPL nucleus. They found that when stimulation of the ipsilateral VPL was preceded by direct stimulation of the contralateral VPL, a reduction in amplitude of the radiation potential was observed.

Scheibel and Scheibel (1966) conducted an extensive study of the fine structure of the Vb complex in young rats, mice, and cats using the Golgi staining technique to reveal detailed structural characteristics of small numbers of neurons. They analyzed, in particular, the structural patterns of three types of neurons: (1) the neurons entering Vb from the dorsal column nuclei (forming the medial lemniscal input to Vb); (2) the thalamocortical relay cells; (3) the corticothalamic neurons. Axons projecting to Vb from dorsal column nuclei spread out once they penetrated into the Vb complex and were arranged in a series of arcs of differing lengths. As particular synaptic regions were reached, each fiber separated and formed into a cone-shaped arbor composed of increasingly smaller branchlets of the parent axon. This pattern constituted the presynaptic field within which were located thalamocortical and corticothalamic neurons.

The thalamocortical relay cell was characterized by Scheibel and Scheibel (1966) as being a medium-sized element composed of dendritic stalks from which secondary dendrites branched out (giving the appearance of short sheaths). Finally, the corticothalamic neurons were found by these authors to be of two types. One type of fiber was arrang-

ed in a series of disk-like fields oriented in the direction of the long axis of the brain stem, while the other type spread out in a cone-like pattern to encompass relatively large areas of the Vb complex.

Aim of This Study

The primary purpose of this thesis was to analyze the contribution of VPL to gross evoked activity in the association cortex of the cat. Using a cryoprobe system to produce a reversible blockade of synaptic activity in VPL, the effect on short latency components, in particular, of evoked activity recorded in primary (S1) vs association (PCA, ALA, PMSA) areas was compared. In addition, the hypothesis of Thompson, Johnson, and Hoopes (1963) concerning the equivalence of all association areas and the undifferentiated nature of projection systems to these areas was reexamined.

Methods

Subjects

Twenty-five adult cats weighing between 1.9 and 4.0 kg were used as subjects. Any cats which appeared to be Siamese or part-Siamese were excluded from the study.

Surgical Procedures

The subjects were initially anesthetized using ether. The epiglottis and throat were topically anesthetized with Cetacaine spray to prevent reflex gagging, and an endotracheal tube was inserted with the aid of a laryngoscope. Supplementary doses of ether were administered as needed via a connection between the endotracheal tube and a small ether-filled bottle.

The left saphenous vein was cannulated. Still under anesthesia, the subject was placed in a walk-in, sound-attenuated room (Industrial Acoustics Company) and mounted in a Kopf model 1204 stereotaxic apparatus, using standard eye and ear bars. At this point, the subject was taken off ether and switched to halothane anesthesia using an Ohio Medical Products vaporizer set at 1-2% concentration with a flow rate of approximately 700ml/min (oxygen). A Godart capnograph was used to monitor the CO_2 level. The animal received ether for approximately 10 min before being switched to halothane anesthesia.

The scalp was incised and the temporal muscles were retracted, exposing the skull surface. A large bone flap, sufficient to expose the marginal and suprasylvian gyri from the pericruciate region to the posterior suprasylvian sulcus, was removed from the right half of the skull. A

small bone flap was removed from the left side of the skull according to previously determined stereotaxic coordinates. Small openings in the dura mater were made at the sites of the cryoprobe penetrations and at the four points in the right hemisphere corresponding to the sites of the recording electrode placements.

A Kopf semichronic headholder was then affixed to the skull with dental cement. Care was taken to assure that the cat's head remained in the proper stereotaxic orientation. The standard eye and ear bars were removed, thus eliminating these pressure points. The wound margins and temporal muscles were infused with lidocaine (Xylocaine hydrochloride, 20mg/ml, repeated every four hours). At this point, halothane administration was terminated and gallamine triethiodide (Flaxedil, 20mg/ml/hr) was administered (IV) to provide a block of neuromuscular activity. Thus, animals typically received halothane for approximately 1 1/2 to 2 1/2 hr. At least 2 hr following termination of halothane administration was allowed before the actual collection of data was begun.

Artificial ventilation was maintained with a Harvard pump (model 606). The frequency was set at 26 strokes per minute with the stroke volume varied to maintain the tracheal CO_2 levels at 3.6 to 4.0% as monitored on a Godart capnograph. Body temperature was monitored with a rectal thermometer and maintained between 37° and 38°C using hot water bottles.

The two cryoprobes and four recording electrodes were lowered onto the surface of the cortex in the areas where the dura had been previously removed. Liquid agar (2% w/v, in physiological saline) at body temperature was applied to the exposed brain areas to maintain the cortical temperature, to prevent drying of the cortex, and to keep the recording

electrodes from shifting position. Figure 1 is a photograph of a typical preparation, with all experimental apparatus in place.

Recording Electrodes

Four bipolar recording electrodes were used. These electrodes were constructed from .24 mm diameter stainless-steel wire, with the final 1 mm of wire scraped bare of insulation. The wires were mounted on either side of a 2 mm diameter support wire with the tips extending 1 mm past the end of the support. The electrodes were inserted into the cortex with the support wires resting on the cortical surface, and the electrode wires extending 1 mm into the cortex. It had been previously found that this type of subsurface electrode provided more stable evoked potentials over the course of the experiment than surface bipolar electrodes. The electrodes were placed in the three association areas PCA, ALA, and PMSA (Thompson, Johnson, and Hoopes, 1963) and the primary somatosensory area, S1 (Woolsey, 1958). Figure 2 illustrates the sites of the electrode placements.

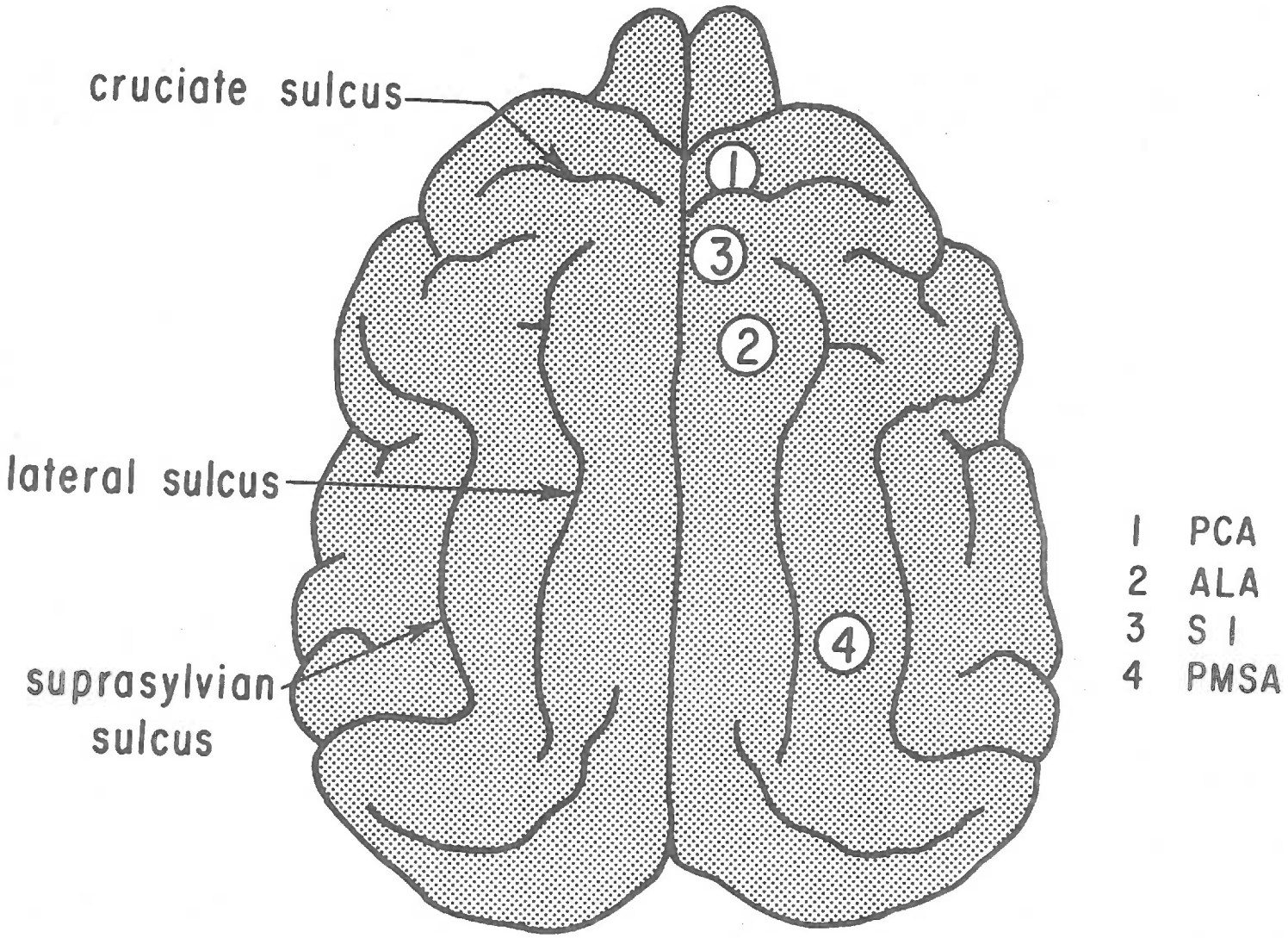
Cryoprobes

The two cryoprobes were placed bilaterally in the nucleus ventralis postero-lateralis (VPL) of the thalamus. The stereotaxic coordinates used were AP: +10.0, vertical:+1.0, lateral: 7.0, according to the atlas of Jasper and Ajmone-Marsan (1954). Following termination of all experimental procedures, the brain was blocked anterior and posterior to the area containing the cryoprobe tracks, removed, and placed in a 10% buffered formaldehyde solution. The cryoprobe sites were verified histologically using 50μ thick frozen sections and Nissl (thionine) staining.

Figure 1. Animal preparation. Semichronic headholder, cortical electrodes and cryoprobes in place.

Figure 2. Dorsal view of cat cerebral cortex showing sites for cortical electrode placements.

CORTICAL ELECTRODE PLACEMENTS



Descriptions of the cryoprobe system have been published (Skinner and Lindsley, 1968; Skinner, 1970). The cryoprobe system allowed localized cooling of the neural tissue at the tip of the probe, thereby providing a reversible blockade of nervous activity. The cryoprobe itself consisted of a U-shaped stainless-steel tube through which the flow of cold methyl alcohol was regulated. A DC heater wire was wrapped around the shaft of the probe, leaving approximately 4 mm bare at the tip. The DC current was supplied by two automobile storage batteries. The entire shaft of the cryoprobe was covered with Epoxylite insulation except for 1mm at the tip which was stripped of insulation. The temperature of the shaft was maintained at approximately 32°C, while the tip temperature was maintained at approximately 3°C. The tip and shaft temperatures were continually monitored via tip and shaft microthermocouples. The tip diameters of the cryoprobes (two values given for each probe due to asymmetry of tip) were 1.19 mm X 1.54 mm and 1.12 mm X 1.07 mm.

Thermoprobe

A thermoprobe was used to determine, *in vivo*, the spread of cooling from the cryoprobe (see Figure 3, p37). The thermoprobe consisted of a thermocouple inserted into a 19 gauge stock shaft with the thermocouple tip protruding 2 mm beyond the base of the shaft.

Recording Apparatus

The signals from the recording electrodes were led through Tektronix 122 preamplifiers, with the filters set at 0.2 Hz - 1000 Hz. The evoked potential signals were then led into amplifiers (Tektronix type 2A63 and 3A72) with adjustable gains. Prior to collection of data, the four amp-

lifiers were calibrated to provide equal gain on a common input signal applied to the Tektronix 122 recording leads. The evoked potentials were then led into a PDP-12 computer for on-line collection and storage of data. The evoked potentials were monitored on a Tektronix 561 oscilloscope.

Stimulation Apparatus

Three modalities of stimulation were used for all animals: somatosensory, auditory, and visual.

Shocks were delivered to the right and/or left hindlimbs by means of 21 gauge hypodermic needles placed subcutaneously along the sides of the paws. The voltage level delivered to each animal was set at 18 V. The shock was delivered by a Devices Mk IV isolated stimulator as three pulses, each pulse lasting 0.2 msec, with an interpulse interval of 4 msec.

The visual stimulus was a light flash from a Grass PS-2 Photostimulator at intensity setting 8 (= 750,000 candlepower, according to specifications of Grass Instrument Company). The light was located 0.7 m in front of the cat's head. Atropine (0.5 mg/ml), used to maintain pupillary dilatation, was applied topically to the cornea (repeated every four hours).

The auditory stimulus was a click from a pulse of a Devices Mk IV isolated stimulator led through a Southwest Technical Products Power Amp 207/A and delivered to an Altec 405-8G loudspeaker. The intensity of the click was measured using a Brüel and Kjaer 2209 Impulse Precision Sound Level Meter, with the diaphragm of the 1" calibrated microphone placed midway between the points where the cat's ears would be during an

actual experiment. The sound pressure level was 113 dB re 0.0002 μbar measured on the Linear scale. The frequency spectrum of the click (determined by octave band measurements) was fairly broad, with its major energy distribution between 250 Hz - 8k Hz. Ambient background noise, due primarily to operation of the respirator, was 63 dB on the Linear scale.

Experimental Design

The basic experimental design included a pre-cool control, cool, and post-cool control series of stimuli presentations. In the pre-cool condition, a stimulus was presented for 100 trials at the rate of one stimulus every 5.011 sec. The computer stored the evoked potentials from the four electrodes beginning 10 msec after stimulus onset and continuing for 512 msec thereafter. Depending on the nature of the cooling condition to be used (see Table 1), either a second and third stimulus modality were presented in the pre-cool condition in an identical manner, or the tips of the cryoprobes were cooled to approximately 3°C and allowed to stabilize for 10 min. Then the same stimuli were presented in an identical manner as in the pre-cool condition. Following the cooling run, the tips of the cryoprobes were allowed to warm up to body temperature (30 min were allowed, based on data from O'Brien & Phillips, 1976). A post-cool control series of stimuli presentations was then run in a manner identical to that in the pre-cool condition.

As can be seen from Table 1, there were a total of 7 different sets possible for each cat. In all cats, the first set to be run was the Bilateral Cool-VPL condition for somatic, auditory, and visual stimuli.

Table 1: Experimental Design*

Cooling Condition	Series	Stimulus Modality
1. Bilateral Cool-VPL	Pre-Cool	Somatic (Bilateral) Auditory Visual
	Cool	Same as Pre-Cool
	Post-Cool	Same as Pre-Cool
2. Bilateral Cool-VPL	Pre-Cool	Somatic (Contralateral)
	Cool	"
	Post-Cool	"
3. Ipsilateral Cool-VPL	Pre-Cool	Somatic (Ipsilateral)
	Cool	"
	Post-Cool	"
4. Ipsilateral Cool-VPL	Pre-Cool	Somatic (Contralateral)
	Cool	"
	Post-Cool	"
5. Contralateral Cool-VPL	Pre-Cool	Somatic (Ipsilateral)
	Cool	"
	Post-Cool	"
6. Contralateral Cool-VPL	Pre-Cool	Somatic (Contralateral)
	Cool	"
	Post-Cool	"
7. Bilateral Cool-LP	Pre-Cool	Somatic (Bilateral) Auditory Visual
	Cool	Same as Pre-Cool
	Post-Cool	Same as Pre-Cool

* "Ipsilateral" and "Contralateral" are used in reference to the cortical hemisphere recorded from.

The order of presentation of stimuli was randomly determined for each cat. Following completion of this set, sets 2 through 6 were run in a randomly determined order for each cat. Depending on the viability of the preparation, after completion of these runs, the cryoprobes were raised 3 mm vertically (placing them in the approximate location of the lateral posterior nucleus of the thalamus), and the seventh set was then run.

In two of the cats, following completion of these sets, the cryoprobes and recording electrodes were removed from the brain, the agar was stripped from the cortical surface and the dura slit so as to expose the entire suprasylvian gyrus. One bipolar surface recording electrode was then positioned on the suprasylvian gyrus and the evoked responses in this gyrus to somatic, auditory, and visual stimuli were systematically mapped in 1 mm steps along its entire extent (50 responses averaged, 3.011 sec between stimuli).

In 10 other cats, following the end of the regular experimental runs, the animals were anesthetized with ketamine hydrochloride (Ketaject, 50 mg/ml),all recording electrodes were removed and a thermoprobe was inserted into the cortex at an angle of 16° with respect to the cryoprobes. The stereotaxic coordinates used for the thermoprobe had been previously determined by adjustment of the thermoprobe with reference to the cryoprobe tip on a stereotaxic zero bar.

Once the thermoprobe had been advanced to within 10 mm of the cryoprobe tip, the cryoprobe system was turned on, the brain tissue was cooled, and the temperature reading of the thermoprobe was recorded. Tem-

perature readings were taken as the thermoprobe was advanced in 1 mm steps toward the cryoprobe tip. When the thermoprobe registered approximately 22°C, it was advanced in 0.5 mm steps. The thermoprobe was halted when it had again recorded a temperature of 20°C after having passed through its lowest recorded temperature. Temperature readings were again taken as the thermoprobe was withdrawn from the brain tissue along the same track.

Following this run, the cryoprobe was turned off, the tissue was allowed to recover and the cryoprobe was raised 1 mm vertically above its previous position. The cryoprobe was then turned on again, the tissue was allowed to cool, and the thermoprobe was inserted into the same track as on the previous run. Temperature recordings were made in a manner identical to that described for the first run. Following this run, two additional runs were made with the cryoprobe raised an additional 1 mm each time. Using this procedure, the spread of cooling from the cryoprobe into the surrounding tissue could be determined without a "pincushion" effect on the brain due to multiple thermoprobe tracks in close approximation to each other.

Data Analysis

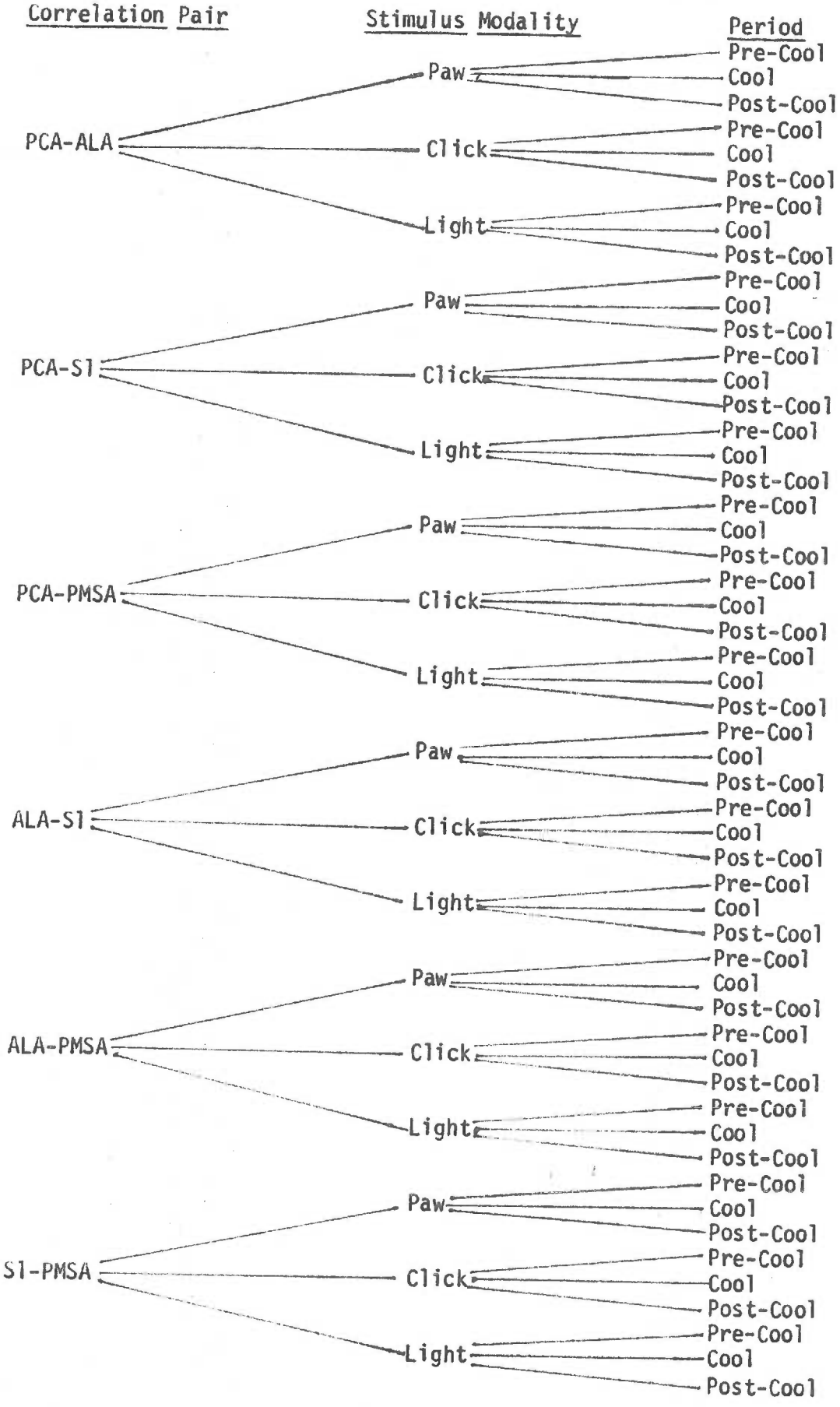
The PDP-12 computer was run on-line, summing the evoked potentials from each set of 100 stimulus presentations, to provide an averaged evoked potential (AEP) for each stimulus modality, in each series. Each AEP was stored in two forms. One form consisted of the AEP for the entire 512 msec poststimulus sampling period (occupying 256 computer addresses - 2 msec/address), while the second form consisted of the AEP

for the short latency component of the response, the first 128 msec (occupying 256 computer addresses - 0.5 msec/address). The short latency AEP was used to examine in detail the early components of the response.

Each AEP was quantified in several different ways, and all comparisons between AEPs were made on a within subject basis. The three major types of quantification were: (1) cross-correlation (Pearson product-moment correlation); (2) peak-to-peak amplitude; (3) latency to specified peaks.

The cross-correlation analysis was used on two types of data. First, during the on-line collection of data, the PDP-12 computed the total area under the curve for the entire 512 msec time period of a single evoked potential and stored these area values for all 100 evoked potential trials for a given stimulus modality and cortical area. Correlation analyses were then run comparing the trial-to-trial fluctuations (100 trials total) of the total area under the EP curve, for a given stimulus modality, in one cortical area vs another cortical area, for either the pre-cool, cool, or post-cool control period. Thus, individual correlation coefficients were obtained for each stimulus modality (total of 3), between each pair of cortical areas (total of 6), for each period (pre-cool, cool, or post-cool, total of 3) for a grand total of 54 correlations per cat. Table 2 summarizes the comparisons made for each subject. The correlation coefficients for the same comparison were summed across all subjects in a given group and a mean correlation coefficient was obtained. The object of this analysis was to determine if changes in the area under the EP waveform occurred syncronously in any two given

Table 2: Summary of possible comparisons for trial-by-trial analysis.



cortical regions.

A second type of correlation analysis involved the point by point comparison of the waveform of the 512 msec AEPs (each AEP was composed of 256 computer addresses). The correlation coefficient computation was based on these 256 values from each of two AEPs from a particular subject. These within subject comparisons were made in two different ways. First, AEPs from the same cortical area but generated by different stimulus modalities were compared (e.g., pre-cool AEPs from area PCA in response to paw shock and click stimuli). A second comparison involved AEPs generated in two different cortical areas in response to the same stimulus modality (e.g., cool AEPs in response to a click stimulus from areas PCA and ALA). As was the case with the computation of the trial-by-trial correlation, a correlation coefficient for each comparison was obtained for each subject in a particular group, and a mean correlation coefficient was obtained by averaging across all subjects in that group.

Since an evaluation of the effect of cooling on the AEP was the primary goal of this study, a number of different analyses were utilized to describe the cooling effect. First, for each cooling condition and stimulus modality used (see Table 1), the shape of the pre-cool and cool AEPs for each subject were compared across the entire 512 msec time interval. Each AEP was segmented into continuous 16 msec bins and the total area under the curve, in each bin, was computed. Difference scores between the pre-cool and cool curves for a given cooling condition and stimulus modality were then computed bin by bin.

It was observed that the thalamic blockade produced by cooling

was associated with a shift in latency of peaks of the AEP waveform (cool AEP compared to pre-cool AEP), i.e., a particular peak in the cool AEP would occur at a longer latency (by several msec) than the corresponding peak in the pre-cool AEP. In this situation, difference scores computed on the basis of a change in bin area between corresponding segments of the pre-cool and cool AEPs would not accurately reflect changes in amplitude of the AEP, since it would be possible to have a shift in latency of a peak during the cool period without a decrease in amplitude relative to the pre-cool period. This would result in large difference scores when in fact the only real difference between the curves was in the latency to the corresponding peaks. Therefore, in order to calculate accurately changes in AEP amplitude over time, it was necessary to artificially shift the cool AEP relative to the pre-cool AEP until the corresponding peaks in each waveform lined up. Then the difference in area under corresponding segments of the AEP waveform between the pre-cool and cool AEPs would accurately reflect amplitude differences.

To determine the degree to which the cool AEP had to be back shifted relative to the pre-cool AEP in order to line up the corresponding peaks, a correlation analysis was run similar to the second type of correlation analysis discussed above, involving the comparison of pre-cool and cool AEPs, address by address, for all 256 computer addresses. However, a <u>series</u> of correlation coefficients was obtained for each comparison, for each cat.

First, the correlation coefficient was computed for the pre-cool vs the cool AEP as they actually occurred in time. Then, the cool AEP

was back shifted one computer address, and a second correlation coefficient was computed. This process was continued until a maximum value for the correlation coefficient had been obtained. In general, 5 shifts (1 address per shift) were sufficient in order to align the respective peaks in the pre-cool and cool curves.

The pre-cool AEP and the shifted cool AEP which was maximally correlated with the pre-cool AEP, were then divided into 16 msec bins and a difference score (cool - pre-cool) was computed, bin by bin, based on the area under the curve in each bin.

This analysis was repeated for each subject in a given cooling condition using a given stimulus modality (see Table 1). In order to reflect variance in scores across subjects as well as the magnitude of difference between pre-cool and cool conditions, paired *t*-tests were then computed for each bin, for all subjects in a particular series (see Table 1). For example, in analyzing the effect of bilateral cooling of VPL on the AEP evoked in PCA by the paw stimulus, 30 *t*-scores were obtained (16 msec/bin X 30 bins = 480 msec). Only the first 480 msec (out of 512 msec) of the AEP were analyzed.

This analysis was not designed to test the statistical significance of the differences obtained between the pre-cool and cool conditions but merely to provide a general overview of where in the 512 msec time period the largest and most consistent differences occurred.

A more important analysis, in terms of testing the statistical significance of pre-cool to cool AEP differences, was the analysis of amplitude changes of selected peaks. For this analysis, the 128 msec

waveform was utilized in order to examine cooling effects on specific early components of the AEP. The amplitude of selected peaks in the pre-cool and cool AEPs and the latency to those selected peaks which were maximally affected (increase or decrease in amplitude) by thalamic cooling was determined. For each cooling condition and stimulus modality, a one-way analysis of variance (fixed factor model, repeated measures) was computed based on the pre-cool, cool and post-cool amplitudes of corresponding peaks in those AEPs.

Results

Isotherm Determination

Figure 3 summarizes the results of the thermoprobe analysis of cooling spread from the cryoprobe. It should be remembered that there was only one actual thermoprobe track made in the brain of each animal. The four separate tracks were generated by raising the cryoprobe in 1 mm steps after each previous track was generated.

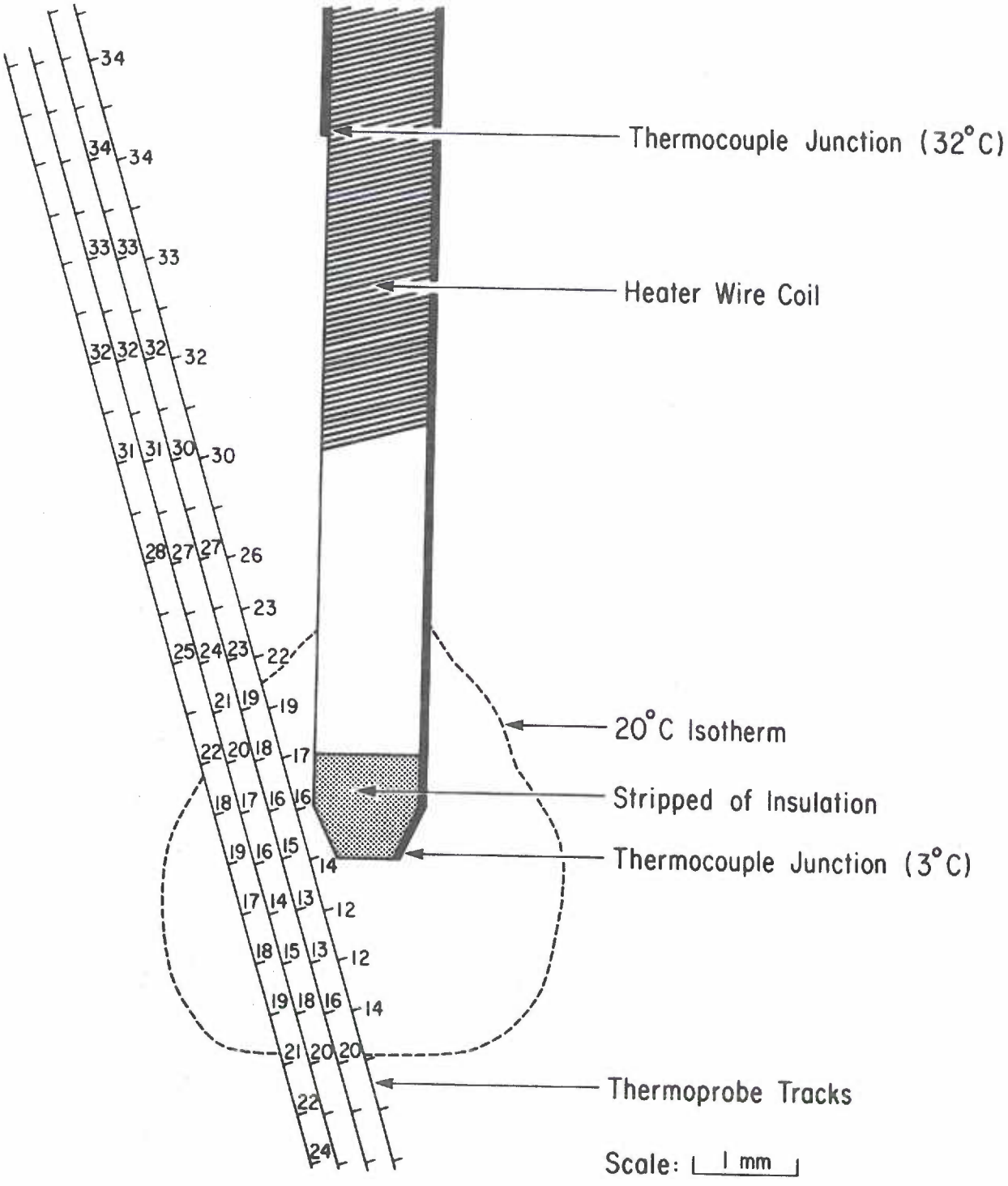
Previous research (Jasper, Shacter, & Montplaisir, 1970) indicated that at approximately 20° to 22°C all cortical synaptic activity was blocked. Despite the difference in location of cooling in this experiment from the Jasper, Shacter, and Montplaisir (1970) paper, this figure of 20°C was used as a guide to estimate the volume of tissue in which there was a complete block of synaptic activity. A 20°C isotherm was drawn based on the data points obtained from the thermoprobe tracks. The volume of tissue included within the 20°C isotherm was 4 mm in diameter at its widest point and extended 2 mm below the tip and tapered off above the tip, along the shaft, for a distance of 2 mm.

Histology

Histological verification of the cryoprobe placements was performed using Nissl (toluidine blue) stained frozen sections. The sections were viewed using a Baush and Lomb microprojector and the sections were compared to photomicrographs from a stereotaxic atlas (Snider & Niemer, 1961). The results obtained from Figure 3 were used as a basis for estimating which thalamic structures were affected by the cooling produced by the cryoprobes.

Figure 3. Schematic diagram of temperature gradient from cryoprobe when cooling system was in operation and placed in VPL. Tracks to the left of cryoprobe indicate path of thermoprobe penetration and temperature in °C at distances from cryoprobe as noted. Dotted line indicates 20°C isotherm based on thermoprobe penetrations.

Spread of Cooling From Cryoprobe



Based on the location of the cryoprobe tips and the characteristics of the 20°C isotherm, the 25 cats used in the present study were divided into VPL and non-VPL cooled groups. The decision to include an animal in a particular group was biased against the VPL group, i.e., only those animals which had a minimum of non-VPL structures included within the 20°C isotherm, relative to the total sample of subjects, were assigned to the VPL group. On this basis, 14 of the 25 cats were assigned to the VPL group (Bilateral Cool-VPL, "BC-VPL"). Unavoidably, even in the BC-VPL group, portions of non-VPL structures such as nucleus reticularis, nucleus lateralis posterior, and internal capsule were also included within the 20°C isotherm. Table 3 lists the confirmed stereotaxic coordinates for each cat included in the BC-VPL group. Figure 4 presents typical results of the histological verification of the cryoprobe placements.

For Cooling Conditions 2 through 6 (see Table 1) the number of subjects varied from 12 to 17. Ns greater than 14 were possible for some of these groups because in several cases in which only one cryoprobe was in use (e.g., the ipsilateral or contralateral cool conditions), it was later found that only one of the cryoprobe placements was not in VPL. In this situation, if the cryoprobe which was not in VPL was not used for cooling during a particular run (e.g., a contralateral cryoprobe during an ipsilateral cool run), then this animal's data could be included in the analysis for that condition but not that for the BC-VPL condition.

The non-VPL group was not homogeneous with respect to the major

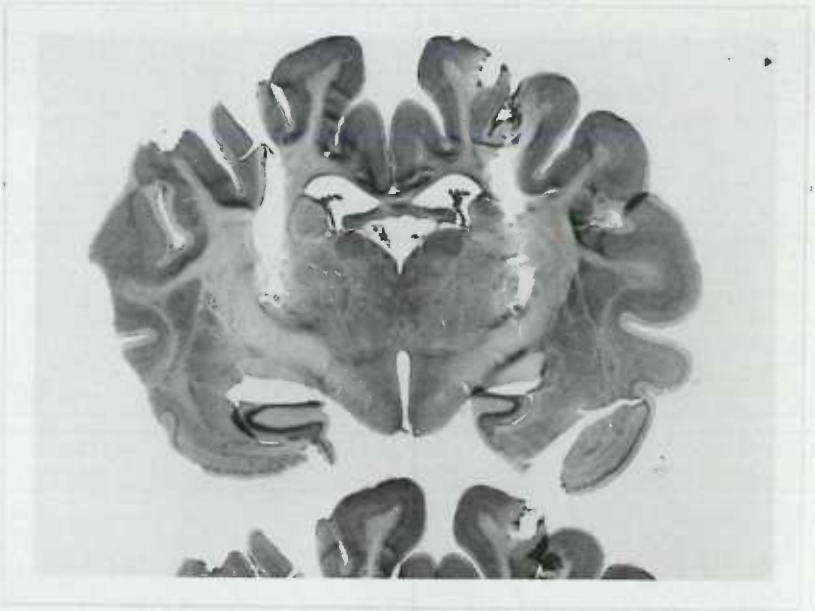
Table 3. Confirmed stereotaxic coordinates for BC-VPL group

Cat #	AP		LAT		VERT	
	L	R	L	R	L	R
33	11.0	11.0	6.5	6.5	1.0	1.0
36	9.5	9.5	6.5	8.5	1.0	1.5
41	9.5	9.5	7.5	7.0	0.5	1.0
43	10.0	10.0	7.5	5.0	0.0	0.0
44	10.5	10.5	7.5	7.5	0.0	1.0
45	10.0	11.0	7.0	7.0	1.0	0.5
46	10.5	10.5	7.5	6.5	0.5	1.0
47	8.5	8.5	7.5	7.0	0.5	0.5
51	10.5	10.5	7.5	7.0	0.0	0.0
53	9.0	9.0	7.5	6.5	0.0	0.0
55	10.0	10.0	7.5	7.0	-0.5	1.0
56	10.5	10.5	7.0	6.0	0.5	0.5
59	9.5	9.5	7.5	7.5	0.0	1.0
60	10.5	10.5	7.5	7.0	-0.5	0.0

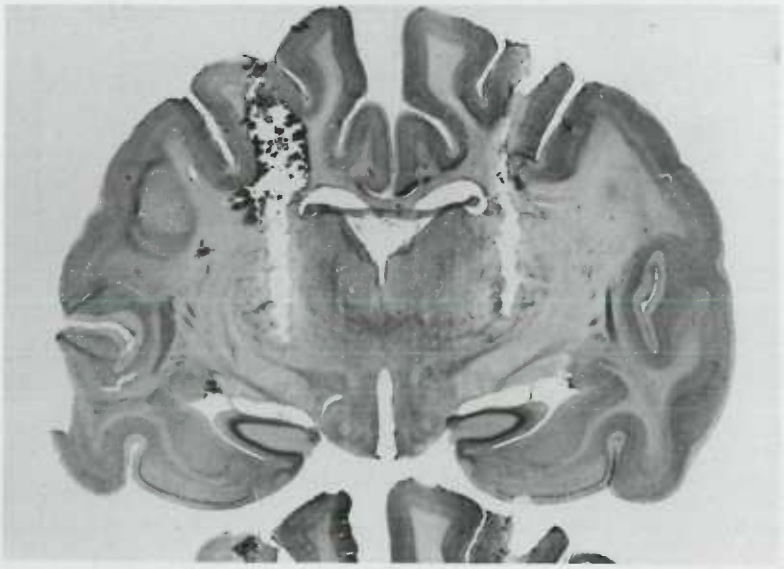
Figure 4. Cryoprobe tracts of cats # 36 and #41. From dorsal to ventral, tracts pass through: suprasylvian gyrus, internal capsule, caudate, nucleus reticularis, nucleus ventralis anterior, nucleus lateralis posterior, ending in VPL.

Verification of Cryoprobe Location

Cat # 36



Cat # 41



structures included within the 20°C isotherm. From cat to cat, structures such as nucleus ventralis anterior, nucleus lateralis posterior, nucleus caudatus, and internal capsule were the major sites contained within the 20°C isotherm. However, in all cases, small portions of VPL were also included within the 20°C isotherm.

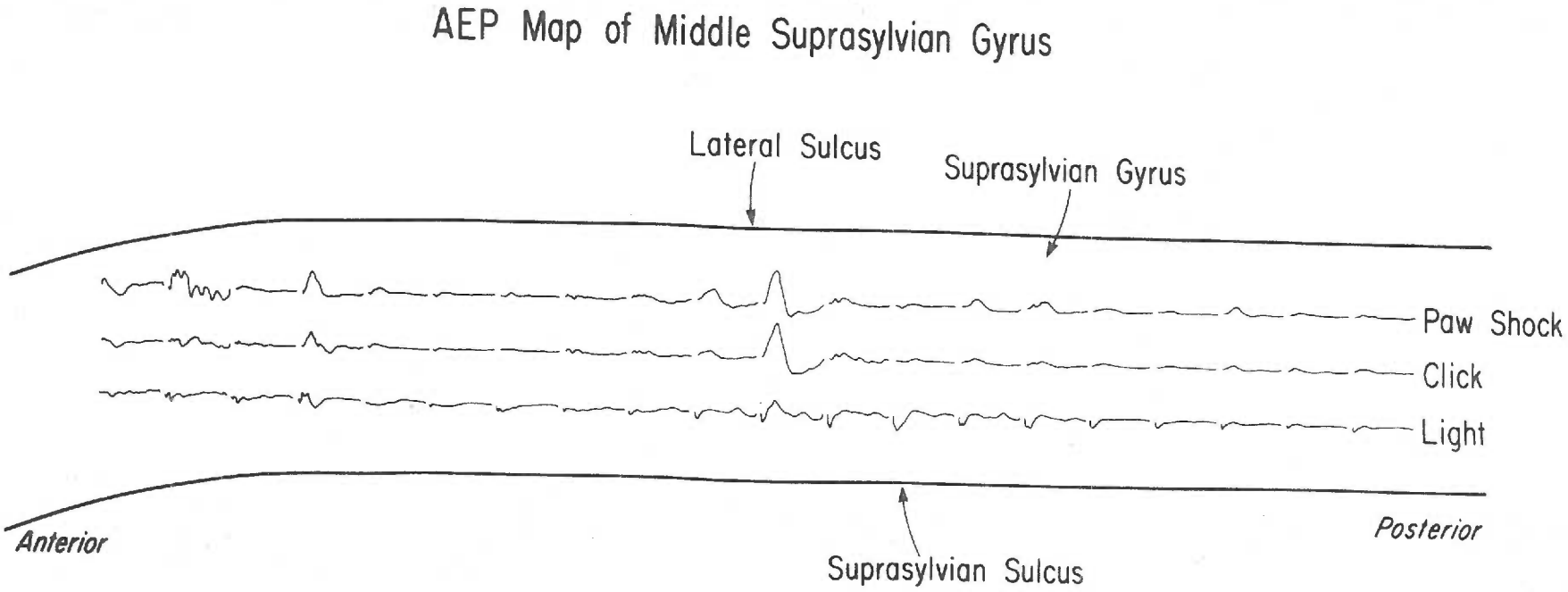
Cortical Mapping

In two cats, following completion of all other experimental manipulations, the evoked potentials recorded from the middle suprasylvian gyrus in response to paw, click, and light stimuli were systematically mapped in 1 mm steps. Figure 5 is a topographical map of the AEPs thus generated from one of the cats. There appear to be two fairly discrete areas on the middle suprasylvian gyrus in which relatively large amplitude AEPs were obtained in response to paw, click, and light stimuli. This would appear to coincide with the location of the anterior and posterior middle suprasylvian association areas (AMSA and PMSA) as described by Thompson, Johnson, and Hoopes (1963). It should be noted that the AEPs elicited by the paw, click, and light stimuli at a given stereotaxic AP value were all recorded from the same site. The AEPs are offset on the figure merely for the sake of clarity. Figure 5 demonstrates that association responses of a nature traditionally found by other workers (e.g., Thompson, Johnson, & Hoopes, 1963) were recordable with the type of preparation used in the present study.

t-Score Analysis

The t-score analysis provided a general indication of the pattern of cooling effects across the entire 512 msec time period of the AEP.

Figure 5. Representation of middle suprasylvian gyrus showing AEPs recorded in response to paw, click, and light stimuli. Response sets (AEPs to paw, click, and light) recorded in 1 mm steps across gyrus in AP direction.

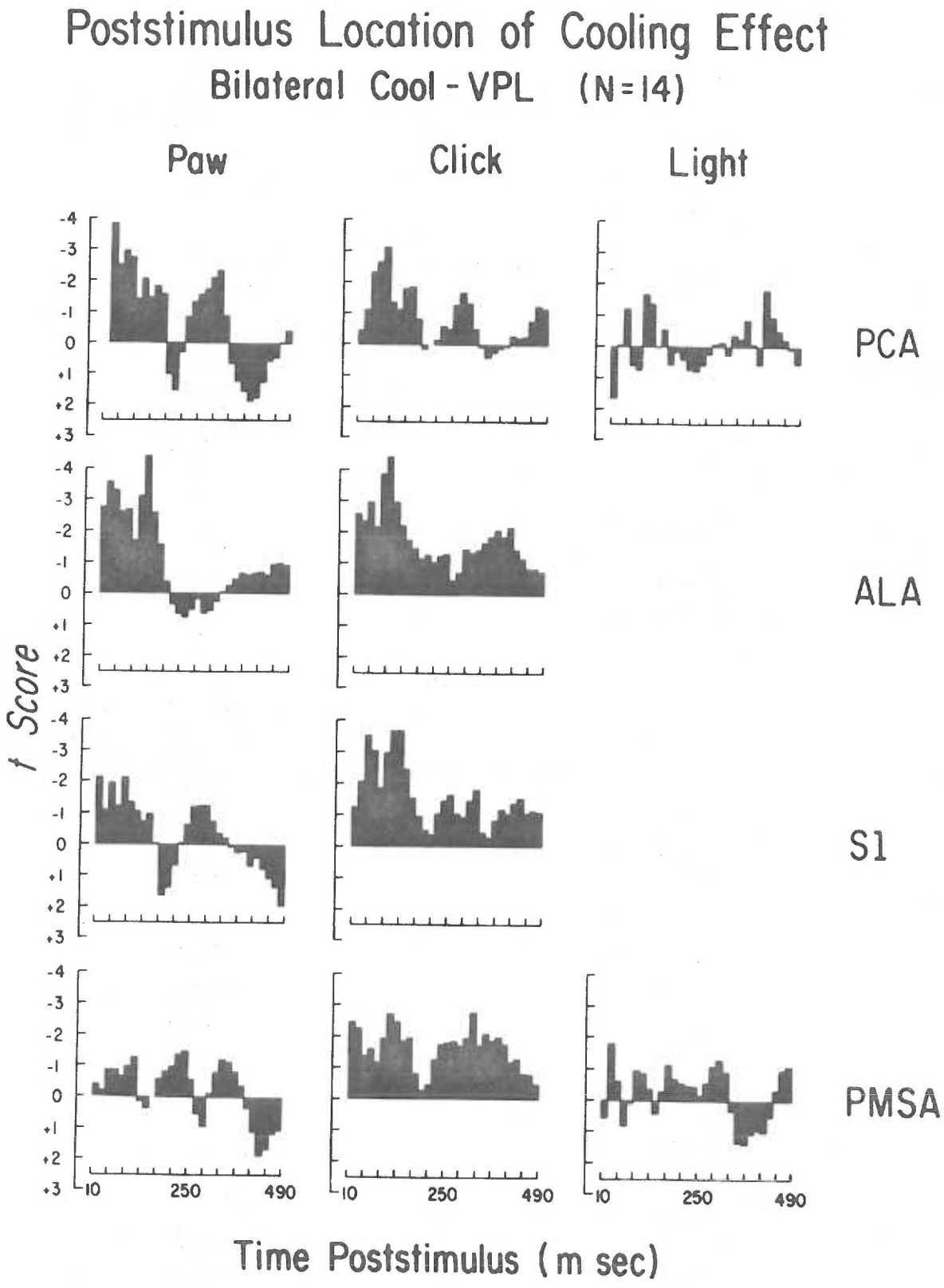

AEP Map of Middle Suprasylvian Gyrus
Lateral Sulcus
Suprasylvian Gyrus
Paw Shock
Click
Light
Anterior
Posterior
Suprasylvian Sulcus

In this analysis, a series of paired t-tests, one for each 16 msec bin in each AEP, were performed on the various VPL cool groups (see Table 1) based on the difference scores calculated by subtracting the value obtained for the area under the curve in each 16 msec bin during the pre-cool condition from that value obtained in the respective 16 msec bin during the cool condition (see Methods section for complete description). This analysis was designed to provide an overall representation of the effect of cooling on the entire 512 msec AEP. However, it was not designed to test the statistical significance of the results thus generated. The t-score was chosen as a means of representing the data because a measure which took into account both the magnitude of difference and variance among subjects was desired.

The t-score histograms generated for the BC-VPL group are shown in Figure 6. The most striking effect seen was the relative lack of effect of cooling upon the AEPs elicited by the light stimulus in PCA and PMSA, and the AEPs elicited by the paw stimulus in PMSA.

The AEPs elicited by the paw stimulus in PCA, ALA, and S1 and the AEPs elicited by the click stimulus in PCA, ALA, S1, and PMSA all showed marked effects of cooling (primarily a reduction in bin area during cooling, a negative t-score). In all these areas during cooling, there was a definite decrease in bin area in the early components of the response, while there was a good deal of variability in the effect of cooling on later components of the response. In particular, there appeared to be some similarity in the effect of cooling on the AEPs elicited by the paw stimulus in areas PCA and S1. Four major components could be dis-

Figure 6. Series of *t*-score histograms showing poststimulus location of cooling effects for Cooling Condition 1 (see Table 1). Histograms for light stimulus in ALA and S1 are missing due to lack of recordable responses in these areas.


Poststimulus Location of Cooling Effect
Bilateral Cool - VPL (N=14)
Paw
Click
Light
PCA
ALA
S1
PMSA
t Score
-4
-3
-2
-1
0
+1
+2
+3
10
250
490
Time Poststimulus (m sec)

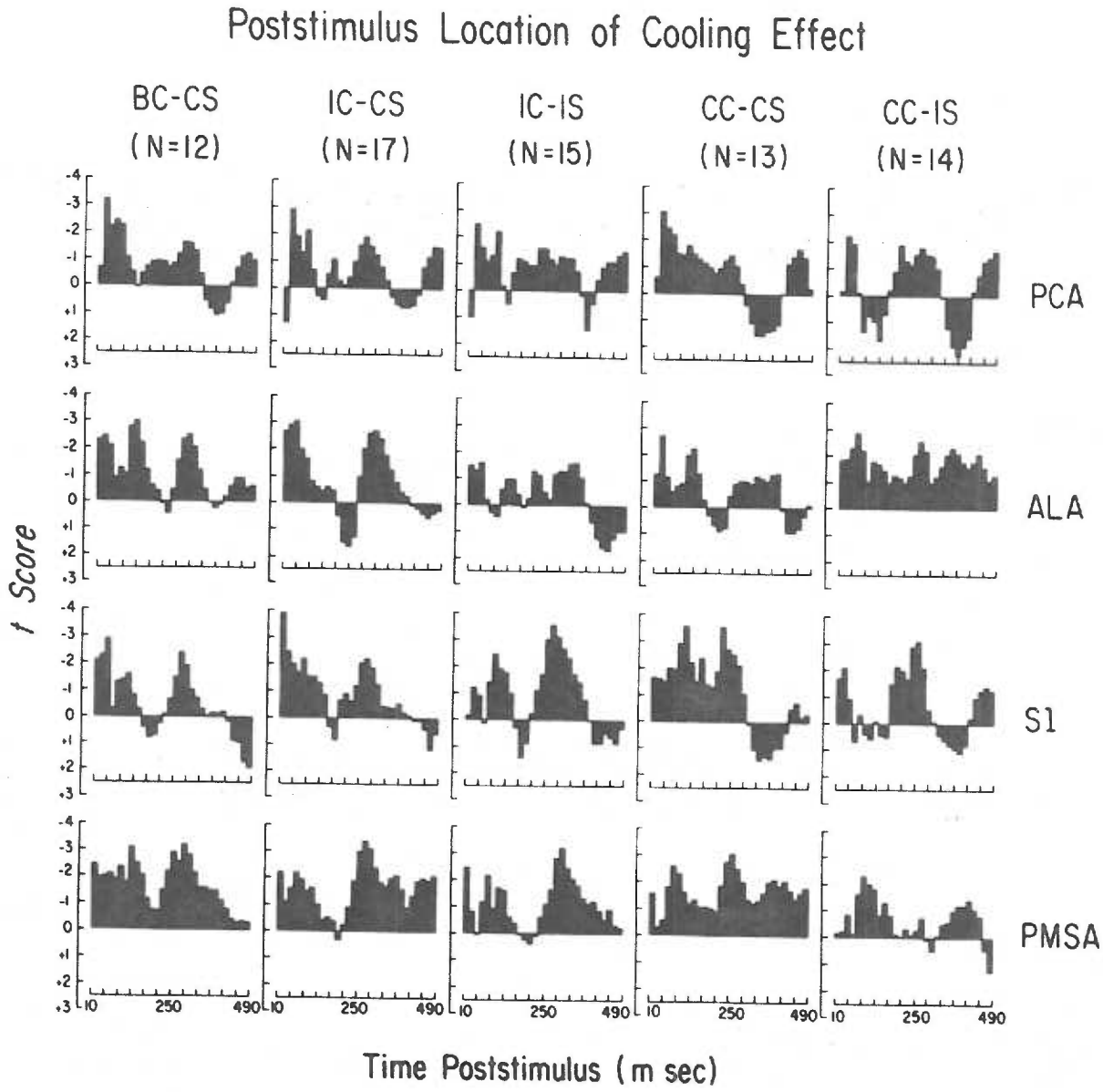
tinguished which closely corresponded temporally in both areas. There was an initial decrease in bin area during cooling (ending at 170 msec poststimulus) followed by a period of enhanced bin area during cooling (ending at 218 msec poststimulus). This was followed by a second period of decreased bin area (ending at 330-346 msec poststimulus) followed by a second period of enhanced bin area.

The pattern of cooling effects seen in ALA in response to the paw stimulus was slightly different, with an initial decrease in bin area followed by a period of increased bin area of similar latencies to that seen in PCA and S1. However, ALA did not demonstrate the second period of decreased bin area during cooling seen in both PCA and S1.

The pattern of cooling effects seen in the AEPs elicited by the click stimulus was somewhat different. Areas ALA, S1, and PMSA showed a general decrease in bin area during cooling throughout the entire AEP waveform, while the pattern of cooling in PCA in response to click resembled the pattern seen in PCA and S1 in response to the paw stimulus.

Figure 7 shows the *t*-score histograms generated for Cooling Conditions 2 through 6 (see Table 1). There appeared to be a differential effect of thalamic cooling on the AEPs elicited by the paw stimulus in S1, depending on whether the ipsilateral or contralateral hindpaw was stimulated, regardless of the location of the thalamic cooling (contralateral or ipsilateral). The Bilateral Cool-Contralateral Shock (BC-CS), the Ipsilateral Cool-Contralateral Shock (IC-CS), and the Contralateral Cool-Contralateral Shock (CC-CS) groups all showed marked decreases in bin area for early components of the AEP. The CC-CS group differed

Figure 7. Series of *t*-score histograms showing poststimulus location of cooling effect for Cooling Conditions 2 through 6 (see Table 1).


Poststimulus Location of Cooling Effect
BC-CS
(N=12)
IC-CS
(N=17)
IC-IS
(N=15)
CC-CS
(N=13)
CC-IS
(N=14)
PCA
ALA
S1
PMSA
t Score
-4
-3
-2
-1
0
+1
+2
+3
10
250
490
Time Poststimulus (m sec)

somewhat from the BC-CS and IC-CS groups in showing smaller effects in the very early bins (up to 90 msec) and a more generalized decrease in bin area during cooling out to about 298 msec.

In contrast, the Ipsilateral Cool-Ipsilateral Shock (IC-IS) and the Contralateral Cool-Ipsilateral Shock (CC-IS) groups did not show the marked reduction in bin area during cooling in the early components of the AEP (up to 90 msec). However, in later components of the AEP (202-378 msec for IC-IS and 170-314 msec for CC-IS) there were large reductions in bin area for both groups.

The t-score histograms from the three association areas did not show the same pattern seen with S1. However, there did appear to be less of a cooling effect (i.e., decreased bin area during the cool period) during the ipsilateral shock as opposed to the contralateral shock conditions. As can be seen from inspection of Figure 7, there was no consistency among the association areas for a given cooling condition in terms of the pattern of effects observed.

The t-score analyses presented in Figures 6 and 7 are of particular use in comparing patterns of cooling effects in association vs primary areas. One possible interpretation of the lack of homogeneity among the association areas in terms of the pattern of cooling effects would be that association areas do not receive identical inputs from subcortical structures.

Peak-to-Peak Analysis

The most consistent result demonstrated by the t-score analysis was an effect on early components of the AEP. With this in mind, the peak-

to-peak analysis was performed on the 128msec AEPs (as opposed to the 512 msec AEPs). The peak-to-peak analysis was used in order to determine specifically which peaks in the AEP waveform were maximally changed by the thalamic cooling. In this analysis, for each pre-cool to cool comparison, the amplitude of the particular peak-to-peak component of the AEP which showed the maximum change (increase or decrease) from the pre-cool to cool condition was determined and the latency to this maximally affected peak was noted.

Typical AEPs used in the peak-to-peak analysis are illustrated in Figures 8 and 9. Figure 8 illustrates AEPs collected in S1. Note the large decrease in amplitude for the initial peak in the ipsilateral cool curve with full recovery of amplitude during the post-cool control. Note also the lack of effect on the peak-to-peak amplitude during the contralateral cool condition. Figure 9, taken from the same animal, illustrates AEPs collected in ALA. There is an effect, similar to that seen in Figure 8, in the ipsilateral cool condition on peak-to-peak amplitude. Note however the longer latency to this affected peak than that seen for the affected peak in S1. Similar to S1, in ALA there is relatively little effect of the contralateral cool condition on the peak-to-peak amplitude.

Figure 10 illustrates the effect of cooling on selected components of the AEP for the BC-VPL group. The % change in AEP amplitude score was computed based on the formula:

$$\frac{(\text{cool AEP amplitude} - \text{pre-cool AEP amplitude})}{(\text{pre-cool AEP amplitude})} \times 100$$

Figure 8. AEPs for cat # 51 in response to contralateral hindlimb stimulation, recorded in area S1, before, during, and after ipsilateral and contralateral cooling of VPL.

CAT # 51

AEPs — CORTICAL AREA S1

CONTRA HINDPAW SHOCK

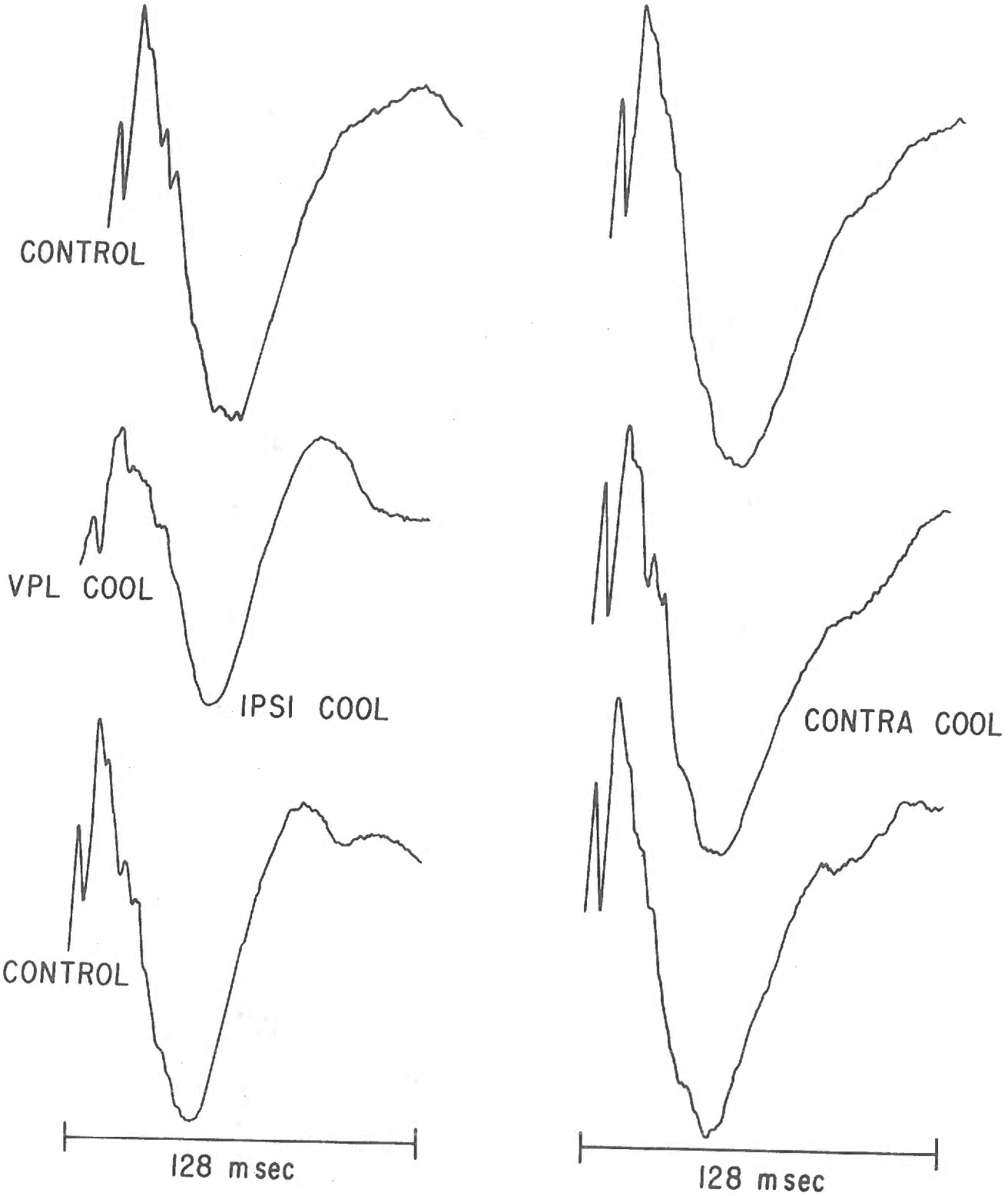


Figure 9. AEPs for cat # 51 in response to contralateral hindlimb stimulation, recorded in ALA, before, during, and after ipsilateral and contralateral cooling of VPL.

CAT #51

AEPs — CORTICAL AREA ALA

CONTRA HINDPAW SHOCK

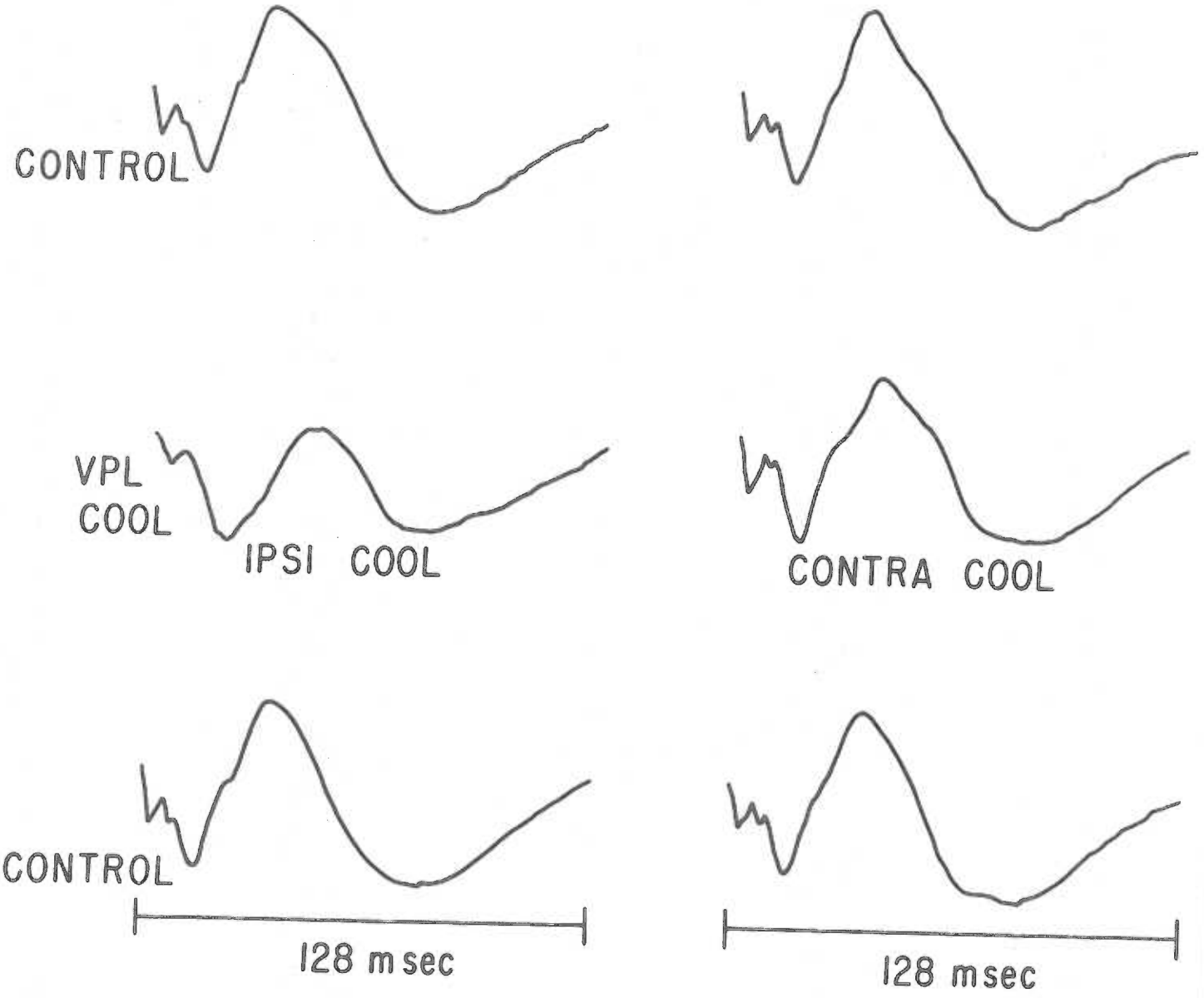
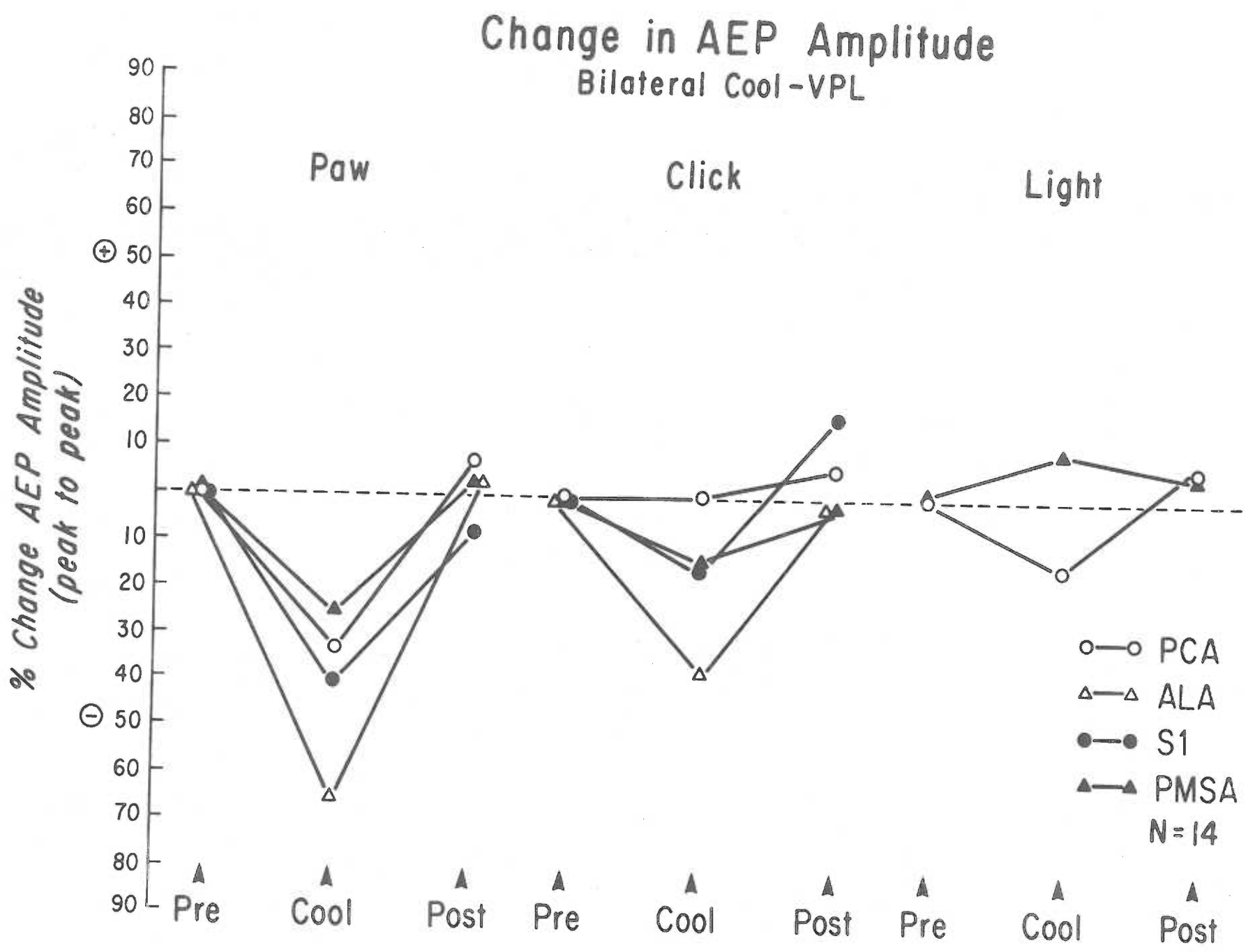


Figure 10. Summary of amplitude data from peak-to-peak analysis for Cooling Condition 1 (see Table 1). Data for light stimulus in ALA and S1 missing due to lack of recordable responses in these areas.


Change in AEP Amplitude
Bilateral Cool-VPL
Paw
Click
Light
% Change AEP Amplitude (peak to peak)
90
80
70
60
⊕ 50
40
30
20
10
10
20
30
⊖ 50
60
70
80
90
Pre
Cool
Post
Pre
Cool
Post
Pre
Cool
Post
PCA
ALA
S1
PMSA
N=14

A series of one-way analyses of variance (repeated measures, fixed factor design) were run to test the statistical significance of the change in AEP amplitude from the pre-cool control to cool to post-cool control for each of the 10 comparisons portrayed in Figure 10. It should be noted that while the data in Figure 10 are plotted in terms of the % change score, these statistical tests were performed on the actual raw data (i.e., AEP peak-to-peak amplitudes).

For the AEPs elicited by the paw stimulus, there was a significant effect of cooling on AEP amplitude in PCA ($F(2,26) = 12.08$, $p < .001$), in ALA ($F(2,24) = 34.52$, $p < .001$), in S1 ($F(2,26) = 9.69$, $p < .001$), and in PMSA ($F(2,22) = 8.41$, $p < .005$). Newman-Keuls tests were run on each individual comparison in all four areas. In all four areas, both the pre-cool and post-cool amplitudes were significantly different from the cool amplitude while the pre-cool and post-cool amplitudes were never significantly different from each other.

For the AEPs elicited by the click stimulus, there was a significant effect of cooling on AEP amplitude in ALA ($F(2,20) = 7.16$, $p < .01$) and S1 ($F(2,26) = 7.25$, $p < .01$) but there was no significant effect of cooling in either PCA or PMSA. Individual comparisons, using Newman-Keuls tests, were made on the results obtained in ALA and S1. In both of these areas, the pre-cool and post-cool amplitudes were significantly different from the cool amplitude while the pre-cool and post-cool amplitudes were not significantly different from each other.

For the AEPs elicited by the light stimulus, no measurable responses were obtained in either ALA or S1. Responses to light were found in PCA

and PMSA, but there were no significant effects of cooling in these two areas.

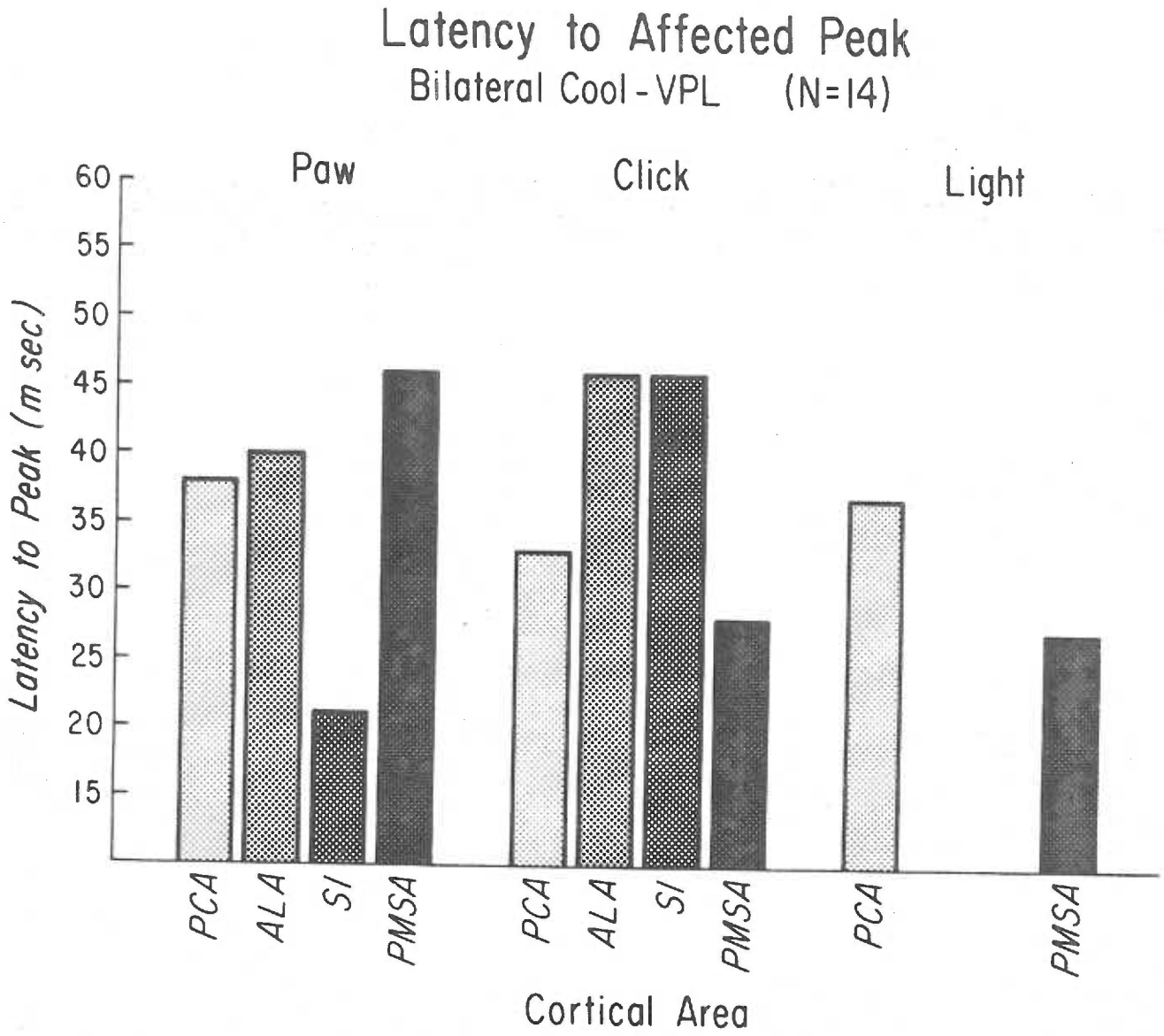
The % change in AEP amplitude in response to paw vs click stimuli in ALA and S1 were compared using paired *t*-tests. In ALA, there was a significantly greater % change in peak-to-peak amplitude in response to paw- vs click-elicited AEPs ($t(13) = -2.53$, $p < .05$). In S1, there was no significant difference between the paw and click stimuli with regard to the % change in AEP amplitude during cooling.

Figure 11 indicates the latency to those peaks (one for each AEP) which were analyzed for amplitude changes in Figure 10. Although Figure 11 shows the mean latency of all peaks analyzed and graphed in Figure 10, only those cortical areas which showed a significant effect of cooling on AEP amplitude were tested for the significance of latency differences (i.e., Paw: PCA, ALA, S1, PMSA; Click: ALA, S1).

A one-way analysis of variance (fixed factor design, repeated measures), performed on the latency to the affected peaks in the four cortical areas in response to the paw stimulus, showed a significant difference in latency among the cortical areas ($F(3,39) = 6.80$, $p < .001$). Individual comparisons were made on pairs of cortical areas using Newman-Keuls tests. PCA, ALA, and PMSA all showed significantly longer latency than S1 to the peaks which were maximally affected by cooling, while PCA, ALA, and PMSA did not differ significantly among themselves in terms of latency.

Latencies to the affected peaks in ALA and S1 in response to the click stimulus were not significantly different from each other. There

Figure 11. Summary of latency data from peak-to-peak analysis for Cooling Condition 1 (see Table 1). Data for light stimulus in ALA and S1 missing due to lack of recordable responses in these areas.

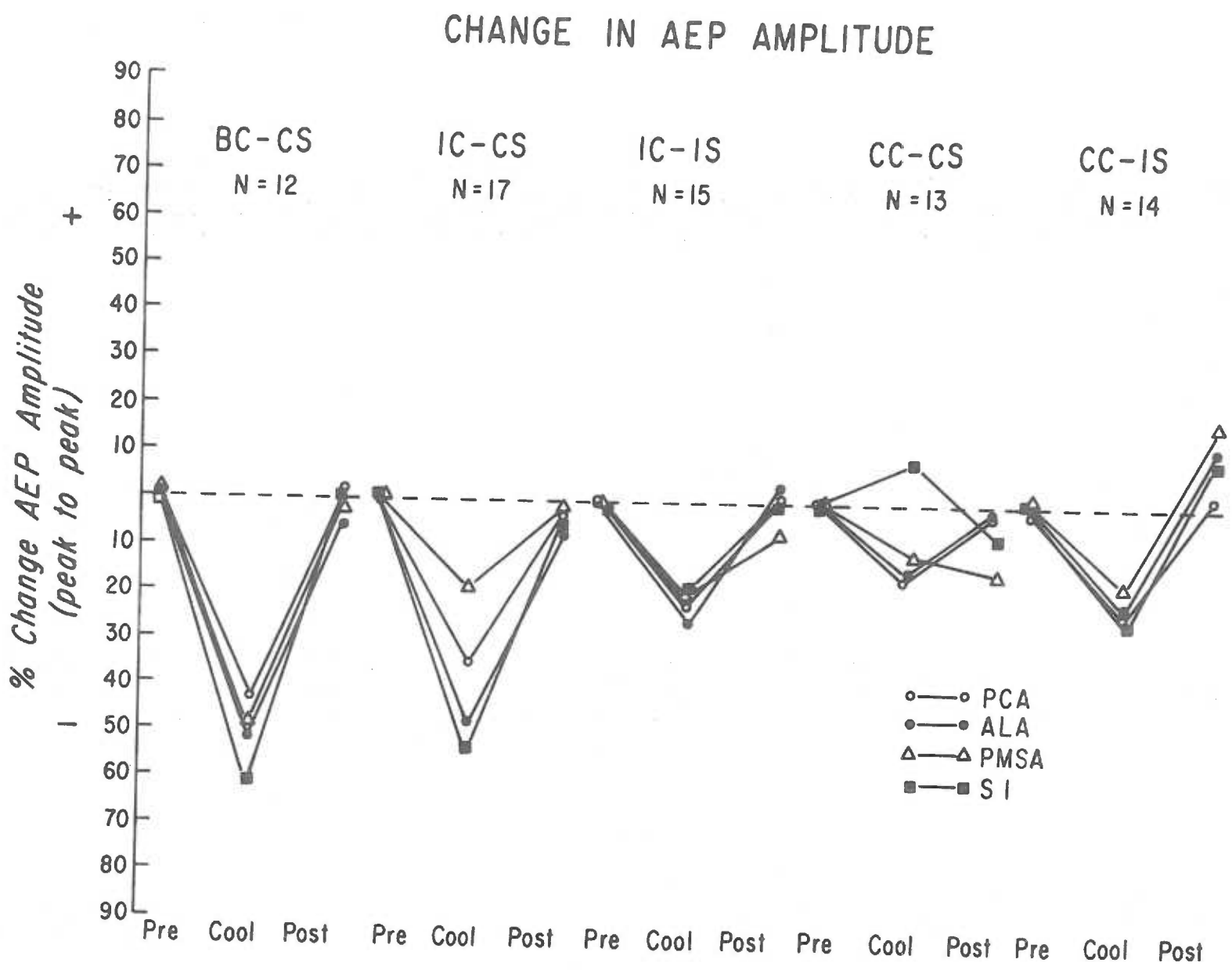

Latency to Affected Peak
Bilateral Cool - VPL (N=14)
Paw
Click
Light
Latency to Peak (m sec)
60
55
50
45
40
35
30
25
20
15
PCA
ALA
SI
PMSA
PCA
ALA
SI
PMSA
PCA
PMSA
Cortical Area

also was no significant difference in the latency to the affected peaks in ALA in response to the paw vs the click stimulus. In S1, latency to the affected peak for the AEPs elicited by the paw stimulus was significantly shorter than the latency to the affected peak for the AEPs elicited by the click stimulus ($F(1,13) = 21.70$, $p < .001$).

In summary, the data analyzed in Figures 10 and 11 showed that there were significant cooling effects in all four areas in response to the paw stimulus. There were only two areas (ALA and S1) which showed significant cooling effects in response to the click stimulus and no cortical areas showed significant cooling effects in response to the light stimulus. Cooling effects in response to the click vs the paw stimulus could be differentiated on the basis of differences in latency (S1) or amplitude (ALA) effects. Thus the data in Figures 10 and 11 demonstrate that cooling of VPL affected primarily the activity evoked by the paw stimulus. In those cortical areas which showed effects on activity elicited by the click stimulus as well, the paw and click effects were clearly differentiated in terms of latency or amplitude.

The % change in AEP amplitude in the four cortical areas during Cooling Conditions 2 through 6 (see Table 1) are indicated in Figure 12. A series of one-way analyses of variance (repeated measures, fixed factor design) were run to test the statistical significance of the change in AEP amplitude from pre-cool control to cool to post-cool control for each of the 20 comparisons indicated in Figure 12. It should be noted that while Figure 12 portrays the data in terms of % change scores, these statistical tests were performed on the actual raw data (AEP peak-

Figure 12. Summary of amplitude data from peak-to-peak analysis for Cooling Conditions 2 through 6 (see Table 1).


CHANGE IN AEP AMPLITUDE
BC-CS
N = 12
IC-CS
N = 17
IC-IS
N = 15
CC-CS
N = 13
CC-IS
N = 14
% Change AEP Amplitude
(peak to peak)
+
−
90
80
70
60
50
40
30
20
10
10
20
30
40
50
60
70
80
90
Pre
Cool
Post
PCA
ALA
PMSA
S I

to-peak amplitudes).

For the BC-CS condition, there was a significant effect of cooling on AEP amplitude in PCA ($F(2,24) = 12.24$, $p < .001$), ALA ($F(2,22) = 16.82$, $p < .001$), SI ($F(2,24) = 18.42$, $p < .001$) and PMSA ($F(2,20) = 6.48$, $p < .01$).

For the IC-CS condition, there was a significant effect of cooling on AEP amplitude in PCA ($F(2,32) = 16.42$, $p < .001$), ALA ($F(2,32) = 10.84$, $p < .001$), and SI ($F(2,32) = 35.35$, $p < .001$), but not in PMSA.

For the IC-IS condition, there was a significant effect of cooling on AEP amplitude in PCA ($F(2,28) = 4.98$, $p < .05$) and ALA ($F(2,26) = 6.95$, $p < .01$) but not in SI or PMSA.

For the CC-CS condition there was a significant effect of cooling on AEP amplitude in PCA ($F(2,24) = 5.06$, $p < .05$) but not in ALA, SI, or PMSA.

For the CC-IS condition, there was a significant effect of cooling on AEP amplitude in PCA ($F(2,28) = 7.58$, $p < .01$), ALA ($F(2,26) = 8.63$, $p < .005$) and SI ($F(2,28) = 9.91$, $p < .001$) but not in PMSA. Table 4 summarizes in tabular form the results of the analyses of variance performed on Cooling Conditions 2 through 6.

Newman-Keuls tests were run on those analyses of variance which showed a statistically significant F value. In all cases, both pre-cool and post-cool AEP amplitudes were significantly different from the cool amplitudes while the pre-cool and post-cool amplitudes were not significantly different from each other.

In order to estimate the percent of the variance in the dependent

Table 4: Summary of results of analyses of variance performed on Cooling Conditions 2 through 6.

Cooling Conditions	Cortical Areas PCA	ALA	SI	PMSA
BC-CS	S	S	S	S
IC-CS	S	S	S	NS
IC-IS	S	S	NS	NS
CC-CS	S	NS	NS	NS
CC-IS	S	S	S	NS

S = significant
NS = not significant

variable (AEP amplitude) that was accounted for by the independent variable (cooling), the strength of association ($\hat{\omega}^2$) (Linton & Gallo, 1975) between the dependent and independent variable was computed for each of the comparisons in Figure 12 that showed a significant effect of cooling. According to Linton and Gallo (1975), the strength of association measure indicates how strong the relationship is between the dependent and independent variables. That is, an ω^2 of .90 indicates that 90% of the variance in the dependent variable is accounted for by the variance in the independent variable, while an ω^2 of .10 indicates that only 10% of the variance in the dependent variable is accounted for by the independent variable (a related measure is the coefficient of determination used in correlation analyses, obtained by squaring r). Thus, by computing ω^2 for a series of analyses of variance, all of which showed statistically significant effects, one can determine if a particular analysis of variance indicates a stronger relationship between the independent and dependent variables than the other analyses of variance.

Table 5 summarizes the results of the strength of association analysis, conducted for the present experiment. In comparing a particular cortical area across the different cooling conditions, it can be seen that the BC-CS and IC-CS conditions had larger ω^2 values than the IC-IS, CC-IS, or CC-CS conditions. This would indicate that there was a stronger relationship between cooling VPL and reduction in peak amplitude for the BC-CS and IC-CS conditions than for the IC-IS, CC-IS, and CC-CS groups.

Table 5: Strength of Association Analysis

Cooling Condition	PCA	ALA	S1	PMSA
BC-CS	.454	.559	.564	.323
IC-CS	.468	.374	.663	X
IC-IS	.204	.291	X	X
CC-CS	.231	X	X	X
CC-IS	.298	.345	.365	X

A series of one-way analyses of variance (fixed factor design, repeated measures) was performed, based on the % change scores, analyzing the differential effect of Cooling Conditions 2 through 6 in each of the four cortical areas. There was no significant difference in % change in AEP amplitude across the different cooling conditions (2 through 6) in PCA, ALA, or PMSA. In S1, there was a significant difference in % change in AEP amplitude across Cooling Conditions 2 through 6 ($F(4,44) = 10.37$, $p < .001$).

Table 6 summarizes the results of the Newman-Keuls tests performed on the individual comparisons for cortical area S1. Only three conditions (BC-CS, IC-CS, and CC-IS) showed a significant effect of cooling on peak-to-peak amplitude so only three comparisons were possible. Both conditions in which the primary lemniscal pathway was blocked (BC-CS and IC-CS) showed significantly greater reduction in peak-to-peak amplitude than the CC-IS group (which was the only condition in which the primary lemniscal pathway was not blocked but which still showed a significant effect of cooling). This is another indication that the cryoprobe system was specifically blocking the primary lemniscal pathway since the IC-IS and CC-CS groups did not show an effect of cooling on peak-to-peak amplitude and while the CC-IS condition did show a significant cooling effect, this effect was significantly less than the effect seen when the primary lemniscal pathway was blocked (in BC-CS and IC-CS conditions).

Figure 13 indicates the mean latency to those peaks (one for each AEP) which were analyzed for amplitude changes in Figure 12. Although Figure 13 shows the mean latency to all peaks analyzed and graphed in

Table 6: Newman-Keuls test comparisons for cortical area S1

	CC-CS	IC-CS	BC-CS	CC-IS	IC-IS
CC_CS		X	X	X	X
IC-CS			0.67	47.58**	X
BC-CS				46.91**	X
CC-IS					X
IC-IS					

** $p < .01$

X: comparison not possible since one of pair did not show a significant effect of cooling on peak-to-peak amplitude (see Table 3).

Figure 13. Summary of latency data from peak-to-peak analysis for Cooling Conditions 2 through 6 (see Table 1).

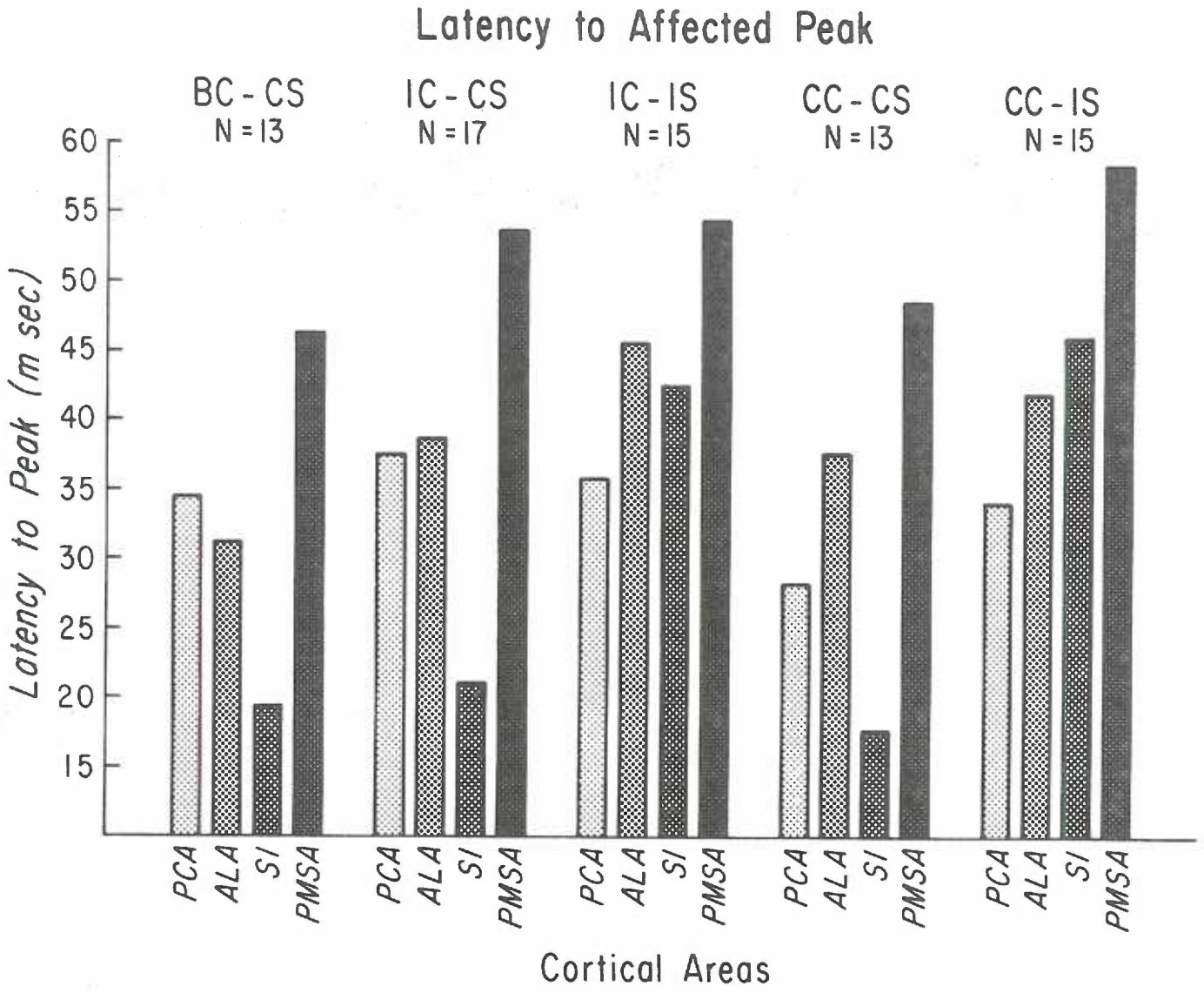

Latency to Affected Peak
BC - CS
N = 13
IC - CS
N = 17
IC - IS
N = 15
CC - CS
N = 13
CC - IS
N = 15
Latency to Peak (m sec)
60
55
50
45
40
35
30
25
20
15
PCA
ALA
SI
PMSA
Cortical Areas

Figure 12, only those cortical areas which showed a significant effect of cooling on AEP amplitude were tested for the significance of latency differences.

A series of one-way analyses of variance (repeated measures, fixed factor design) were performed to test the significance of differences in latencies to the maximally affected peaks in each of the four cortical areas. There was no significant difference in latency to the affected peak, across Cooling Conditions 2 through 6 in PCA or PMSA. However, there was a significant difference in latency to the affected peak across Cooling Conditions 2 through 6 in ALA ($F(4,44) = 2.88$, $p < .05$) and S1 ($F(4,44) = 15.64$, $p < .001$).

Individual comparisons made using the Newman-Keuls test revealed that in ALA there was a significant difference in latency to the affected peaks only between the IC-IS group and the BC-CS group ($p < .05$). In S1, there was a significant difference in latency to the affected peak only between the CC-IS group and both the IC-CS group and the BC-CS group ($p < .01$). In considering the results of the Newman-Keuls tests and in examining Figure 13, it should be remembered that comparisons of latency differences were made only between those conditions which had shown a significant effect of cooling on peak-to-peak amplitude.

In summary, the data analyzed in Figures 12 and 13 demonstrated that AEPs elicited by the paw stimulus recorded in the cortical association areas could be affected by blockade of "secondary" pathways. That is, in the BC-CS and IC-CS groups, the major lemniscal pathway (posterior columns of spinal cord, synapsing in the gracile and cuneate nuclei,

crossing and ascending in the medial lemniscus, synapsing in the Vb complex) was blocked, with the result that 7 of 8 cortical areas showed significant cooling effects. In the other groups (IC-IS, CC-IS, CC-CS) the major lemniscal pathway was not blocked, however 6 of 12 cortical areas showed significant cooling effects. The strength of association analysis demonstrated that cooling VPL in the IC-IS, CC-IS, and CC-CS conditions accounted, in general, for less of the total difference between pre-cool and cool conditions than the BC-CS and IC-CS groups. That is, the relationship between cooling and reduction in peak amplitude, although statistically significant, is not as strong for the IC-IS, CC-IS, and CC-CS groups as it is for the BC-CS or IC-CS groups. However, the fact that there were statistically significant cooling effects in those groups in which the major lemniscal pathway was not blocked, indicates that VPL probably does <u>not</u> affect activity in the cortical association areas in the same way as it does in SI.

The major thalamic sites cooled in each of the non-VPL group animals is indicated in Table 7. As can be seen from this table, there was no non-VPL site consistently cooled in this group and therefore it was felt that grouped analysis of such data could not be meaningfully interpreted. Therefore, these data were not included as a single group in the data analysis.

Nucleus lateralis posterior (LP) was the principal thalamic site cooled in 4 of the non-VPL group animals (cats # 32, 41, 44, 46). Data from these particular subjects were grouped and statistical analyses performed (one-way analysis of variance, repeated measures, fixed factor

Table 7: Principal subcortical sites cooled for non-VPL group

Cat #	Thalamic Site
32 (LP run)	internal capsule, nuc. lateralis posterior
33 (LP run)	nuc. ventralis anterior
41 (LP run)	nuc. lateralis posterior
44 (LP run)	nuc. ventralis anterior, nuc. lateralis posterior, nuc. reticularis, internal capsule
46 (LP run)	nuc. ventralis anterior, nuc. lateralis posterior, nuc. reticularis, internal capsule
42 (VPL run)	internal capsule
48 (VPL run)	internal capsule
50 (VPL run)	internal capsule
54 (VPL run)	globus pallidus, nuc. reticularis
57 (VPL run)	amygdala, globus pallidus
61 (VPL run)	nuc. caudatus

design) on the change in peak-to-peak amplitude (from pre-cool to cool to post-cool) of the AEPs elicited by paw, click, and light stimuli. For the paw stimulus, there was a significant effect of cooling on AEP amplitude in PMSA ($F(2,6) = 8.41$, $p < .05$) but not in PCA, ALA or S1. For the click stimulus, there was a significant effect of cooling on AEP amplitude in PCA ($F(2,6) = 5.70$, $p < .05$) but not in ALA, S1, or PMSA. There was no significant effect of cooling on AEP amplitude in response to the light stimulus in PCA or PMSA (no recordable responses in ALA or S1). Care must be taken in interpreting these results because of the extremely small sample size, but the data do indicate that spread of cooling to LP from VPL probably did not account for the cooling effects observed in the BC-VPL group.

Correlation Analyses

Figure 14 presents the results of the trial-by-trial correlation analysis. Each point represents the mean of 11 individual correlation coefficients. The relatively low correlation values indicate that AEP magnitude does not fluctuate synchronously in the cortical areas examined. This finding does not support the hypothesis of Thompson, Johnson, and Hoopes (1963) that a common thalamic projection system is responsible for activity in the cortical association areas.

Figure 15 presents the results of the cortical-pair correlation analysis, while Figure 16 presents the results of the stimulus-pair correlation analysis (see Methods - Data Analysis section for full description of the correlation analyses). A number of points can be briefly summarized from the data in these two figures: (1) the magnitude of

Figure 14. Summary of trial-by-trial correlation analysis. Some data for light stimulus missing due to lack of recordable responses in S1 and ALA.

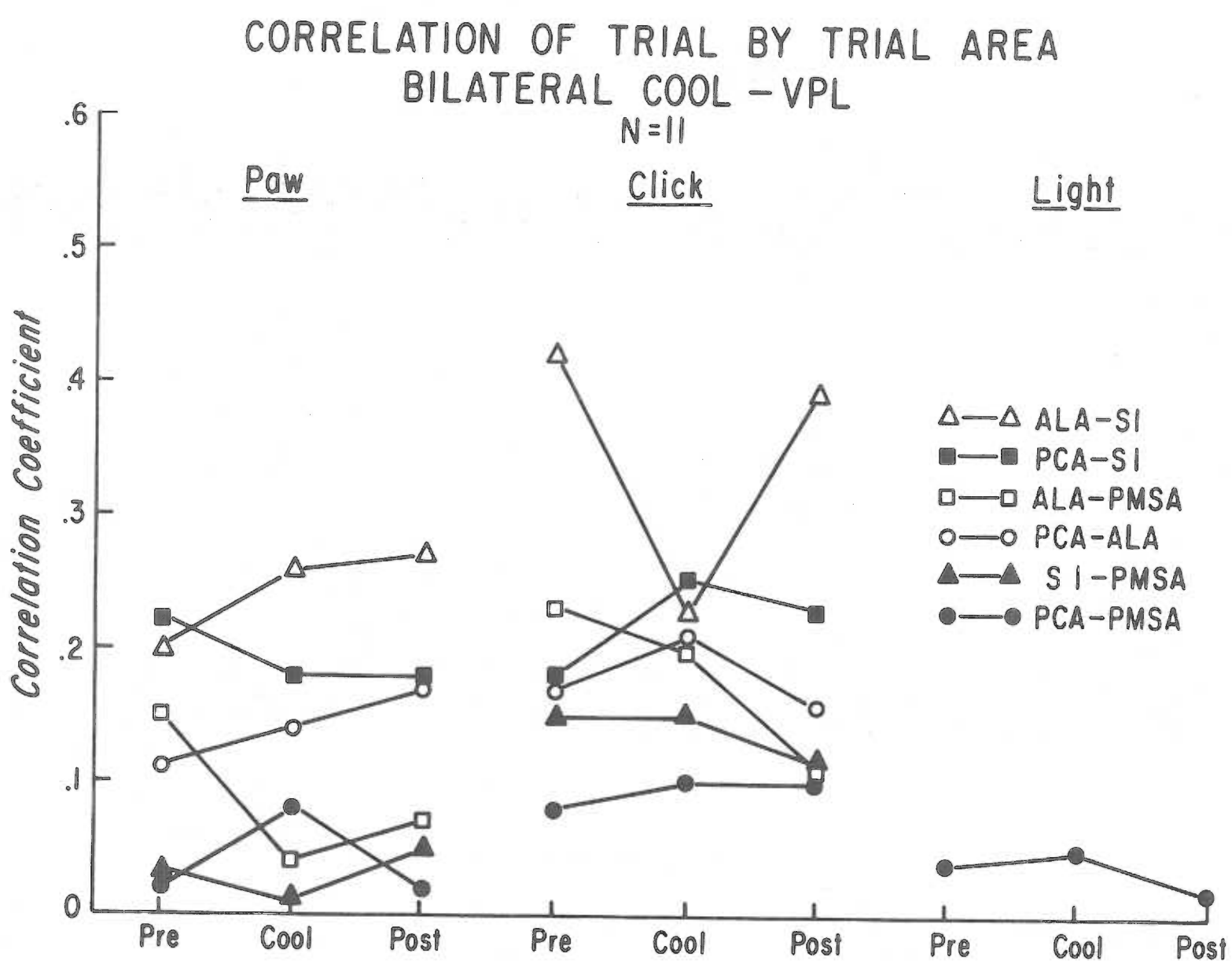

CORRELATION OF TRIAL BY TRIAL AREA
BILATERAL COOL – VPL
N=11
Paw
Click
Light
Correlation Coefficient
.6
.5
.4
.3
.2
.1
0
Pre
Cool
Post
Pre
Cool
Post
Pre
Cool
Post
ALA-SI
PCA-SI
ALA-PMSA
PCA-ALA
SI-PMSA
PCA-PMSA

Figure 15. Summary of cortical-pair correlation analysis. Some data for light stimulus missing due to lack of recordable responses in S1 and ALA.

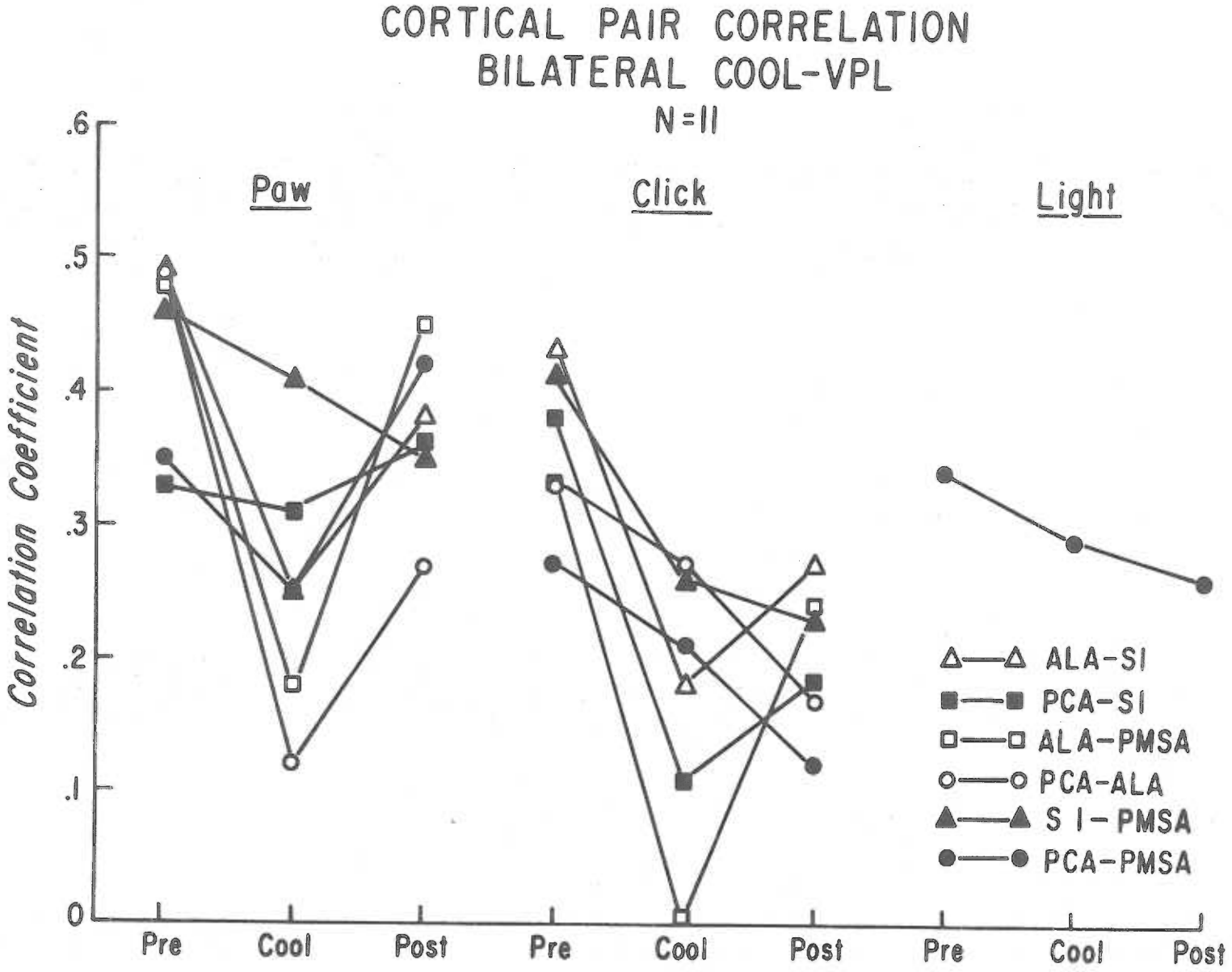
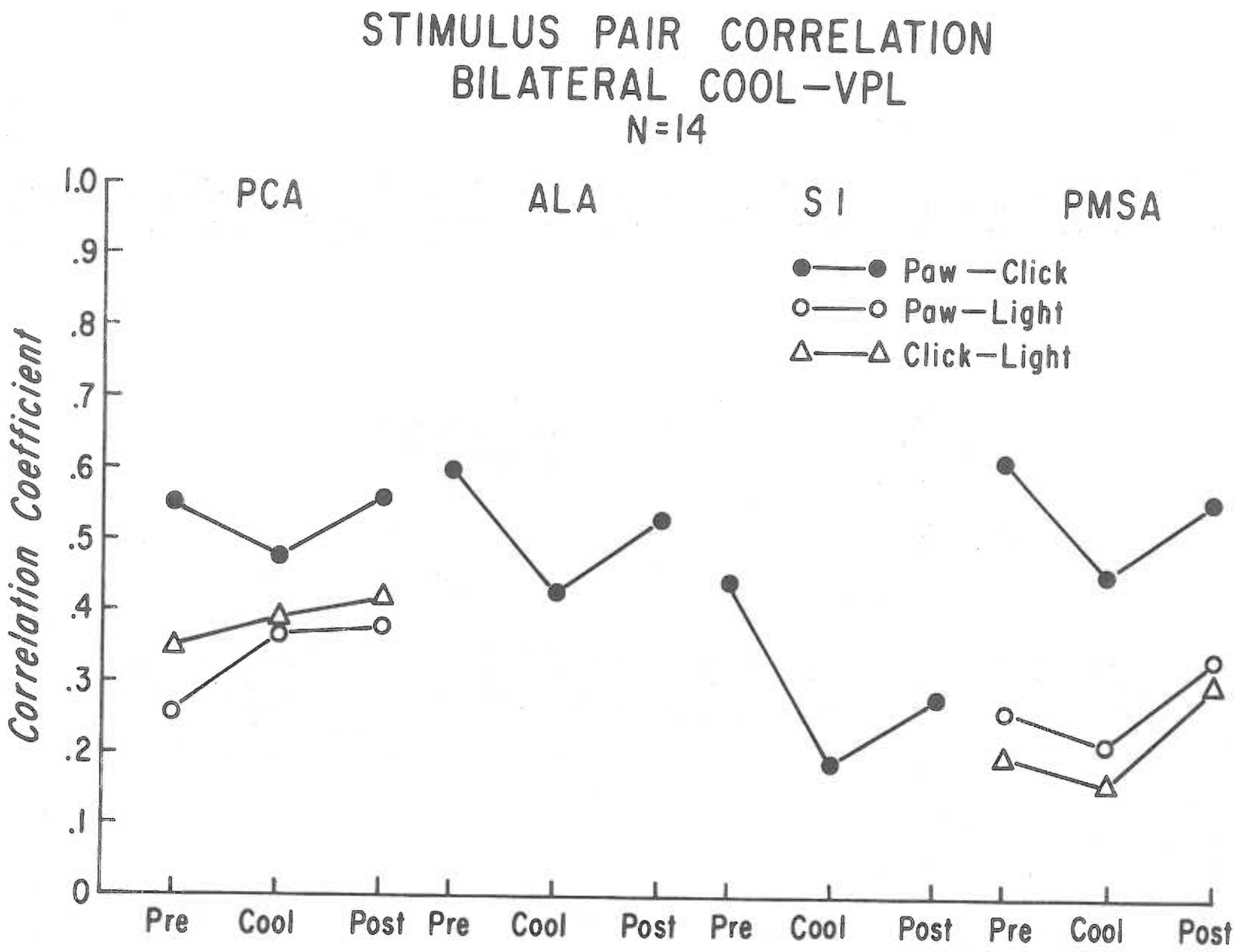

CORTICAL PAIR CORRELATION
BILATERAL COOL-VPL
N=11
Paw
Click
Light
Correlation Coefficient
.6
.5
.4
.3
.2
.1
0
Pre
Cool
Post
Pre
Cool
Post
Pre
Cool
Post
ALA-SI
PCA-SI
ALA-PMSA
PCA-ALA
S I - PMSA
PCA-PMSA

Figure 16. Summary of stimulus-pair correlation analysis. Some data for light stimulus missing due to lack of recordable responses in S1 and ALA.


STIMULUS PAIR CORRELATION
BILATERAL COOL–VPL
N=14
PCA
ALA
S I
PMSA
Paw — Click
Paw — Light
Click — Light
Correlation Coefficient
1.0
.9
.8
.7
.6
.5
.4
.3
.2
.1
0
Pre
Cool
Post
Pre
Cool
Post
Pre
Cool
Post
Pre
Cool
Post

the correlation values is about the same for either the stimulus-pair or cortical-pair analyses; (2) cooling of VPL does not decrease waveform similarity for responses to two stimuli recorded in the same cortical area (stimulus-pair analysis); (3) cooling of VPL usually does decrease waveform similarity for responses to the same stimulus, recorded in two cortical areas (cortical-pair analysis).

Discussion

Physiology of Cooling Effect

Some discussion of the physiological basis of the effect of neural cooling is necessary in order to understand the observed effect of thalamic cooling on cortical evoked potentials. Hodgkin and Katz (1949) studied the effect of temperature changes on the resting membrane potential and the action potential of the giant axon of the squid. While care must be taken in applying results based on a poikilothermic animal (squid) to a homoiothermic one (cat), the findings of Hodgkin and Katz (1949) still have relevance for gaining an understanding of the physiological basis of the effect of neural cooling.

They found that varying the temperature over the range of 5° - 20°C of a solution which bathed an isolated squid giant axon produced relatively little effect on the amplitude of the action potential. The amplitude of the resting potential showed an average decrease of 0.5 mV (from 20° to 5°C), while the amplitude of the action potential showed an average decrease of 5 mV over the same temperature range. The most substantial effect of cooling that they found was exerted on the duration of the rising and falling phase of the peaks of the action potential. They found that the Q_{10}s varied from 2.07 to 2.70 over the range of 5° - 20°C for the rising phase of the action potential. For the falling phase, the Q_{10}s varied from 3.3 to 5.3 over the same temperature range.

Katz and Miledi (1965) examined the effect of a decrease in temperature upon the synaptic delay at the frog neuromuscular junction. They

found that between 19° and 2°C there was an increase in the synaptic delay with an average Q_{10} of 3.14. They attributed the increased delay to an effect of temperature on the release of Ach after arrival of the nerve impulse as opposed to a possible effect on diffusion across the synapse or an effect on the receptor-Ach interaction.

Jasper, Shacter, and Montplaisir (1970) studied the effect of local cortical cooling on evoked activity in the cerebral cortex of cats. In particular, for somatic evoked potentials recorded in S1, they found that peak latencies increased with decreasing temperature with an average Q_{10} of 1.4. Peak amplitude decreased with decreasing temperature with an average Q_{10} of 2.0.

It would appear that cooling affects both synaptic and axonal processes in neurotransmission. The question as to which factors underlie the observed effects of cooling on gross evoked activity is a more complicated question. In comparing the results of Hodgkin and Katz (1949) and Katz and Miledi (1965) with those of Jasper, Shacter, and Montplaisir (1970), there does not appear to be a direct correspondence between the effect of cooling on axonal conduction and the observed increase in latency of peaks in the cortical evoked potential, based on the Q_{10}s obtained for each process. Similarly, the Q_{10}s obtained for the effect of cooling on synaptic processes and the effect on peak amplitude of cortical evoked potentials do not correspond. Since in the present study a particular nucleus was cooled, the observed effects would appear to be due primarily to effects on synaptic processes. According to Katz and Miledi (1965), transmitter release would appear

to be the synaptic process most likely to be affected by cooling.

Additional evidence that, with the cooling temperatures used in the present experiment, only synaptic processes were affected, comes from the work of Benita and Conde (1972). They studied cooling effects along the dentato-rubro-thalamic pathway in cats. Anterior to the red nucleus, they were able to record two types of responses elicited by contralateral dentate stimulation. The responses were distinguishable on the basis of their ability to follow high frequency stimulation of the contralateral dentate nucleus (the first response could, the second could not follow high frequency stimulation). This would indicate that the first response was an asynaptic fiber response while the second response had at least one synapse intervening between the stimulation and recording sites. They found that, with a cryoprobe inserted into the red nucleus, temperatures of approximately -10°C were necessary to completely block the first response (as well as the second) while temperatures as high as 15°C in some cases were able to block the second response alone. They interpreted their data as indicating that fibers of passage required a much lower temperature to achieve a block of activity than synaptic processes. Considering the average tip temperature of the cryoprobes used in the present study. it would seem likely that synaptic processes only were affected.

Generation of Association Response

These considerations raise the more general question concerning the underlying factors giving rise to evoked activity recorded in the present study. Some workers (e.g. Goldring, Sheptak, & Karahashi, 1967)

have questioned whether association responses are due to local or more distant generation. The use of bipolar electrodes in the present study would appear to limit the possibility of volume conduction from distant generators playing a significant role.

In addition, the results of Thompson et al. (1969) comparing the averaged evoked potential and the unit poststimulus histogram support the notion of local generation of the association response. Further, Thompson, Johnson, and Hoopes (1963) found a similarity in the change in amplitude of the evoked response, with increasing cortical depth, for primary and association responses (i.e., both showed an inversion of the response at approximately the same depth). Landau (1967) stated that only the demonstration of response reversal across a cell layer demonstrates that an evoked response is not a distant, volume conducted phenomenon.

Thus, taking all these factors into consideration, it would appear to be unlikely that the responses recorded in the present study were due to volume conduction from distant generation sites.

Drug Effects

Some questions could be raised concerning the possible influences of specific drugs used in the present experiment. While the use of the pre-cool control, cool, and post-cool control design provided a rigorous within-subject check on possible drug effects, consideration of the influence of the principal drugs used in the present study (i.e., halothane and gallamine triethiodide) is useful.

Duncan and Kaventos (1959) studied the rate of absorption and elim-

ination of halothane in mice. They found that total halothane in mice decreased exponentially with a half-clearance rate of about 30 minutes (compared with a half-clearance rate of 100 minutes for ether). If one supposes no significant interspecies differences in half-clearance rates, one can calculate that when data collection began in the present study, approximately 94% of the halothane absorbed by the animal was eliminated.

With regard to the specific effects of the anesthetic on the CNS, Davis, Quitmeyer, and Collins (1961) studied the effect of halothane on evoked potentials recorded in VPL and the midbrain reticular formation in response to stimulation of the radial nerve. They found that halothane depressed the amplitude of the evoked potentials in a dose-dependent manner, with rapid recovery of amplitude following cessation of administration of halothane.

There is not complete agreement with regard to the possible effects of gallamine triethiodide on the CNS. Davis, Collins, and Rondt (1958) reported that infusion of gallamine triethiodide had no effect on evoked responses recorded in VPL or the reticular formation. In contrast, Halpern and Black (1968) reported that intravenous administration of gallamine triethiodide produced an augmentation of cortical afterdischarge. Koelle (1975) however felt that gallamine triethiodide and other quaternary ammonium neuromuscular blocking agents should produce minimal CNS effects due to their inability to effectively penetrate the blood-brain barrier.

Cooling Effects on Association Responses

The results of this experiment present a complicated picture of the

effect of cooling VPL upon cortical evoked responses in association areas. One issue of fundamental importance is whether the responses recorded were indeed association responses (type II NPRs). Several steps were taken to assure that this was the case in the present study. First, the cortical locations selected for recording in the present experiment were based primarily on the evoked response maps from Thompson, Johnson, and Hoopes (1963). Secondly, in two cats, evoked response maps were determined for the middle suprasylvian gyrus. Figure 5 shows the results for one such mapping study. It can be seen from inspection of the figure that there are apparently two fairly discrete areas on the middle suprasylvian gyrus where it was possible to record AEPs in response to paw, click, and light stimuli. These two areas would seem to coincide with areas AMSA and PMSA as described by Thompson, Johnson, and Hoopes (1963).

A third check on whether or not type II NPRs were being recorded was the comparison of AEPs from S1 and the three association areas. For example, Figures 8 and 9 show respectively AEPs collected from S1 and ALA in response to the paw stimulus. It can easily be seen that the AEPs in S1 show the short latency activity characteristic of a primary response while the AEPs in ALA are dominated by a longer latency waveform.

A final check on whether association responses were present was simply the ability to record responses to all three modalities from the same electrode site. This provided an immediate check on whether the electrode was in an association area. There is no ready explanation

for the lack of response to the light stimulus in ALA. The polysensory nature of ALA has been well documented by previous workers (e.g. Thompson, Johnson, and Hoopes, 1963; Buser and Bignall, 1967). The fact that AEPs elicited by light stimuli were recorded in both PCA and PMSA indicated that the light stimulation apparatus was functioning properly and the visual pathways were intact. Since responses to both click and paw stimuli were obtained in ALA it was felt that the electrode placement used in the present experiment was in an association area.

Returning to the main question of the effect of cooling, it would seem that theoretically, if the cooling blockade had been restricted exclusively to synapses within VPL then one would have predicted no cooling effects on the AEPs elicited by click and light stimuli. Obviously, from inspection of Figures 6 and 10, this was not the case in the present experiment. Although statistical tests performed on data presented in Figure 10 showed no significant cooling effects on the AEPs elicited by the light stimulus in any area, there were significant cooling effects on selected components of AEPs elicited by the click stimulus in both ALA and S1.

This raises several possible questions concerning the interpretation of all data in this experiment. First, there is the question of response specificity in S1, i.e., the appearance of AEPs elicited by click stimuli in a primary somatosensory area. Based on results of Thompson, Johnson, and Hoopes (1963) and Buser and Imbert (1961) there appears to be a great deal of overlap in the pericruciate area between polysensory areas and the primary somatosensory area. In fact, Thomp-

son, Johnson, and Hoopes (1963) found that the hindlimb projection area for SI overlapped a portion of the postcruciate association area. It is therefore likely that the recording of AEPs elicited by click stimuli in the present study was due to overlap of association and primary response fields.

The second question raised by Figure 6, and in particular, Figure 10, concerns the specificity of the cooling effects. If there were complete nonspecificity in the effect of cooling then it would not be possible to make any inferences concerning the contribution of VPL to cortical association responses. However, the data in Figures 10 and 11 do reveal some response specificity with regards to the cooling effects.

First, there is the fact that AEPs elicited by the paw stimulus showed significant cooling effects in all areas while there were no significant cooling effects in any area in response to light and only 2 of 4 areas showed a significant effect of cooling in response to the click stimulus. Secondly, with regard to the two areas which showed significant cooling effects in response to the click stimulus, it is possible to clearly differentiate between the click and the paw stimulus cooling effects. Thus, in ALA, although AEPs elicited both by click and paw stimuli showed cooling effects, there was a significantly greater decrease in AEP amplitude for the AEPs elicited by the paw vs the click stimuli during cooling. Also, in SI, examination of the latency to the maximally affected peak revealed that the affected peak for the AEPs elicited by the paw stimulus had a significantly shorter latency than the maximally affected peak for the AEPs elicited by the click stimulus.

Further evidence that VPL was indeed blocked comes from the fact that the maximally affected peak for the AEP elicited by the paw stimulus in S1 had an extremely short latency (significantly shorter than affected peaks for the paw stimulus in all other areas). The initial short latency activity in S1 is due to direct relay through VPL. However, this in no way proves that cooling effects in association areas are due to the blockade of VPL. They could be attributed to a spread of cooling to adjacent thalamic structures.

Thus, based on a combination of the above findings, it appears that there was some specificity in the type of cooling effects observed. For the AEPs elicited by the click stimulus, the cooling effects are an index of the degree to which non-VPL structures were affected by the cooling. Effects on the AEPs elicited by the paw stimulus are due to a combination of cooling VPL and non-VPL structures. From the known dimensions of the 20°C isotherm produced by a functioning cryoprobe, nucleus reticularis and nucleus lateralis posterior of the thalamus were the non-VPL thalamic structures most probably affected by the cooling.

Since only 2 of 4 areas showed significant cooling effects for AEPs elicited by the click stimulus and there were no significant cooling effects for AEPs elicited by the light stimulus, it would seem possible that the non-specific effects observed in the present experiment were not that strong and therefore were not significant contributors to the overall cooling effect for the paw stimulus. However, if the area surrounding VPL which was affected by cooling normally was predominated by somatic representation, then this also could account for the speci-

ficity observed in the cooling effects.

Huang and Lindsley (1973) mapped evoked responses to auditory, visual, and somatic stimuli in pulvinar and nucleus lateralis posterior (LP) and found a regional distribution of responsiveness for the different modalities. Evoked activity in response to the paw stimulus was concentrated in those regions of pulvinar and LP which were near VPL while visual and auditory evoked activity were concentrated in more posterior regions of pulvinar and LP. These data would appear to support the hypothesis that a non-VPL structure could account for the modality specific effects observed in the present study. However, in the four non-VPL group animals in which LP was specifically cooled in the region of predominant somatic representation, only one of four cortical areas showed a significant effect of cooling on AEP amplitude in response to the paw stimulus. This would support the notion that the cooling effects observed on peak amplitude of AEPs elicited by the paw stimulus are due to blockade of VPL and not other thalamic structures.

Inspection of Figure 6 does indicate that there were extensive non-specific cooling effects but the t-score analysis was not intended to measure the statistical significance of the cooling effects but rather to provide an overall picture of the pattern of effects. The peak-to-peak analysis was a more powerful measure in that it was designed to provide a means of testing the statistical significance of effects of cooling on selected components of the AEP.

In summary, analysis of AEPs from the BC-VPL group in Figures 10 and 11 demonstrated that cooling in the region of VPL had a significant

effect on selected components of AEPs elicited by the paw stimulus in all cortical areas examined, primary (S1) and nonprimary (PCA, ALA, PMSA). However, the peak maximally affected by cooling in the region of VPL in S1 had a significantly shorter latency than the peaks affected in PCA, ALA, or PMSA. These findings bear directly on the main question posed in this thesis: Does VPL contribute significantly to the early components of the waveform of the association AEP? Based on all of the above data, it does not appear possible to definitively answer this question.

Several alternatives appear plausible. First, since there was a difference in latency to the peak maximally affected between S1 and the association areas, it does not seem likely that there is a direct fiber system from VPL to the association areas of a nature similar to that existing between VPL and S1. However, a system of small diameter, unmyelinated fibers from VPL to association areas (similar to the system proposed by Bignall [1967a] for the projection from the lateral geniculate to the association areas) could account for the results obtained in the present study.

Alternatively, VPL could project to other thalamic areas (e.g. the posterolateral association nuclei: pulvinar and LP) and from there project to the association cortex. The results of this study do not support this possibility since specific cooling of LP resulted in significant effects on AEP amplitude in only 1 of 4 cortical areas analyzed for the paw stimulus. If VPL did project to LP and from there to association cortex, then the pattern of cooling effects observed when LP was cooled

should have been similar to that noted when VPL was cooled. It should be emphasized that because of the small sample size on which the analysis of the effects of blockade of LP was based, the results of this analysis should not be weighted too strongly.

Cooling Conditions 2 through 6 were run in order to determine if there was more than one means by which VPL could influence components of the cortical association response. However, interpretation of these results are open to the same question regarding specificity of cooling as was discussed for Cooling Condition 1. In the IC-CS condition and the BC-CS condition, cooling resulted in a blockade of the main pathway for input of somatosensory information to VPL and then to S1. In the other cooling conditions (IC-IS, CC-CS, and CC-IS) this main pathway was not blocked.

Statistical analyses performed on the data presented in Figure 12 indicated that during blockade of the main projection system (BC-CS, IC-CS), a total of 7 of 8 cortical areas showed a significant reduction in peak amplitude. During the other cooling conditions, there was a mixture of significant and nonsignificant results, with a total of 6 out of 12 areas showing a significant reduction in peak amplitude. In S1 for the IC-IS and CC-CS conditions, there was no significant decrease in peak amplitude, while in the CC-IS condition there was a decrease in peak amplitude in S1, but the latency to this affected peak was significantly longer than that seen with the primary pathway (in BC-CS and IC-CS) blocked.

Despite the lack of effect on the early components of the primary

response in the IC-IS, CC-CS and CC-IS conditions, there were significant decreases in peak amplitude in association areas in several instances. This finding raises the possibility that VPL modulates activity in the association cortex by several different mechanisms.

The findings of the present study with regard to the possible role of VPL in the early components of the association response raise further questions with regard to Thompson, Johnson, and Hoopes' (1963) hypothesis concerning the role of thalamic nuclei in generating cortical association responses. They postulated that a common central association system (mainly midline thalamic nuclei) projected in an equivalent and undifferentiated manner to cortical association areas. However, the findings of the present study suggest that non-midline thalamic structures (whether VPL or others) do contribute significantly to early components of the association response.

Further evidence that the association system isn't as simple as envisioned by Thompson, Johnson, and Hoopes (1963) is provided by the analyses illustrated in Figures 14, 15, and 16. Based on Thompson, Johnson, and Hoopes' (1963) hypothesis of a common projection system to all association areas, one would predict that there would be a high correlation in terms of evoked activity between different association areas, since presumably, all activity in all association areas is due to a common generator.

Clearly, the data in Figure 14 do not support this hypothesis. Correlations of fluctuation in total area under the evoked potential curve were extremely low, indicating that association areas are rela-

tively independent of each other. Cooling of VPL resulted in neither a consistent increase nor decrease in the correlation coefficient, indicating that VPL itself does not play a major role as a synchronizer or desynchronizer of excitability in different association areas.

Figure 15 summarizes the results of the cortical-pair correlation. Recall that this analysis is based on the correlation of waveform similarity between two given cortical areas for a particular stimulus modality (in Figure 15, the correlations are based on the AEP waveform, while in Figure 14 the correlations are based on the total area under each individual evoked potential [total of 100] that composed the AEP - see Methods for further details). The correlations are, in general, higher than those seen in Figure 14, but inspection of the paw data, for example, shows that the pre-cool correlation of waveform similarity between two association areas (e.g., PCA-ALA) is no different than the correlation of similarity between an association area and a primary area (e.g., ALA-SI). Based on Thompson, Johnson, and Hoopes' (1963) hypothesis, one would have predicted that an association area would show less similarity in waveform compared with a primary area as opposed to a second association area. During the cool condition, there was a fairly consistent drop in the correlation coefficients, compared with the pre-cool condition, across all three stimulus modalities. This would appear to indicate that the effect of cooling was in part, to block a portion of the system which contributes to the similarity of the waveforms.

Figure 16 summarizes the results of the stimulus-pair correlation

analysis which compared the degree of waveform similarity between AEPs derived from two different stimulus modalities in the same cortical area. In the pre-cool condition, the correlations are uniformly low. Again, this conflicts with the correlation analyses performed by Thompson, Johnson, and Hoopes (1963) which indicated that there was a great deal of similarity between association responses derived from two different modalities in any given cortical association area. During the cool condition, there was no consistent effect on the size of the correlation coefficient.

Thus, the data in this paper indicate that the association cortex is more complexly organized than was originally thought by early workers. While midline thalamic nuclei do contribute to the generation of evoked responses in cortical association areas, more lateral thalamic structures apparently also modulate activity in these areas. It would seem that the cortical association areas are not merely separate projection zones for the same activity, but highly differentiated areas which do not exhibit a great deal of similarity among themselves. This suggests the possibility that functional differences among the various association areas underlie the observed differences in the characteristics of the AEP waveform.

Summary and Conclusions

The contribution of VPL to gross evoked activity in the association cortex of the cat was investigated. Averaged evoked potentials (AEPs) were collected in response to paw, click, and light stimuli, in association areas PCA, ALA, and PMSA and in primary sensory area S1. Activity in VPL was reversibly blocked using a cryoprobe system to produce localized cooling of neural tissue. The effect of this blockade on the amplitude and waveform of the AEPs was determined.

Reduction in amplitude of the short latency components of the AEP in S1 in response to the paw stimulus was an indication that VPL was indeed blocked. However, reduction in amplitude of certain components of AEPs elicited by the click stimulus was an indication that the blockade produced by the cryoprobe system was not completely confined to VPL. The fact that only 2 of 4 cortical areas showed cooling effects on AEPs elicited by the click stimulus and no cortical area showed cooling effects on AEPs elicited by the light stimulus was an indication that the blockade was restricted primarily to a somatic specific area.

It was not possible in the present experiment to positively determine if VPL was responsible for the somatic-specific effects. Areas adjacent to VPL (e.g., the lateral posterior nucleus) could have accounted for the effects observed. However, specific cooling of the lateral posterior nucleus did not produce strong effects on AEP amplitude. Thus, although other interpretations of the results are possible, it seems reasonable to conclude that the cooling effects observed on AEP amplitude were due to blockade of activity in VPL.

The nature of the pathway by which VPL affects activity in the association cortex is another question. The data presented in this study could be interpreted as supporting the concept of a direct fiber projection via a system of small diameter, unmyelinated fibers from VPL to the association cortex. Alternatively, VPL could project to other thalamic nuclei which in turn directly affect activity in association cortex.

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