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STRUCTURE AND CONNECTIONS OF THE CINGULATE VOCALIZATION REGION IN THE RHESUS MONKEY

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INTRODUCTION

Many primate utterances are simple vocalizations that may be associated with brainstem activity and contain limited information about the internal state of the animal. Sequences of tone and amplitude modulated vocalizations which have associative content form the basis for more complex communication within a species. These complex vocalizations are organized at suprabulbar levels, including the cerebral cortex.

In nonhuman primates and cats the anterior cingulate and supplementary motor cortices have been implicated in vocalization. It is not clear at present what the specific role of these cortices is in vocalization. In the human there is the additional contribution of Wernicke's and Broca's areas for the comprehension and production of speech. As will be discussed later, a number of studies support the view that species-specific vocalizations are dependent on auditory association cortices. However, projections of auditory association areas to the cingulate vocalization region have not been analyzed and auditory projections to cingulate cortex may not be necessary to initiate vocalization but rather for modulation of vocal output. Internal states seem to be responsible for emitted sounds in nonhuman primates and thus may be more effective in evoking vocalization. As a major component of the limbic system, cingulate cortex seems to be involved in monitoring internal states. Thus, specific connections among limbic structures associated with

the cingulate vocalization region may have a role in triggering vocalizations associated with emotional states.

The goal of the present chapter is to analyze the corticocortical connections of anterior cingulate cortex which may account for its role in vocalization and communication in primates. This effort will concentrate on the following issues. First, since the vocalization field in cingulate cortex crosses cytoarchitectonic borders, what are the common connections of these areas? Second, in view of the fact that vocalizations in primates are often made in response to noxious stimuli, and in light of evidence that vocalization is modulated by opiate compounds, where does cingulate cortex interface with pathways associated with the pain systems? Third, what are the sources of direct and indirect auditory inputs to the cingulate vocalization region? Fourth, what are the connections of cingulate cortex with the motor system necessary to carry out the act of vocalization? Finally, a qualitative model will be presented which integrates the various cingulate connections that might subserve triggering and modulation of vocalization.

THE CINGULATE VOCALIZATION REGION

Smith (1945) reported that the most prominent response obtained from electrical stimulation of monkey anterior cingulate cortex was vocalization. Although he outlined a broad region of responsive cortex, subsequent electrical stimulation studies by Kaada (1951), Jürgens and Ploog (1970), Jürgens (1976) and Müller-Preuss at al. (1980) suggest a more limited region in rostral cingulate cortex (Fig. 1). Ablation studies support this localization since phonation is severely disrupted when lesions are centered in cortex rostral to the genu of the corpus callosum (Sutton et al., 1974; Aitken, 1981; Fig. 2A). Animals with such lesions have limited spontaneous as well as discriminatively-conditioned vocalizations (Aitken, 1981). Moreover, ablation of anterior cingulate cortex in young monkeys abolishes the characteristic cry emitted when an infant monkey is separated from its mother (MacLean, 1985). In contrast, lesions of lateral neocortical areas appear to have no influence on the production of vocalizations (Fig. 2B).

Precise localization of vocalization areas on the medial surface of the human brain is difficult. Notwithstanding, the following observations appear justified in comparing the role of anterior cingulate cortex in the human to that of other primates in vocalization. First, no vocalization or language disturbances have been reported for cases in which limited lesions were made in area 24 dorsal to the corpus callosum. These include observations made after neurosurgical intervention for relief of intractable pain, drug addiction, or psychiatric disorders (Le Beau, 1952; Tow and Whitty, 1953; Ballantine et al., 1967; Foltz and White, 1968; Kanaka

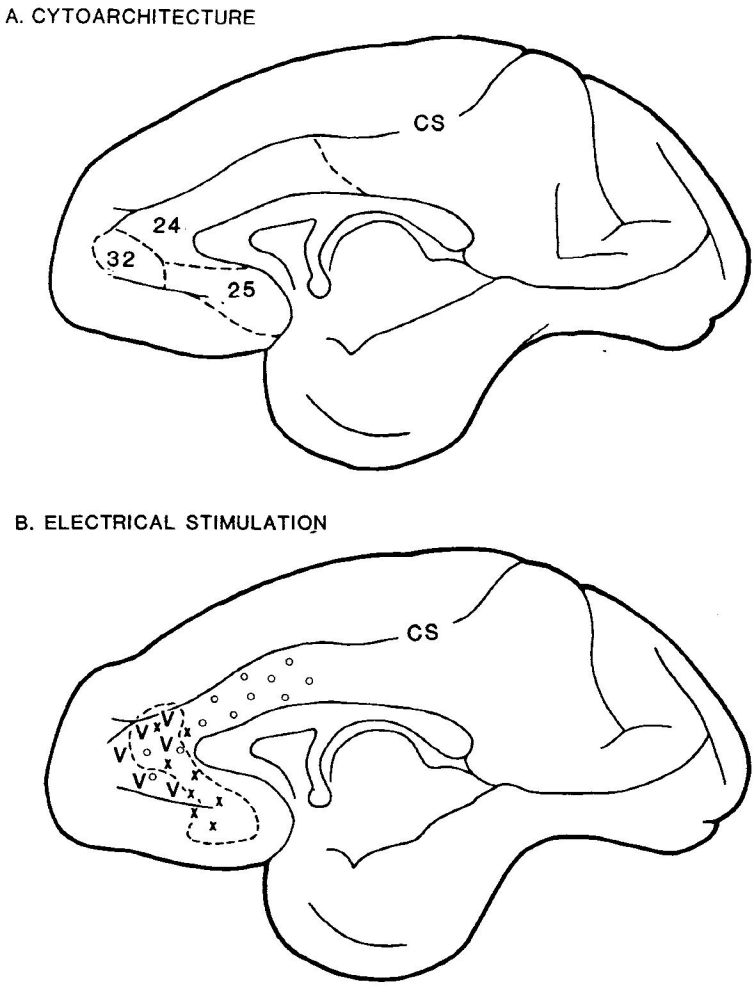

Fig. 1. A. Cytoarchitectural areas in anterior cingulate cortex of the rhesus monkey; B. Composite of points where electrical stimulation has been previously reported to evoke vocalization; CS refers to the cingulate sulcus. Symbols in B refer to the following studies: o, Smith (1945); v, Kaada (1951); dashed line, Jürgens and Ploog (1970); x, Müller-Preuss et al. (1980).

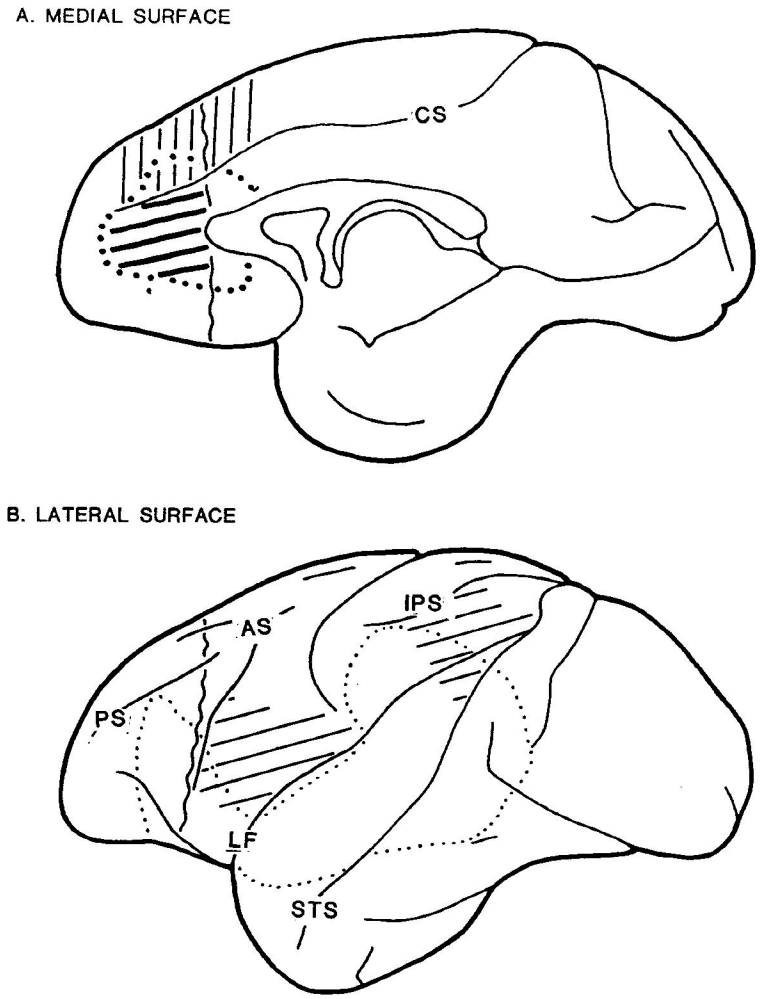

Fig. 2. A. Summary of the extent of ablations that interfered with vocalization as reported in previous studies. These included lesions which affected performance of discriminative calls (Sutton et al., 1974; large dots), those which severely disrupted conditioned and spontaneous vocal behavior (Aitken, 1981; heavy oblique lines), lesions in the supplementary motor area which increased the latency of a vocal response (Sutton et al., 1985; vertical lines), and a prefrontal lobectomy extending to wavy vertical line (Franzen and Myers, 1973), extrapolated from the lateral to the medial surface. B. Ablations of lateral cortical areas which did not affect vocalization as reported by Sutton et al. (1974; area within dotted line) and Aitken (1981; thin oblique lines). AS, arcuate sulcus; IPS, intraparietal sulcus; LF, lateral fissure; PS, principal sulcus; STS, superior temporal sulcus.

and Balasubramaniam, 1978). In addition, Talairach et al. (1973) failed to evoke vocalization with electrical stimulation of caudal area 24. Second, bilateral infarction of anterior cingulate cortex including cortex anterior to the rostrum of the corpus callosum results in akinetic mutism (Nielsen and Jacobs, 1951; Barris and Schuman, 1953) but within 10 weeks speech is restored (Jürgens and von Cramon, 1982). In the latter instance, speech was characterized by monotonous intonation and these authors suggested that anterior cingulate cortex is involved in "volitional control of emotional vocal utterances". Furthermore, infarcts of medial cortex likely involving both cingulate and supplementary motor cortices produce a form of transcortical motor aphasia in which spontaneous conversational speech is disrupted, but repetition, naming, and comprehension are preserved (Rubens, 1975; Goldberg et al., 1981). This differs from monkey cases in which both spontaneous and conditioned vocalizations are disrupted by rostral cingulate lesions.

Observations based on electrical stimulation and ablation of medial cortex in the rhesus monkey (summarized in Figs. 1B and 2A) suggest that the cortex which is critical for vocalization lies around the rostrum of the corpus callosum. Although the cingulate sulcus borders this region dorsally, there are no landmarks that define its rostral and ventral extents. A number of cytoarchitectonic classifications have been made of the primate anterior cingulate region (Brodmann, 1909; von Economo, 1929; Rose, 1927; von Bonin and Bailey, 1947; Vogt et al., 1987). Comparison of these maps with the area which is involved in vocalization indicates that the latter region is structurally heterogeneous. Figure 1A depicts the topography of cytoarchitectonic areas in anterior cingulate cortex. It is evident that vocalization can be evoked from cortex which lies at the confluence of three regions: areas 24, 32, and 25. In light of these observations the following question arises: if vocalization is a function of more than one cytoarchitectonic area, what is the basis for the common function? It is likely that there are connections that are shared by each area which operate to form a functional unit which can be referred to as the cingulate vocalization region.

COMMON CONNECTIONS OF CINGULATE AREAS INVOLVED IN VOCALIZATION

The search for afferent connections that functionally unify areas in the cingulate vocalization region may be guided by the following considerations. Projections from extrinsic sources may be selective for the cingulate vocalization region or a number of larger projection fields could overlap to functionally unify the region. A common output from the cingulate vocalization region could be generated from an overlap by two or more widespread connections. Connections which are particularly dense in the

cingulate vocalization region are of more interest than are light and topographically limited connections. Finally, it should be noted that injections are usually limited in extent in experimental cases and so the observations from selected cases cannot be viewed as necessarily representing an entire connection. Three classes of connections stand out as being particularly important to integrating activity of the cingulate vocalization region: those that interconnect the cingulate vocalization subdivisions; those originating in the amygdala; and those arising from superior temporal cortices. In addition, a final common output of the anterior cingulate areas to the periaqueductal gray may serve to unify the functions of these areas.

Intracingulate Connections

In the rhesus monkey areas 32, 24, and 25 are interconnected as demonstrated in both radiolabeled amino acid and enzyme transport studies (Pandya et al., 1981; Vogt and Pandya, 1987). These connections arise primarily from layer III and layer V pyramidal neurons. The distribution of retrogradely labeled neurons following an area 32 horseradish peroxidase (HRP) injection is presented in Figure 4 in another context; however, it can be seen that both rostral area 24 and area 25 had many labeled neurons. Similar connections have been reported for a part of this region in the squirrel monkey by Jürgens (1983). The intracingulate connections of these pyramidal neurons could serve as the basis for coordinating the output of the three subdivisions of the vocalization region.

Connections with the Amygdala

Electrical stimulation of the amygdala can produce vocalizations (Jürgens and Ploog, 1970). Although these responses could be associated with the reinforcing properties of the stimulus (Jürgens, 1976), evidence is presented in this volume by Lloyd and Kling that the amygdala is involved in coding the "affective content" of conspecific vocalizations. Since cingulate cortex also has been implicated directly in coding of the emotional significance of stimuli (Gabriel et al., 1980), it is likely that the joint action of the cingulate vocalization region and the amygdala is important for the affective component of some vocalizations. The amygdala stands out from other brain regions from a hodological viewpoint because its medial cortical projections seem to be directed primarily to the cingulate vocalization region.

The accessory basal and lateral basal amygdaloid nuclei have strong projections to inner layer I and layer II of cingulate cortex (Porrino et al., 1981; Jürgens, 1983; Amaral and Price, 1984). In addition area 24, at least, projects to the lateral basal nucleus (Pandya et al., 1973). It is important to note that the projection

from the amygdala is one of the clear instances in which the vocalization region is fully included by a major afferent projection (Vogt and Pandya, 1987). Therefore, although the amygdala may not be directly involved in producing vocalization, it may transmit signals to rostral cingulate cortex associated with certain emotional states and thus lower the threshold for eliciting vocalization from anterior cingulate cortex.

Superior Temporal Connections

Projections of temporal cortex will be described in more detail shortly; however, two points are of particular note at this juncture. First, projections from the superior temporal cortex to the medial surface are preferentially directed to the cingulate vocalization region (Fig. 3A). Second, projections from hippocampal (Rosene and Van Hoesen, 1977) and parahippocampal areas TL and TF (Vogt and Pandya, 1987) to the vocalization region appear quite sparse. This suggests that the hippocampus may not be involved in vocalization.

Periaqueductal Gray

Of pivotal importance to evoking vocalization is the final common pathway by which activity in areas of the cingulate vocalization region is relayed to the laryngeal motor neurons. Kelly et al. (1946) showed that facio-vocal control was spared following ablations of the mesencephalic/diencephalic junction but not after those in the periaqueductal gray and the adjacent tegmentum. A study by Jürgens and Pratt (1979) clarified these findings in a critical way by demonstrating that periaqueductal gray lesions abolished vocalization produced by electrical stimulation of anterior cingulate cortex. In all mammals studied, it appears that layer V pyramidal neurons in anterior cingulate cortex project to the periaqueductal gray (Morrell et al., 1981; Mantyh, 1982; Wyss and Sripanidkulchai, 1984). Thus it is likely that the neurons that conduct impulses from the cingulate vocalization region concerning the internal state of the animal and/or responses of specific stimuli, directly activate brainstem vocalization pathways.

In conclusion, the part of anterior cingulate cortex which is involved in vocalization is cytoarchitectonically heterogeneous and includes parts of areas 25, 24, and 32. This cingulate vocalization region may be consolidated as a functional unit by intrinsic connections as well as afferents from the amygdala and superior temporal cortex. Furthermore, the common pathway by which vocalization is evoked via the cingulate vocalization region is centered on layer V pyramidal neurons which project to the periaqueductal gray.

NOXIOUS STIMULI: A POSSIBLE TRIGGER FOR VOCALIZATION

As a general rule a limited number of essential functions are attributed to a single cortical area or connection. The cingulate vocalization region stands apart from this perspective because it is not composed of a single cytoarchitectonic area, no single input to this region can be ascribed a function primarily in vocalization, and numerous other functions have been attributed to this region in addition to vocalization. Other functions of the anterior cingulate cortex include a role in autonomic and other somatic motor activity (Kaada, 1951), affective responses to painful stimuli (Ballantine et al., 1967; Foltz and White, 1968), attention (Watson et al., 1973), significance coding of sensory stimuli (Gabriel et al., 1980), maternal and play behaviors (Murphy et al., 1981) and monitoring internal states (Bachman et al., 1977). In this context it appears that vocalization at the cortical level may be triggered by a number of inputs to the cingulate vocalization region. These inputs may be most effective during alteration in the internal state of the animal. Painful stimuli alter internal states and may be thus quite effective in evoking vocalization. Secondary responses to stimulation of nociceptors could include those associated with a withdrawal reflex organized in the spinal cord, and autonomic responses due to activation of sympathetic afferents which may reach the vocalization region via polysynaptic pathways. All of these activities could occur within seconds of nociceptor activation to produce vocalization.

Although the cellular mechanisms for each of the above noted events have not been defined yet, there is evidence that anterior cingulate cortex is involved in affective responses to noxious stimuli (Ballantine et al., 1967; Foltz and White, 1962). Vocalization may be a part of this response. Although the cingulotomy procedure which involves ablations of dorsal area 24 and/or the underlying white matter does not interfere with vocalization or speech, it does alter responses to painful stimuli. As stated by Foltz and White (1962) one patient reported after such an operation, that the pain was still present but did not concern her. It is likely that this patient's threshold for vocalization in response to painful stimuli was altered.

One of the primary behavioral roles of cingulate cortex is in coding of significant stimuli as a part of learning (Gabriel et al., 1980), an aspect of which is learning to avoid noxious stimuli. Ablations of cingulate cortex in experimental animals interfere with the ability to learn to avoid shock, i.e. active avoidance learning (Peretz, 1960; Thomas and Slotnick, 1963; Lubar, 1964). Lesions of the parafascicular nucleus in cats also disrupt this learning (Kaelber et al., 1975). The parafascicular nucleus projects to the cingulate cortex of both cats (Robertson and Kaitz, 1981) and monkeys (Vogt et al., 1979, 1987). Thus far one source of putative

nociceptor input can be proposed for the cingulate vocalization region and that is from the parafascicular and centrolateral divisions of the intralaminar thalamus. Neurons in these nuclei respond in a graded fashion to noxious stimuli and there is little or no somatotopic organization in their receptive fields (Casey, 1966; Dong et al., 1978; Peschanski et al., 1981). Thalamic nuclei such as those of the midline region, including the centrodensocellular, rhomboid and paraventricular nuclei, which are associated with limbic cortices including cingulate cortex, also may have a role in nociception, but there are no physiological studies addressing this issue.

Vocalizations emitted during distress, associated with separation of infant monkeys from their mothers, and those produced by electrical stimulation of the thalamus in guinea pigs are enhanced with naloxone, an opiate receptor antagonist (Herman and Panksepp, 1978, 1980). It is striking that layer V of anterior cingulate cortex in monkey has particularly high opiate receptor binding (Wamsley et al., 1982). The most direct way to modulate vocalization at the cortical level is likely through opiate receptors located on layer V pyramidal neurons that project to the periaqueductal gray. However, the localization of opiate receptors has not yet been accomplished with this level of resolution. Some interneurons in rodent cingulate cortex are immunoreactive for enkephalin and appear to form synapses with layer V pyramids (Sar et al., 1978). Additionally, axosomatic synapses are formed between multipolar and pyramidal neurons which are symmetric and so are likely inhibitory in function (Peters and Proskauer, 1979). Thus it is proposed that interneurons containing opioid compounds may be capable of directly inhibiting pyramidal cells which project to the periaqueductal gray.

Responses to noxious stimuli may not be dependent solely on cingulate cortex, and it is proposed here that the amygdala operates in conjunction with cingulate cortex to produce these responses. This suggestion is made because the amygdala has receptors and connections that are similar to those of cingulate cortex. For example, like cingulate cortex, opiate receptors are concentrated in the amygdala, particularly in the lateral basal nucleus which projects to cingulate cortex (Wamsley et al., 1982). Thalamic projections to the amygdala, like those to cingulate cortex, arise from the paraventricular, central superior, centrodensocellular, reuniens and paracentral nuclei (Aggleton et al., 1980). It is also interesting to note that these thalamic nuclei which project to both the amygdala and cingulate cortex also have high binding of opiate compounds (Wamsley et al., 1982). Thus it would appear that both the amygdala and the cingulate vocalization region are involved in affective responses to painful stimuli and associated vocalizations. The hypothesis of a joint role of these structures may explain why opiate antagonists are so potent in enhancing distress vocalizations.

In conclusion, it is possible that a number of inputs associated with sensory responses such as painful ones including resultant activity in the thalamus and amygdala could summate to evoke vocalization. In addition, a direct role of the opiate system in vocalization can be postulated whereby enkephalinergic interneurons may inhibit the activity in layer V neurons thus inactivating control of vocalization by the cingulate vocalization region. Finally, the cingulate vocalization region and lateral basal nucleus of the amygdala may operate jointly in producing vocalization and each would be an important site for the actions of opiate antagonists.

AUDITORY AFFERENTS: MODULATION OF THE VOCALIZATION REGION'S OUTPUT

Although it is possible that auditory stimuli directly trigger vocalization in some species, it is more likely that projections from auditory cortices provide feedback for modulation of tonal qualities. The possible role of auditory cortex in modulating vocalization responses is supported by observations that neurons in the superior temporal gyrus respond to species-specific vocalizations (Newman and Wollberg, 1973) and bilateral ablations of auditory cortex interfere with discrimination of these vocalizations (Hupfer et al., 1977; Heffner and Heffner, 1984, 1986). There have been no systematic studies of auditory projections to the cingulate vocalization region. Auditory input could reach this part of the brain directly from auditory association cortices or indirectly through the prefrontal cortex.

Direct Auditory Connections

In the rhesus monkey a tritiated amino acid injection into the dorsal temporal proisocortex and TS1 of Galaburda and Pandya (1983) resulted in labeling over much of the cingulate vocalization region (Fig. 3A). This included rostral area 24, caudal and ventral parts of area 32 and rostral area 25 in addition to parts of area 14. An injection of HRP into area 32 and adjacent area 14 is presented in Figure 4. This area received 17% of its cortical input from auditory association cortices based on the distribution of all HRP labeled neurons in the cortex. More than 60% of these labeled neurons in auditory cortices came from TS1, while most of the remainder were in areas Pro, TS2 and TS3. It has also been observed that there are projections from the cingulate vocalization region back to auditory cortex in the squirrel monkey (Müller-Preuss et al., 1980).

Indirect Auditory Connections

There is evidence of impairment of auditory discrimination following dorsolateral prefrontal ablations (Weiskrantz and Mishkin, 1958; Gross and Weiskrantz, 1962). The possible role of auditory

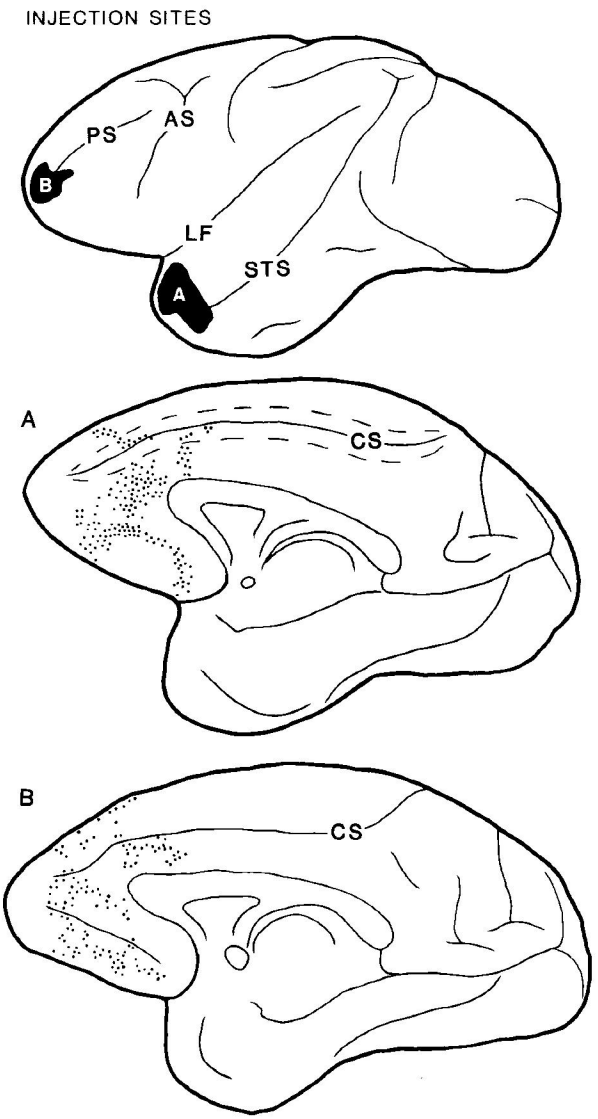

Fig. 3. Tritiated amino acid injections into rostral superior temporal cortex including areas Pro and TS1 (A, black area) and into frontal polar area 10 (B, black area). In each instance there were labeled terminals in the cingulate vocalization region as shown on the medial side of the hemisphere in A and B (dots).

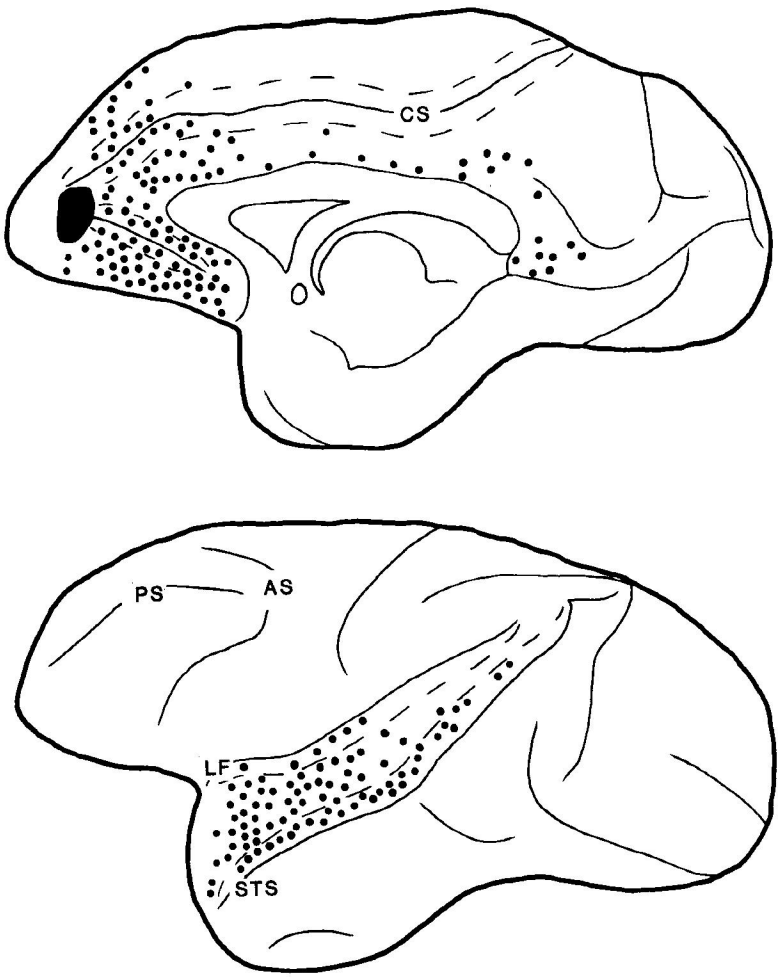

Fig. 4. Distribution of labeled neurons following an HRP injection into area 32. A preponderance of labeled neurons was in auditory association areas and rostral cingulate areas 24 and 25.

responsive neurons in prefrontal cortex in vocalization is supported by the observations of Newman and Lindsley (1976) who showed that cells around the principal sulcus responded to species-specific vocalizations in addition to other auditory stimuli. There are several sites within the prefrontal cortex that receive input from auditory association regions. These include periarcuate (area 8), peri-principalis (areas 46 and 10) and ventrolateral area 12 (Barbas

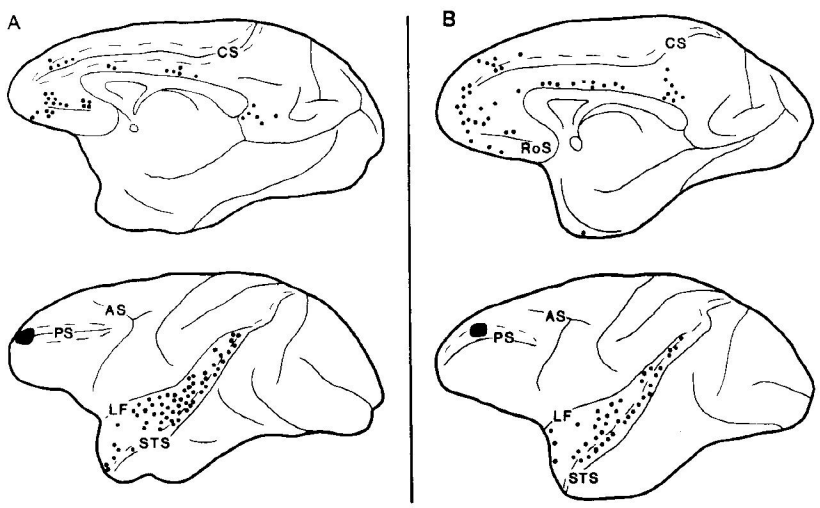

Fig. 5. Distribution of labeled neurons following HRP injections into rostral area 10 (A.) and dorsal area 46 (B.). Each case had extensive HRP labeling of neurons in auditory association cortices along the superior temporal gyrus as well as in parts of the cingulate vocalization region.

and Mesulam, 1981, 1985; Barbas, in preparation; Chavis and Pandya, 1976; Jones and Powell, 1970).

An analysis of the proportion of retrogradely labeled neurons in auditory association areas after an HRP injection within the prefrontal cortex revealed that of all known auditory recipient prefrontal regions at least two appear to be major targets of auditory projections. In other words these latter regions received 15% or more of all their cortical connections from auditory areas. Thus, a dorsolateral region at the tip of the principal sulcus (area 10) received 25% of its total cortical connections from auditory association regions (Fig. 5A). In addition, a mid-dorsal, peri-principalis region (dorsal area 46) received more than 15% of its total cortical projections from auditory association regions (Fig. 5B). In these cases, most projections originated in auditory association areas TS1, TS3, TS2, PaAlt and Tpt described by Galaburda and Pandya (1983). However, the majority of auditory projections to dorsal areas 46 and 10 originated in areas TS1-TS3 (70%), and fewer came from more caudal and architectonically more differentiated auditory association areas PaAlt and Tpt.

Both of the dorsolateral prefrontal areas that appear to be major targets of cortical auditory association projections, in turn, are closely related anatomically with the cingulate vocalization

region. Thus dorsal area 46 projects to medial area 32. The frontal polar area 10 projects to components of all cingulate areas associated with vocalization, including areas 32, 25 and rostral area 24 (Fig. 3B). Auditory projections, therefore reach the cingulate vocalization region both directly and indirectly. Direct projections from auditory association cortices reach areas 32 and 25, while indirect auditory input may reach the cingulate vocalization region via auditory recipient prefrontal areas 46 and 10.

CONNECTIONS BETWEEN THE VOCALIZATION REGION AND DORSAL AREA 24

Although electrical stimulation of dorsal and caudal parts of area 24, i.e. above the corpus callosum, does not evoke vocalization, it is possible that this area modulates the activity of the cingulate vocalization region. For example, Foltz and White (1968) found that cingulotomies for relief of pain improved verbal communication in two aphasic patients. Cats with ablations in a similar place showed significantly more vocalization (Lubar and Perachio, 1965). Suppression of attack evoked by electrical stimulation of the hypothalamus has been possible also with electrical stimulation of dorsal area 24 in cats (Siegel and Chabora, 1971). Finally large lesions of dorsal area 24 in monkeys (Showers, 1959) resulted in hyperkinetic animals and almost constant vocalization. These latter calls seemed to have no apparent association with other animals in the colony or its surroundings. Thus, it appears possible that dorsal area 24 plays a role in inhibiting vocalizations generated within the more ventrally situated cingulate region.

Although direct connections between the vocalization region and dorsal area 24 are not extensive, such connections have been reported. Pandya et al. (1981) showed that area 24 projects to area 25. In addition, in Figure 4, it can be seen that there are retrogradely labeled neurons in dorsal area 24 following an HRP injection in area 32. This connection will assume more importance when discussing the supplementary motor area and its role in vocalization, because it is this dorsal part of area 24 which is most heavily interconnected with the supplementary motor area. Interactions at the cortical level between the supplementary motor area and the vocalization region are likely mediated by dorsal area 24.

CONNECTIONS OF THE VOCALIZATION REGION WITH SUPPLEMENTARY MOTOR CORTEX

The supplementary motor area is thought to be involved in intentional or preparative motor processes (Goldberg, 1985).

Although it has been implicated clinically in speech in a number of reports, its role at a mechanistic level in the human is unclear as is its role in vocalization in nonhuman primates. Most clinical reports of patients with supplementary motor area infarction due to occlusion of the anterior cerebral artery have concomitant involvement of the cingulate vocalization region. In these cases there is marked reduction or absence of spontaneous speech and difficulty in initiating speech (Racy et al., 1979; Alexander and Schmitt, 1980; Brust et al., 1982). In only one case was there limited involvement of area 24 in addition to the supplementary motor area (Masdeu et al., 1978). In this latter case reduced spontaneous speech and word recall were reported one month following the infarct. Laplane et al. (1977) reported another series of patients who had undergone surgical ablations of the medial cortical surface involving the supplementary motor area, dorsal parts of area 24 and medial parts of areas 6 and 9. These individuals initially had an arrest of speech followed by a reduction in spontaneous speech. Within 8 to 15 months these clinical signs had subsided.

Two other observations implicate the supplementary motor area in the initiation of speech. First, electrical stimulation of this area interrupted speaking or evoked vocalization of short syllables (Penfield and Jasper, 1954). Second, spontaneous speech increases blood flow in supplementary motor cortex (Larsen et al., 1978). In light of the above clinical observations it is reasonable to state that the supplementary motor area is involved in speech by initiating the production of its basic components such as syllables and vowels. It appears that the affective component of speech is not a function of this area in humans.

The role of the supplementary motor area in vocalization in nonhuman primates is not yet resolved. Smith (1945) could evoke vocalization in monkey by electrical stimulation of this area only immediately after evoking it from rostral cingulate cortex. Sutton et al. (1985) ablated the supplementary motor area and areas 9 and 6 (Fig. 2A) and found that there was an increase in the latency of vocal responses but not in the "efficiency" of vocal and nonvocal responses. Finally, Kennard's (1955) presumptive cingulate cortex lesions in cats were likely in supplementary motor cortex and the cats "purred more and seemed to do so inappropriately and at all times." Thus, there may be a functional link between the supplementary motor and cingulate vocalization regions but its precise role is not yet clear.

There is no evidence of direct connections between the supplementary motor and cingulate vocalization regions. Limited connections do exist, however, between the supplementary motor area and area 24 dorsal to the corpus callosum. Damasio and Van Hoesen (1980) have reported reciprocal connections between anterior cingulate and supplementary motor cortices in rhesus monkey. In

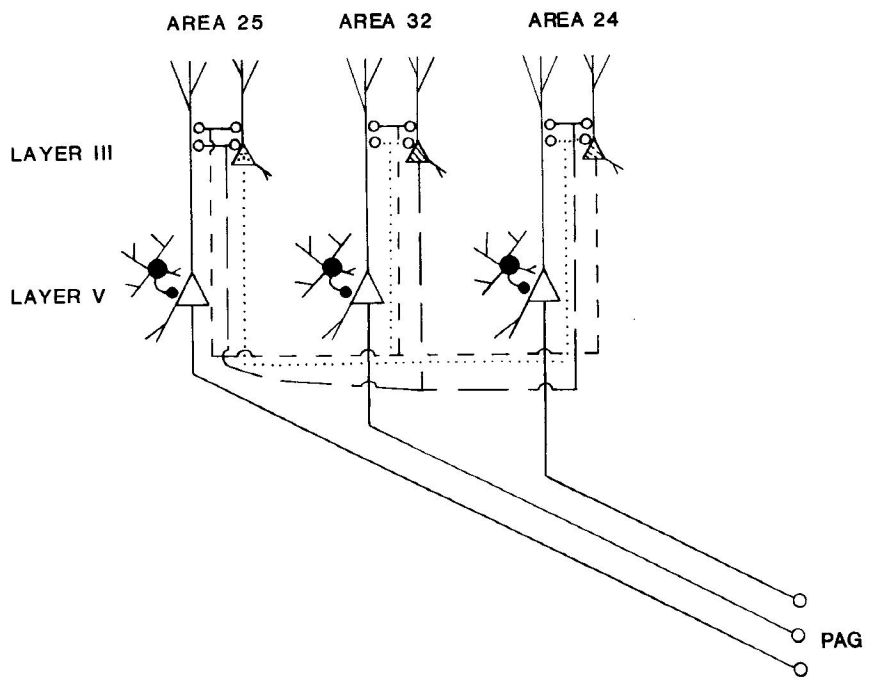

Fig. 6. Architecture and intrinsic connections of the cingulate vocalization region. Large layer V pyramidal neurons which project to the periaqueductal gray (PAG) are the primary components of this model. Intracingulate connections of layer III and layer V neurons and inhibitory interneurons modulate the activity of the largest projection cells.

addition, Pandya et al. (1981) presented a case in which a large injection of tritiated amino acids was made into area 24 and had anterograde transport into the supplementary motor area. The critical part of area 24 that is involved in these connections is a dorsal and caudal part of area 24 (Van Hoesen, personal communication).

In conclusion, if the supplementary motor area influences the cingulate vocalization region at the cortical level, it would have to be primarily through a series of corticocortical connections mediated by dorsal area 24. This indirect linking might be the reason for the limited role that the supplementary motor cortex plays in nonhuman primate vocalization.

STRUCTURAL MODEL OF THE VOCALIZATION EVENT

Statements in this chapter about the role of anterior cingulate cortex in vocalization and its specific connections can be presented as a model with three essential components. First, the intrinsic structure of the cingulate vocalization region and its projections to the periaqueductal gray. Second, connections associated with nociceptive pathways and the amygdala for triggering activity in the cingulate vocalization region. Third, connections with auditory association cortices for modulation of activity in the vocalization region.

In the circuit model in Figure 6 a large layer V pyramidal neuron which projects to the periaqueductal gray is presented for each area in the cingulate vocalization region. Activity in the vocalization region is integrated by excitatory activity in layer III and layer V pyramidal neurons which project among the three areas. In addition, enkephalinergic interneurons (filled cells) are incorporated in each area to provide for direct inactivation of vocalization by inhibiting the layer V pyramidal neurons.

Putative nociceptor input is transmitted via the parafascicular and centrolateral nuclei of the thalamus to pyramidal cells with dendrites mainly in deep layer III as shown in Figure 7. Limbic system projections relating to significance coding of vocal events may arise in the amygdala and terminate in layers superficial to the thalamic input. The summation of activity in the layer V projection neurons could lead to their discharge and activation of vocalization via the periaqueductal grey. Finally, numerous corticocortical connections are in place for modulating the basic vocalization response. Of greatest importance are those of direct origin in auditory association cortices and indirect origin in prefrontal cortices.

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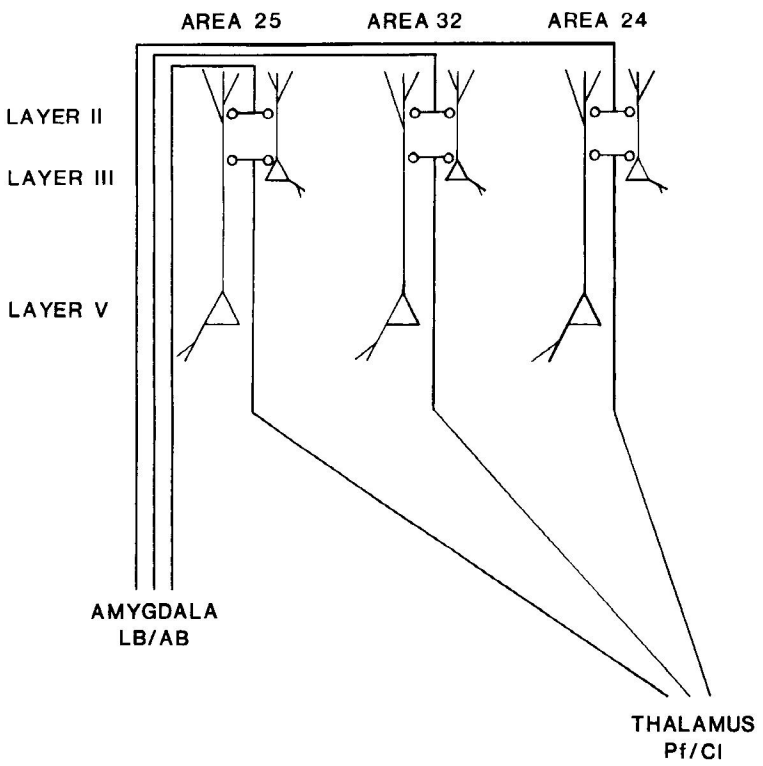

Fig. 7. Connections critical for triggering vocalization are those associated with nociceptor activation, the output of which is transmitted to cingulate cortex via the parafascicular (Pf) and centrolateral (Cl) nuclei of the thalamus. Projections from the amygdala to the vocalization areas terminate superficial to the thalamic inputs. Projections from the amygdala may be involved in affective responses to painful stimuli and determine the emotional significance of associated vocalizations.

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