

THE UNIVERSITY OF CALGARY

The Effect of Stimulation on Burst Firing in Cat Primary
Auditory Cortex

by

Denise M. Bowman

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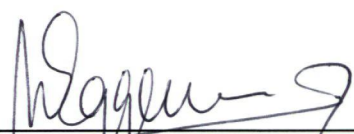
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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "The Effect of Stimulation on Burst Firing in Cat Primary Auditory Cortex" submitted by Denise M. Bowman in partial fulfillment of the requirements for the degree of Master of Science.




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Date Sept 2, 1994

Abstract

There is a high incidence of burst firing during periods of stimulation and spontaneous activity in the neocortex. This study examined the effect of auditory stimulation on the occurrence, spike count, and temporal structure of short time scale bursts (≤ 50 ms) in the extracellular recordings of 99 single units in cat primary auditory cortex. Burst firing in the first 100 ms following stimulus presentation was compared to burst firing 500 ms after stimulus presentation and to spontaneous burst firing. Short time scale bursts were present in the spike trains of single units during stimulation, following stimulation, and during periods of spontaneous activity. Generally, the proportion of the single unit response composed of bursts was greater in post stimulation and spontaneous periods than during stimulation. Burst rate was also higher in post stimulation and spontaneous periods than during periods of click stimulation. However, the single spike rate was significantly higher during periods of stimulation than during post stimulation and spontaneous periods. An examination of the auto-correlograms and higher order interspike intervals of single unit responses indicated that during stimulation, spike trains contain an excess of brief first order intervals, and a shortage of long higher order interspike intervals, relative to a spontaneous baseline. The low incidence of burst firing during stimulation opposes the view that bursts serve as a mechanism to emphasize or amplify particular stimulus related responses in the presence of ongoing spontaneous activity in the primary auditory cortex. There is also little evidence to support the notion that brief bursts of 3 or more spikes occasionally emitted by single auditory cortical units during stimulation represent sparse patterns or neural codes, as intraburst intervals were not serially dependent. Periods of elevated burst firing were observed in spike trains 0.5-1.0 s after click stimulation, indicating that stimulation may have prolonged after effects on firing activity in the primary auditory cortex.

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The Effect of Stimulation On Burst firing in Cat Primary Auditory Cortex

I. Introduction

It is axiomatic in the study of neural electrophysiology that the primary instrument for information transfer in the nervous system is the action potential. The invariant form of the action potential requires that cortical neural coding be based on the frequency or pattern of spikes emitted by a single cell or group of cells in a network. In some instances, a variation in the firing rate of a single unit is thought to constitute a neural code in the cortex (i.e. Hubel & Wiesel, 1968). Such 'rate' codes are based on the elevation or depression in the firing rate of an individual neuron in response to a particular stimulus, and can be detected by examining alterations in the mean firing rate. The timing of the action potentials in such a rate code is assumed to be a random statistical parameter of the spike train (Vaadia & Aertsen, 1992). Therefore, the interspike intervals in the spike train of a 'rate' coding neuron are independent or uncorrelated. Single cortical units may also code for a stimulus without significant variations in their average discharge rate (Vaadia & Aertsen, 1992). Alterations in the temporal pattern of action potentials emitted by a single unit may constitute a neural code for a particular stimulus or stimulus parameter (Cattaneo, Maffei, & Morrone, 1981; Dayhoff & Gerstein, 1983 a,b). The interspike intervals within such a 'pattern' would be serially dependent, and the pattern would have a tendency to recur under similar stimulus conditions (Dayhoff & Gerstein, 1983 a,b). The firing pattern of a group of neurons can also constitute population or spatiotemporal code in the cortex (Aertsen & Ardnt, 1993). These multiunit spatiotemporal codes, like single unit patterns, have a tendency to repeat under similar stimulus conditions (Abeles, Bergman, Vaadia, & Aertsen, 1993).

Analyses of single unit activity in the mammalian central nervous system have led to the characterization of several distinct neural discharge patterns (i.e. Llinás, 1988;

Connors & Gutnik; 1990). A number of studies indicate that neurons are capable of emitting clusters or 'bursts' of action potentials over brief time intervals *in vitro* (i.e. Jahnsen & Llinás, 1984; Chagnac-Amatai & Connors, 1989; McCormick & Feeseer; 1990), and *in vivo* (i.e. Legendy & Salcman, 1985; Eggermont et al., 1993). The term 'burst' however, is not uniquely defined as burst firing can be observed on many different time scales (Legendy & Salcman, 1985; Eggermont, Smith & Bowman; 1993), and can be generated by a number of different mechanisms (Friedman & Gutnik, 1987; Steriade, Jones, and Llinás, 1990; Connors & Gutnik, 1990; Kobayashi, Nagao, Fukuda, Hicks, & Oka, 1993). The burst may constitute a rate code (i.e. Smith & Smith, 1965), or the spikes within a burst may have a particular temporal structure and thus represent a temporal code (Dayhoff & Gerstein, 1982 b). Moreover, the burst may play an important role in impulse propagation in weakly connected neural networks where multiple spikes emitted within a brief time period may serve to amplify the post-synaptic neural response and ensure the contiguous activation of the pre- and post-synaptic cell (Traub & Miles, 1991).

There is a high incidence of burst firing during periods of stimulation and spontaneous activity in many cortical regions (i.e. Dayhoff & Gerstein, 1983 b; Legendy & Salcman; 1985; Connors & Gutnik, 1990; Phillips & Sark, 1991; Douglas, Martin, & Whitteridge, 1991; Eggermont et al., 1993, Gigg, Patterson, & Rose, 1993). Thus, the burst, on the basis of its distinct temporal structure, could also have a significant role in information transfer and coding in the primary auditory cortex.

Anatomy and Tonotopic Organization of Mammalian Primary Auditory Cortex

The auditory cortex is a laminar structure that can be segregated into several fields on the basis of its tonotopicity and connectivity patterns with subdivisions of the major thalamic nuclei. Anatomical and electrophysiological studies indicate that thalamic

afferents from the medial geniculate nucleus terminate mainly on cortical layer IV and deep layer III (Phillips, 1988). However, the thalamic input to these layers is indirectly distributed throughout cortex via numerous vertical cortico-cortico connections (Phillips, 1988). Tonotopically organized cortical fields include AI (primary auditory cortex), AAF (anterior auditory field), PAF (posterior auditory field), and VPAF (ventroposterior auditory field). The tonotopic cortical fields are surrounded by a peripheral auditory belt or secondary auditory areas. These areas include AII (second auditory field), DP (dorsoposterior field), V (ventral field), and T (temporal area) (Clarey, Barrone, & Imig, 1992). The secondary auditory regions lack significant tonotopic organization and receive thalamic input mainly from nontopic nuclei.

In cat primary auditory cortex (region AI), low frequencies are represented in the posterior region, and high frequencies anteriorly. Adjacent tonotopic fields have a common frequency range at their borders, and thus form a mirror image of frequency representation with respect to AI. In AI, single neurons or neural clusters perpendicular to the cortical surface are sensitive to a common frequency range. These units typically exhibit narrow frequency tuning, however a subset of neurons are more broadly tuned or have multi-peaked tuning curves (Evans & Whitfield, 1964, as cited by Clarey et al., 1993). Two tone suppression studies and examinations of neural response properties in the awake animal indicate that the excitatory frequency response area of some AI neurons are surrounded by inhibitory domains.

The two dimensional organization of frequency in the primary auditory cortex suggests that other stimulus parameters may be represented in the isofrequency bands of cortex (Phillips, 1988). A number of studies have indicated that the binaural response properties of neurons may be segregated within an AI isofrequency band (Clarey et al., 1992). Other researchers have suggested that the degree of frequency tuning exhibited by AI neurons are also segregated within specific regions of cortex (Schreiner & Mendelson,

1990). Narrowly tuned neurons with high frequency selectivity were found in the central region of dorsal ventral AI. These neurons exhibited poor responses to broad band stimuli. In contrast, broadly tuned neurons were represented in more dorsal and ventral cortical regions. Broadly tuned neurons were highly responsive to broadband stimuli. Clarey and colleagues (1992) suggest that the response properties of these neurons likely reflect the presence of strong inhibitory domains in narrowly tuned units. Therefore, the primary auditory cortex may be organized along a number of different stimulus dimensions on the basis of intrinsic physiology and extrinsic connectivity patterns.

Mechanisms of Burst Generation

Burst firing in the mammalian central nervous system can be attributed to a number of different mechanisms. Examinations of the electrophysiology of single cortical units *in vitro* and *in vivo* suggest that burst firing may be attributed to intrinsic membrane properties of cortical neurons or to an extrinsic thalamic drive (Chagnac-Amatai & Connors, 1989; Steriade, Jones, & Llinás, 1990).

Burst discharges in thalamic slice preparations consist of two components: a slow, depolarizing low threshold spike (LTS); and a cluster of fast action potentials riding on the peak of the slowly depolarizing component (Jahnsen & Llinás, 1984). The LTS is completely inactivated at membrane potentials positive to -55 mV, and reaches a maximum amplitude at -70 mV. In contrast, the fast spiking component has an activation threshold of -40 mV. The LTS was shown to be sensitive to Co^{++} and Cd^{++} and disappeared when the slice was maintained in Ca^{++} free medium. Thus, Jahnsen and Llinás proposed that the low threshold burst component is dependent on the conductance of Ca^{++} through voltage gated ionophores now known as 'T type' channels (Llinás, Sugimori, & Cherskey, 1989). The LTS was also dependent on a second voltage dependent conductance that was inactivated at membrane potential levels positive to -55 mV, and

deinactivated by membrane hyperpolarization. The findings of the study further indicated that the fast spiking component of the thalamic burst discharge was dependent on kinetically fast Na⁺ conductances.

Similar conductances are believed to underlie burst firing in the inferior olive (Llinás & Yarom, 1981), hippocampus (Wong & Prince, 1981) and cortex (Friedman & Gutnik, 1987; Chagnac-Amatai & Connors, 1989). Connors and Gutnik (1990) suggest that burst firing in sensorimotor slice preparations may be attributed to mechanisms similar to those described in the thalamus, however, observations of 'intrinsic' bursters were limited to cortical layers IV and V. This proposed layer dependence of 'intrinsic' burst firing in sensorimotor cortex is in contrast to observations of burst activity in the thalamus, brainstem, and prefrontal cortex where most neurons are able to generate rebound Ca⁺⁺ dependent bursts of action potentials (Steriade & Llinás, 1988).

A few studies also suggest that the activation of excitatory amino acid (EAA) receptors may have an important role in neocortical burst firing (Silva, Amatai, & Connors, 1991; Kobayashi, Nagao, Fukuda, Hicks, & Oka, 1993). Kobayashi et al. demonstrate that the iontophoretic application of both N-methyl-D-aspartate (NMDA) and non-NMDA EAA receptor antagonists to somatosensory cortical neurons *in vivo* reduce bursting activity. An examination of the interval statistics of the spike trains emitted by these cortical neurons revealed that AP5, an NMDA receptor antagonist mainly inhibits short or intraburst spike intervals, whereas DNQX, a non-NMDA receptor antagonist, inhibited both the short and long interspike interval components of ISI histograms. Thus, the investigators propose that the activation of NMDA and non NMDA EAA receptors may play an important role in cortical burst generation. Silva et al. (1991) similarly demonstrate that NMDA receptor antagonists alter the neural activity of intrinsically bursting neurons in layers IV and V of somatosensory cortex slice preparations.

Several other studies suggest that high threshold Ca^{++} dependent spikes (HTS) may support regenerative or burst firing in the neocortex. Gutnik, Connors, and Prince (1982) observed anomalous inward rectifying currents in slice preparations of guinea pig neocortex when outward K^+ conductances are suppressed. These anomalous currents were attributed to both high threshold Ca^{++} (activation at -40mV) and slowly inactivating Na^+ conductances. Similar conductances are also observed in sensorimotor cortex slice preparations (Connors, Gutnik, & Prince, 1982). Connors and colleagues further suggest that these persistent conductances, when combined with synaptic currents, produce a depolarizing shift in membrane potential that leads to repetitive spike discharge in epileptogenic preparations. More recently, Aroniadou, Maillis, and Stefanis (1993) have provided convincing evidence for the existence of the same high threshold Ca^{++} conductances in the visual cortex of the adult rat.

Although compelling, the findings describing the intrinsic membrane properties of bursting neurons in slice preparations of neocortex may not provide a complete description of the mechanisms underlying cortical burst firing *in vivo*. Cortical neurons are the constituents of a large neural network and therefore receive many excitatory and inhibitory inputs (Douglas & Martin, 1990). These synaptic inputs can alter the membrane properties of neocortical neurons *in vivo*. Furthermore, neural activity in the cortex is modulated by the thalamus, and therefore cortical burst firing may be influenced or even driven by the rhythmic activity of thalamic relay neurons (Steriade, Jones, & Llinás, 1990). However, Eggermont et al. (1993) found that auto-correlograms derived from bursting sections within the spike trains of single auditory cortical neurons demonstrated no greater periodicity than the correlograms of isolated spike sections. This finding suggests that burst firing and rhythmic firing are not necessarily controlled by the same mechanisms in the cortex. Time dependent auto- and cross-correlograms of pairs

of units indicate that some of the most obvious rhythmically firing neurons in the study demonstrated an independence of burst firing on short time scales (20-30 ms). The difference in size, duration and clustering of the bursts generated by pairs of units suggest that bursts are not controlled by an input common to both units, rather the mechanisms that control firing within a burst likely arise from the intrinsic properties of individual units or from the network properties of primary auditory cortex.

Proposed Functions of the Burst Discharge

Burst Firing and Impulse Propagation

Burst firing is an efficient and reliable way to propagate impulses in neural networks with low connection strengths (Traub & Miles, 1991). The time constant of pyramidal neurons (30 - 40 ms) is greater than the interspike intervals found within a burst. Therefore, a burst in a presynaptic cell will illicit a series of EPSPs that summate effectively in the post-synaptic cell it innervates. Consequently, even subthreshold EPSPs can evoke spiking or bursting in the post-synaptic cell (Traub & Miles, 1991). It has been suggested that the contiguous activation of a pre and post-synaptic cell and the dendritic depolarization of the post-synaptic cell above a critical threshold are the key components of Hebbian synaptic modification, the principal model of formation and stabilization of synaptic connections in the CNS (Hebb, 1949). Thus, burst firing may also play an important role in the modification and stabilization of synaptic connections in the cortex.

Several lines of research have indicated that neural activity patterns play a crucial role in the development and maintenance of orderly connections in the CNS (i.e. Brown, Kairiss, & Keenan, 1990; Jones, 1990; Shatz, 1990). Alterations in the level or pattern of peripheral neural discharge have a powerful influence on the development of neural connectivity in the mammalian visual system (Shatz, 1990). Suppression or variation in

retinal firing patterns influence the formation of ocular dominance columns in the neocortex (Stryker & Strickland, 1984; Stryker & Harris, 1986), and the segregation of cell layers in the LGN (Stretevan & Shatz, 1986). Eggermont et al. (1993), examined the effect of age on spontaneous burst occurrence in primary auditory cortex. The incidence of burst firing was significantly higher in kittens than adult cats when age related differences in firing rate are taken into account. Therefore, burst firing may have an important role in the formation and stabilization of synaptic connections in developing sensory pathways.

Although many of the early studies of synapse modification emphasize the physical pruning and strengthening of connections in maturing neural networks, more recent investigations have focused on functional changes in synaptic connectivity at higher levels of the adult CNS (Jones, 1990; Bear & Kirkwood, 1993). A number of studies have shown alterations in the receptive field properties of mature somatosensory cortex and the frequency tuning of primary auditory cortical neurons following peripheral lesioning, pharmacological manipulation, or behavioral training (Merzenich, Kaas, Well, Nelson, Sur, & Felleman, 1983; Calford & Tweedle, 1988; Recanzone, Schreiner & Merzenich, 1993; Weinberger, Javid, & Lapan, 1993). Alterations in the receptive field properties of the adult cortex have also been shown to depend on underlying changes in the temporal pattern of neural activity arriving from the periphery (Clark, Allard, Jenkins, & Merzenich, 1988). These observations are consistent with the findings outlining early post-natal development in the visual system (see Shatz, 1990 for review). It has been suggested that such parallels in the developmental and adult plasticity research may indicate that similar mechanisms underlie both processes in the mammalian CNS (Singer, 1990; Shatz, 1990).

Functional modification in the strength of synaptic connectivity is thought to be the physiological basis of learning and memory at higher levels of the mammalian CNS

(Brown et al., 1990; Jones, 1990; Singer, 1990; Bear & Kirkwood, 1993). A number of studies have indicated that some regions of the hippocampus are susceptible to a powerful form of activity dependent synaptic plasticity referred to as long term potentiation or LTP (i.e. Bliss & Lømo, 1973). Induction of LTP in the CA1 region of the hippocampus usually requires the synchronous activation of the pre and post-synaptic cells, and post-synaptic depolarization which allows Ca^{++} ions to flow through NMDA receptor channels (Madeson, Malenka & Nicoll, 1991). Singer (1990) also suggests that these mechanisms may play an important role in experience dependent synaptic modification in the visual system. There are therefore many similarities between LTP induction in the hippocampus and synaptic plasticity in the neocortex (Bear & Kirkwood, 1993; Singer, 1990).

Several studies have suggested that NMDA receptors may play a pivotal role in the mediation of synaptic plasticity in adult neocortex (Baranyi & Szente, 1987; Artola & Singer, 1987; Gruelle, Luhmann & Singer, 1988; Kirkwood, Dudek, Gold, Aizenman, & Bear, 1993)). Applications of the EAAs L-glutamate and NMDA in combination with acetylcholine and norepinephrine to visual cortex *in vivo* produced a selective enhancement of responses to a conditioned visual stimulus, and a selective reduction in the responses to non conditioned stimuli. The combined application of all pharmacological agents produced a larger change in neural responsivity than EAAs or neuromodulators individually. Furthermore, Artola and Singer (1987), found that the selective NMDA antagonist AP5 blocked the induction of LTP by high frequency stimulation of the optic radiation in visual cortex slice preparations. Kirkwood and colleagues (1993) found that theta-burst stimulation (5-7 Hz) induced LTP in layers II and IV of visual cortex *in vitro*. In contrast, low frequency stimulation (1-3 Hz) produced long term depression (LTD) in layer III from either a potentiated or naive state.

These observations are consistent with the induction of LTP and LTD in the CA1 region of the hippocampus (Bear & Kirkwood, 1993).

Although the findings of these studies provide strong support for the crucial role of NMDA receptors and a Hebbian form of synaptic modification in cortical plasticity, the application of these findings to observations of adult cortical plasticity *in vivo* are limited for a number of reasons. First, there is a significant decline in the contribution of NMDA receptors to synaptic transmission in the neocortex postnatally (Iwakiri & Kumatsu, 1993). Furthermore, observations of robust neocortical potentiation are either limited to the slice preparation, or require significant pharmacological intervention (i.e. Artola & Singer, 1987; Gruelle et al., 1988; Bear & Kirkwood, 1993). Finally, there is increasing empirical support for NMDA receptor independent mechanisms of LTP in the neocortex (Aroniadou-Anderjaska et al., 1993). Aroniadou-Anderjaska et al. (1993) demonstrated that tetanic stimulation of the white matter in slices of visual cortex induced LTP in cortical layer III, even in the presence of AP5. However, applications of nimodipine and nifedipine effectively block LTP in the same preparations. On the basis of these observations the investigators propose that the flow of Ca^{++} through dihydropyridine sensitive channels ('L' type channels) may underlie this form of NMDA receptor independent LTP in the visual cortex. Llinás (1988) similarly posits that the low threshold conductance (LTC, or 'T' type channels) may play an important role in the development of neural networks in the motor pathway. It is interesting to note that both NMDA mediated and non NMDA mediated potentiation involve the influx of Ca^{++} ions into the post-synaptic cell.

Although there have not been any direct links made between burst firing and synaptic plasticity in the neocortex, a series of studies examining the influence of passive avoidance training on the neural discharge patterns in a number of regions in the chick forebrain indicate that increases in neuronal burst firing are observed at particular time periods following passive avoidance training (Mason & Rose, 1987; Gigg, Patterson &

Rose, 1993 & 1994). The authors suggest that such increases in burst firing may be directly associated with long-term memory consolidation for the task (Gigg et al., 1994). These findings, when considered in conjunction with the effects of burst firing in a neural network and the observations of burst firing in developing sensory systems outlined earlier, suggest that the burst discharge may play an important role in the functional alteration of synaptic connectivity in the cortex.

Burst-Firing As A Neural Code

As outlined earlier, the term 'neural code' can refer to the variation in the firing rate of a single unit under particular experimental conditions. The interspike intervals in the spike train of such a 'rate' coding neuron are independent or uncorrelated. Although there is experimental evidence to support the existence of such 'rate codes' in the cortex (i.e. Mountcastle, 1957; Hubel & Wiesel, 1968), more recent findings indicate that the timing of spikes emitted by single neurons may also play a very significant role in neural processing (see Cariani, 1994; Vaadia & Aertsen, 1992 for review). Alterations in the temporal pattern of spikes in a spike train emitted by a single unit may constitute a neural code for a particular stimulus or stimulus parameter (Dayhoff & Gerstein, 1983 a,b; Middlebrooks, Clock, Xu & Green, 1994). The interspike intervals within such a 'pattern' would be serially dependent, and the pattern would recur under similar stimulus conditions (Dayhoff & Gerstein, 1983 a,b). The firing pattern of a group of neurons can also constitute a population or 'spatiotemporal' code where the interspike intervals between a number of units are serially dependent, and have a tendency to repeat under similar experimental conditions (Abeles, Bergman, Vaadia, & Aertsen, 1993; Aertsen & Ardnt, 1993).

Each model of neural coding requires that the spike trains emitted by coding units have certain statistical properties. A 'rate' code model assumes that the most important

statistical parameter of a spike train is the frequency of spike occurrence or mean discharge rate (Vaadia & Aertsen, 1992). The relative timing of spikes within the spike train of a 'rate' coding neuron is inconsequential, as interspike intervals are assumed to be a random parameter. In contrast, a 'pattern' model of the neural code presupposes that a key feature of the spike train is the temporal sequence of action potentials (Dayhoff & Gerstein, 1983 a). The interspike intervals of such neural patterns are assumed to be ordered. Consequently, interval durations are treated as a nonrandom parameter of the spike train. It therefore follows that by providing an accurate quantitative description of neural firing one can determine the form of the neural code utilized by a particular cell or group of cells in the CNS.

Quantification of the Burst Discharge

Several investigators define burst firing in terms of the distribution of time intervals between spikes in a spike train. Smith and Smith (1965) computed the interspike interval distribution of spike trains emitted by spontaneously active frontal cortex neurons in the awake cat. The interval distribution of a spike train containing bursts was found to consist of two roughly Poissonian components. Thus, according to these investigators, the burst is best conceived of as a "Poissonian Shower", where the first component is an instance of high frequency Poissonian activity, and the second component is the interburst interval, where periods of bursting are gated on and off at random instances in time.

Similarly, Legendy and Salcman (1985) utilize a burst detection method derived from Poissonian assumptions to analyze burst firing in the spontaneously active striate cortex of the cat. The detection device, called the "Poissonian Surprise", is the negative logarithm of the probability of the occurrence of a burst consisting of a given number of spikes in a particular time interval when it is compared to a Poissonian spike train with

the same mean firing rate. The investigators found that cortical spike trains contained many significant bursts. Significant bursts had a probability of occurring in a Poisson spike train of 10^{-10} or less. These "surprising" bursts could extend over several seconds and contain more than 100 spikes.

Eggermont et al. (1993) computed the observed probability of bursts (pairs, triplets..etc.) from the higher order interspike interval histograms of single units over a 50 ms time window in spontaneously active auditory cortical neurons. The observed probability of the occurrence of a particular burst was then compared to the predicted probability of a burst containing the same number of spikes over a 50 ms time window according to a Poisson distribution for the same mean firing rate. The observed probability of 2 spike (pairs), 3 spike (triplets), and 4 spike (quadruplets) bursts was significantly higher than the expected probability of a Poisson process with the same mean firing rate. The auto-correlation constructed from the higher order interval histograms of most units also clearly indicated an excess of short intervals (or bursts) when compared to the expected Poissonian distribution, although a small subset of units demonstrated firing behavior closer to Poisson.

In all three studies a Poissonian model, which is characterized by its well defined distribution of independent events, provides a quantitative basis for detecting bursts in the spike trains of single cortical units. If the statistics of a burst could be accurately estimated by a Poissonian process, then burst firing may be conceived of as brief periods of elevated firing or a form of a 'rate' code. However, the findings of these studies indicate that the spike trains of spontaneously active cortical units contain an excess of short order intervals or bursts when compared to a Poissonian process.

Mandl (1993) suggests that the interval statistics derived from the spike trains of visual cells in cat superior colliculus approach a two-state pseudo-Markov model of neural discharge proposed by Elkholtz and Hyvärinen (1970) (see also Smith & Smith,

1965). According to Mandl, three key assumptions are made when modeling a spike train with a pseudo-Markov process (1) the spike generation mechanism is able to switch between two independent states; (2) the number of consecutive spike discharges (or interspike intervals) within a particular state is an integer valued random variable; (3) the duration of intervals within a given state is an independent stochastic variable. Applications of this pseudo-Markov model to the spike trains emitted by single units in Mandl's study met the first two of the three key requirements of a pseudo-Markov process. The interval histograms derived from the spike trains of most cells within the visual regions of the superior colliculus were well modeled by the combination of a truncated Poisson distribution and a Wiener process distribution. 'Implicit' bimodal histograms usually contained a peak at intervals less than 8 ms and a long decaying tail at intervals of greater than 8 ms. In contrast 'explicit' bimodal interval histograms contained two distinct broad peaks. The distribution of short intervals reflected the 'bursting state' of a particular neuron and were characterized by a truncated Poisson interval distribution. Longer intervals corresponded to the 'resting state' of a neuron and were characterized by a Wiener distribution. Elimination of all spikes from one particular state had no effect on the interval duration of the other state. The number of consecutive spikes found in one state prior to switching to another state was also independent of the number of spikes already generated for each unit in the study. These findings demonstrated that the 'bursting' and 'resting' states of superior colliculus neurons were statistically independent. To examine the degree of serial correlation of intervals within a spike train, the relationship between the duration of pairs of intervals were estimated from joint interval distribution histograms (JIDS). In such a histogram interval pairs with related durations produce clusters of points within the histogram. These clusters were evident in regions corresponding to short duration intervals in most JIDs. To assess the degree of independence between consecutive interspike intervals Mandl (1993) estimated

the first moments of the probability distributions of the intervals by calculating the means of the rows and columns of the JIDs, and plotted column vs. row and row vs. column means for each histogram. When the row means were plotted against the column means for long intervals, the points formed a straight line orthogonal to the x and y axes, indicating that consecutive intervals within the 'resting' state were statistically independent. In contrast, the row and column means of short duration intervals fell on a diagonal line with respect to the x and y axes and therefore indicated a linear positive correlation between consecutive intervals within the 'bursting' state. Such serial correlation of intervals within a burst violates a key component of the pseudo-Markov process in which the duration of intervals within a given state is assumed to be an independent stochastic variable.

Clearly, attempts to model the interval statistics of the burst discharge by combining a Poisson distribution with a Wiener process distribution or a second Poisson distribution, which assume that the interspike interval is a random parameter, have only met with limited success. One interpretation of these results is that the interspike interval or the timing of spikes within a burst is an ordered process where intervals are serially dependent. It is also possible that the statistics of a burst may be modeled by a single distribution of random events that has not yet been tested experimentally.

Bursts as Temporal Codes

In most sensory systems there is evidence for the temporal coding of complex stimulus parameters in the spike trains of both peripheral and central neurons (see Cariani, 1994). The locking of a neural response to the presentations of a stimulus or stimulus parameter represents one form of a temporal code. In the somatosensory system the temporal patterns of mechanical skin vibration are encoded by the temporal discharge pattern of afferent discharges (i.e. Johnson & Hosiao, 1992). In the auditory system neural responses to complex transient stimuli also reflect the temporal structure of the

stimulus (i.e. Clarey et al., 1992). In both systems, different classes of peripheral nerve fibers encode a particular range of frequencies so that when considered collectively the fibers are able to encode a wide range of stimulus frequencies. However, there is a substantial decrease in the limiting rate of transient responses (i.e. click responses) as one progresses from lower levels of the auditory system to the auditory forebrain. In the auditory nerve the limiting click rate is approximately 3 kHz, where as in the inferior colliculus and thalamus the rate decreases to 100 - 200 Hz (Clarey et al., 1992). Most studies suggest that the limiting click rate in cortical neurons is in the range of 25-50 Hz, a value lower than that of thalamic neurons (Phillips, Hall, & Hollet, 1989; Eggermont, 1991). In the somatosensory system it appears that although first order interspike intervals are progressively disrupted by spike jitter and the occurrence of intervening spikes, non successive interspike intervals associated with stimulus periodicities endure into the cortex (Mountcastle, 1993). Mountcastle suggests that it is the differences in the non successive interspike intervals rather than differences in the discharge rates of afferent fibers that are used to discriminate between different vibration frequencies.

It has been suggested that bursts play an important role in temporal coding of stimuli in the CNS. Cattaneo et al. (1981) indicate that although complex cells in striate cortex rarely emit bursts of action potentials spontaneously, burst-firing can be observed in response to drifting gratings. The interval statistics of the spike trains emitted by single cortical neurons during visual stimulation were examined by constructing interspike interval histograms. Isolated spikes had long mean interspike intervals (~ 100 ms) and no explicit modal interval, where as clustered spikes had shorter mean interspike intervals (~ 50 ms), with clear modal intervals of about 3 ms. When compared to the response properties of isolated spikes, only clustered spikes were tuned to the spatial frequency, velocity, and orientation of the grating. These investigators indicate further that the most salient effect of a stimulus on the interval statistics of a complex cell discharge is to

increase the number of short interspike intervals. On the basis of these experimental observations the authors suggest that bursts or clustered spike discharges of complex cells may carry information about specific parameters of a visual stimulus.

Mandl (1993) similarly noted that the temporal characteristics of neural discharges in the visual superior colliculus varied consistently and systematically with stimulus velocity. Specifically, there is an increase in the synchronization and occurrence of short interspike intervals or bursts with increasing stimulus velocity. Mandl speculates that the systematic stimulus-related variations in the temporal structure of spike discharges may have an important role in the recognition, representation and transmission of information about relevant stimulus parameters in a neural network.

Guido and colleagues (1992) examined the contribution of burst and tonic responses to the receptive field properties of the lateral geniculate nucleus. In particular, the extracellular responses to drifting sine wave gratings were divided into burst firing dependent on low threshold (LT) calcium conductances, and tonic responses. LT bursts consisted of a silent period of 100 ms or longer followed by a burst of action potentials with a mean interspike interval of ≤ 4 ms. Response-versus-spatial-frequency and response-versus-contrast response functions, indicated that the proportion of LT bursting in the total response did not vary significantly with alterations in spatial frequency or contrast of the stimulus. In particular the authors note that the ratio of LT bursting is no greater during periods of stimulation where spatial frequency or contrast are varied than during periods of spontaneous activity. However, response-versus-temporal-frequency functions indicated a progressive increase in the LT burst ratio with increasing temporal frequency.

There is a high incidence of burst firing during periods of stimulation and spontaneous activity in cat primary auditory cortex (i.e. Phillips & Sark, 1991; Eggermont et al., 1993). Phillips and Sark demonstrated that single units in the primary auditory cortex

may emit a train of up to 5 spikes in response to the onset of a tone pulse in the pentobarbital anesthetized cat. Peri stimulus time histograms (PSTHs) were constructed to examine the relationship between the timing of the stimulus and the response. The PSTHs seldomly indicated periodicity's in spike timing. However, normalized response histograms in which the timing of successive spikes in a train were measured relative to the time of the first spike, rather than the stimulus onset, showed that the second and later spikes in a burst occurred at a preferred interval of about 2 ms. The standard deviation of interspike intervals were smaller than the standard deviation of latency between stimulus onset and the first spike in most responses. Coefficients of variation (CV) ranged from 0.16 to 0.86, indicating that the standard deviation of a given interval was always smaller than its mean and suggesting that the interspike intervals were more regular than a Poisson process (CV=1). With the exception of threshold levels of stimulation, the interspike intervals of the burst responses were invariant across a wide range of stimulus intensities and repetition rates. In contrast, increasing stimulus intensities had a profound effect on the number of spikes in a burst and the first spike latency. As stimulus intensity increased, spikes which occurred later in the burst were deleted, and the first spike latency decreased without altering the length of interspike intervals of successive spikes in the burst. On the basis of these observations the authors argue that the interspike intervals within a burst carry very little information about an auditory stimulus. They suggest that the generation of bursts of action potentials in response to an optimal transient stimulus provides a salient neural signal in the midst of ongoing spontaneous activity. Cortical burst firing in this context represents a mechanism for emphasizing or amplifying a particular stimulus related response rather than coding for a specific stimulus parameter. However, it is necessary to qualify this suggestion with the observation that burst firing is also pervasive during periods of spontaneous activity in cat primary auditory cortex (Eggermont et al., 1993). Eggermont et al. (1993) characterized

spontaneous bursts on a short time scale (50 ms) as having a relatively well defined interval between the first two spikes in a burst (3-15 ms) followed by higher order interval values with increasing modal latencies in the ketamine anesthetized cat.

Other researchers have suggested that specific brief duration (< 50 ms) spike clusters may serve as a code for stimulus location in the ectosylvan sulcus region of the temporal cortical lobe. Middlebrooks et al. (1994) utilized an artificial neural network to classify the temporal spike patterns of single auditory associated cortical neurons according to sound location. The temporal spike patterns of most units were found to vary systematically in both the timing and number of spikes with sound position. Therefore, bursts may serve as temporal codes for stimulus location in auditory associated regions of temporal cortex.

Several studies suggest that certain recurrent temporal patterns of action potentials emitted by single units or a group of units may serve as neural codes in the visual and frontal cortex (Dayhoff and Gerstein, 1983 a,b; Legéndy & Salcman, 1985; Strehler & Lestienne, 1986; Villa & Abeles, 1990; Vaadia & Aertsen, 1992; Abeles et al., 1993).

One line of research suggests that specific recurrent temporal patterns of action potentials may serve as a neural code for a stimulus or stimulus parameter. Dayhoff and Gerstein (1983 b) utilize two pattern detection methods to detect "favored" spike patterns in the spike trains emitted by single crayfish claw and striate cortical units: the quantized Monte Carlo method and the template method. Each spike train is quantized by making any time interval between 0 and a spike an integer multiple of a particular quantized interval. The quantization method allowed for the detection of particular sequences of spikes with slight interval jitter (5 ms). To test the significance of the occurrence of a particular quantized pattern, the original spike train interval distribution was compared to shuffled versions of the same interval distribution. In the shuffled version, interspike intervals are not serially dependent, therefore it was possible to determine whether a

particular pattern occurred just because there was a large number of intervals of a particular length. If the occurrence of a pattern is random, then the shuffled spike train would match the original. A match implies a lack of serial dependence of interspike intervals in the spike train. If there was not a match, the significance of any excess counts were tested by calculating the probability density function derived from the 99 shuffled versions of the spike train. Any significant favored patterns were then used as templates to detect slight variations of a pattern in the entire spike train. A weighting function based on the template allowed for the detection of patterns that contained too many or too few spikes. The occurrence of such imperfect patterns in the spike trains could then be calculated by shuffling the spike train 99 times, and comparing the number of template matches in the original spike train to the number of matches in the shuffled spike train. The significance of any excess was determined by calculating the probability density function from the 99 shuffled versions. "Favored" patterns were therefore defined as the excessive recurrence of certain ordered or serially dependent groups of intervals in a spike train and could contain random spikes.

Applications of the technique developed by Dayhoff and Gerstein to spike trains in cat striate cortex during periods of visual stimulation indicated that 16 out of the 27 spike trains tested contained highly significant patterns. Patterns consisted of up to 7 spikes, allowing for interval jitter of 5 ms and the addition or loss of an occasional spike. The interspike intervals of the favored patterns illustrated in the article appeared quite variable and short (< 52 ms). The authors further note that the response latencies of all "favored" patterns fall within a range of 50 ms, and half fall within a range of 20 ms, indicating that patterns are quite well timed to stimulus presentations. However, there was no other systematic relationship between the presence of favored patterns and stimulus conditions. On the basis of these observations Dayhoff and Gerstein suggest that the availability of such "favored" discharge patterns in the striate cortex and crayfish claw may indicate that

such patterns may serve as neural codes in the nervous system. Strehler and Lestienne (1986) similarly suggest that identical three spike clusters or triplets in the striate cortex of monkeys may serve as stimulus responses. However, these authors suggest that the triplet codes observed in their study have a very high temporal precision (jitter < 0.2 ms). Segundo (1986) posits that the pattern of excitatory and inhibitory post-synaptic potentials which arise from recurrent neural discharge patterns act as "passwords" which specifically triggers a post-synaptic response.

Several studies suggest that the temporal pattern of multi-unit activity may also serve as a form of neural code (Legendy & Salcman, 1985; Villa & Abeles, 1990; Vaadia & Aertsen, 1992; Abeles et al., 1993). Legendy and Salcman (1985) found that recurrent burst discharges of pairs of spontaneously active striate cortical neurons occurred within a short time period of one another. Moreover, recurring bursts emitted by one unit were occasionally accompanied by time locked repeating bursts on several other units. Therefore, according to Legendy and Salcman, recurrent synchronized multi-unit burst firing may play a role in "feature binding" in the striate cortex.

Abeles et al. (1993) suggest that the precise timing of the discharges of a group of cortical units following stimulus presentation may constitute a synchronous drive that triggers spike generation in a neuron receiving inputs from a number of neurons emitting such "compound" firing patterns. These multi-unit firing patterns were detected by constructing a Joint Peristimulus Time Histogram (JPSTH), and calculating the coincident firings of small groups of neurons. Multi-unit correlations in the frontal cortex of an awake monkey were examined by plotting the delayed firing intervals of one or several units relative to the delayed firing intervals of a reference unit. Relatively large counts in particular bins of the histogram indicated the recurrence of particular firing intervals between a number of units. The significance of such peaks in the JPSTHs were estimated by a "surprise" calculation ($-\ln(\text{probability of getting the peak by chance})$).

The observed probability of some peaks were as low as $\exp(-16)$ or 1 in 10 million. Moreover, Abeles et al. suggest that similar events were encountered hundreds of times in their spike train recordings. Recurrent firing patterns were also observed in the delayed response of single neurons in frontal cortex (Abeles et al., 1993). One unit in the study generated 19 different patterns that were each repeated 14 times or more. These neural patterns could last up to 100 ms and have a jitter of 3 ms or less. The role of compound firing patterns in cortical neural coding will not be considered further, as this study is concerned with the temporal structure of spike trains emitted by single cortical units over a brief time window (50 ms).

To summarize, it has been suggested that single unit burst firing may serve to enhance impulse propagation in weakly connected neural networks (Traub & Miles, 1992). Other investigators posit that periods of burst firing following conditioned learning tasks may be associated with memory consolidation (i.e. Mason & Rose, 1987). Alternatively, brief bursts of action potentials emitted by single units may represent favored or recurrent discharge patterns and therefore serve as neural codes for stimulus features in the neocortex (i.e. Dayhoff & Gerstein, 1983 b).

The present study investigates the effect of auditory stimulation on the occurrence, spike count, and temporal structure of short time scale bursts (50 ms) in the lightly anesthetized cat. Burst firing in the first 100 ms following stimulus presentation is compared to burst firing 500 ms after stimulus presentation and to spontaneous burst firing, in order to delineate the short term and long term effects of stimulation on burst firing relative to a spontaneous baseline. Two different auditory stimuli, clicks and broad band noise, are utilized in this study. Therefore, the influence of different auditory stimuli on burst occurrence, spike count, and structure is also examined. Serial dependence between interspike intervals during periods of stimulation will also be tested.

The first hypothesis being tested in the present study, is whether bursts in the period immediately following stimulus presentation represent neural patterns. If bursts are neural patterns, then the interspike intervals within a burst should be ordered and have a tendency to recur under similar experimental conditions. Moreover, the presentation of different stimuli should have an influence on the interval statistics or temporal structure of the burst if bursts code particular features of a stimulus. The second hypothesis tested in the present study is whether short time scale bursts serve as a mechanism to emphasize a stimulus related response in the presence of ongoing spontaneous activity. If burst occurrence increases in stimulated conditions without accompanying changes in temporal patterning, then burst firing may play a role in the amplification of neural signals in the cortex. Finally, if the incidence of burst firing is highest in the post stimulation period, it is possible that bursts serve some other internal state related function such as memory trace or consolidation in the primary auditory cortex.

II. Methods

Surgical Procedure

Cats were premedicated with 0.25 mL/kg body weight of a mixture of 0.9 mL of atropine sulphate (0.5 mg/mL) and 0.1 mL of Acepromazine (0.25 mg/mL) subcutaneously. After a period of approximately 30 minutes a 25 mg/kg dose of Ketamine was given intramuscularly and a 20 mg/kg dose of sodium pentobarbital was administered interperitoneally. After shaving and cleaning the head, an incision was made in the skin covering the skull. Durocain (20 mg/mL) was injected subcutaneously and gently massaged over the surface of the skull. The skin flap was removed, and overlying muscle was cleared from the skull. Three small holes were drilled in the region of the frontal cortex and fine jeweler's screws were inserted as an anchor for a large screw that was affixed to the skull upside down with dental acrylic. The dental acrylic was allowed to solidify for 15 minutes, and an 8 mm diameter hole was drilled over the right temporal lobe. If necessary the hole was enlarged with bone rongeurs until the anterior and posterior ectosylvian sulci were fully exposed, insuring complete exposure of the primary auditory cortex. If possible, the dura was left intact, and the exposed region was covered with light mineral oil. Following surgery, the cat was placed in a sound treated room on a vibration isolation frame (TMC micro-g), and the head was anchored in position with the single large screw. The atropine/Acepromazine mixture was administered every 2 hours, and light anesthesia was maintained with intramuscular injections of ketamine (2-5mg/kg/hr). Wound margins were regularly infused with durocain, and light mineral oil was added to the exposed regions when required. Temperature of the animal was maintained at 38° C with a thermostatically controlled blanket (Harvard Medical Systems). Animals were sacrificed with an overdose of sodium pentobarbital upon the completion of each experiment.

Acoustic Stimulation Procedure

Acoustic stimuli were presented from a single speaker (Foster RM 765 or Realistic Minimus 3.5) placed with its center 50 cm in front of and oriented perpendicular to the cat's auditory meati. The sound treated room was made anechoic for frequencies above 625 Hz by covering walls and ceilings with acoustic wedges (Sonex 3") and by covering exposed areas of the vibration isolation frame, equipment and floor with acoustic wedges as well. Calibration and monitoring of the sound field was done by placing a B&K (type 4134) microphone facing the loudspeaker above the cat's head.

Two types of acoustic stimuli were presented in this study; clicks and broad band noise. Click trains (1 s in duration) were presented every 3 seconds. In some instances, click presentation alternated between rates of 1, 2, 4, 8, 16, and 32 clicks per second, respectively (Figure 1a & b). This particular sequence of six click trains lasted a total of 18 seconds, and each train was repeated 50 times. A set of 21 click trains with rates varying between 1 to 32 per second (4 rates per octave), were also utilized in this study (Figure 2a & b). The 21 click trains had a total duration of 63 seconds and were repeated 10 times each. All click stimuli were produced by 0.1 ms rectangular electric pulses. Broad band noise was presented continuously for 500 ms followed by a silent period lasting from 0 to 70 ms, and a second 500 ms period of noise (Figure 3a & b). Only the responses to the first 100 ms of the noise stimuli are examined. Broad band stimuli are placed in 15 groups or sets, where each set is repeated 20 times and lasts for a total of 2 s (1 s of noise stimulation followed by a 1 s silent period). Spontaneous activity was sampled periodically over a 900 s period.

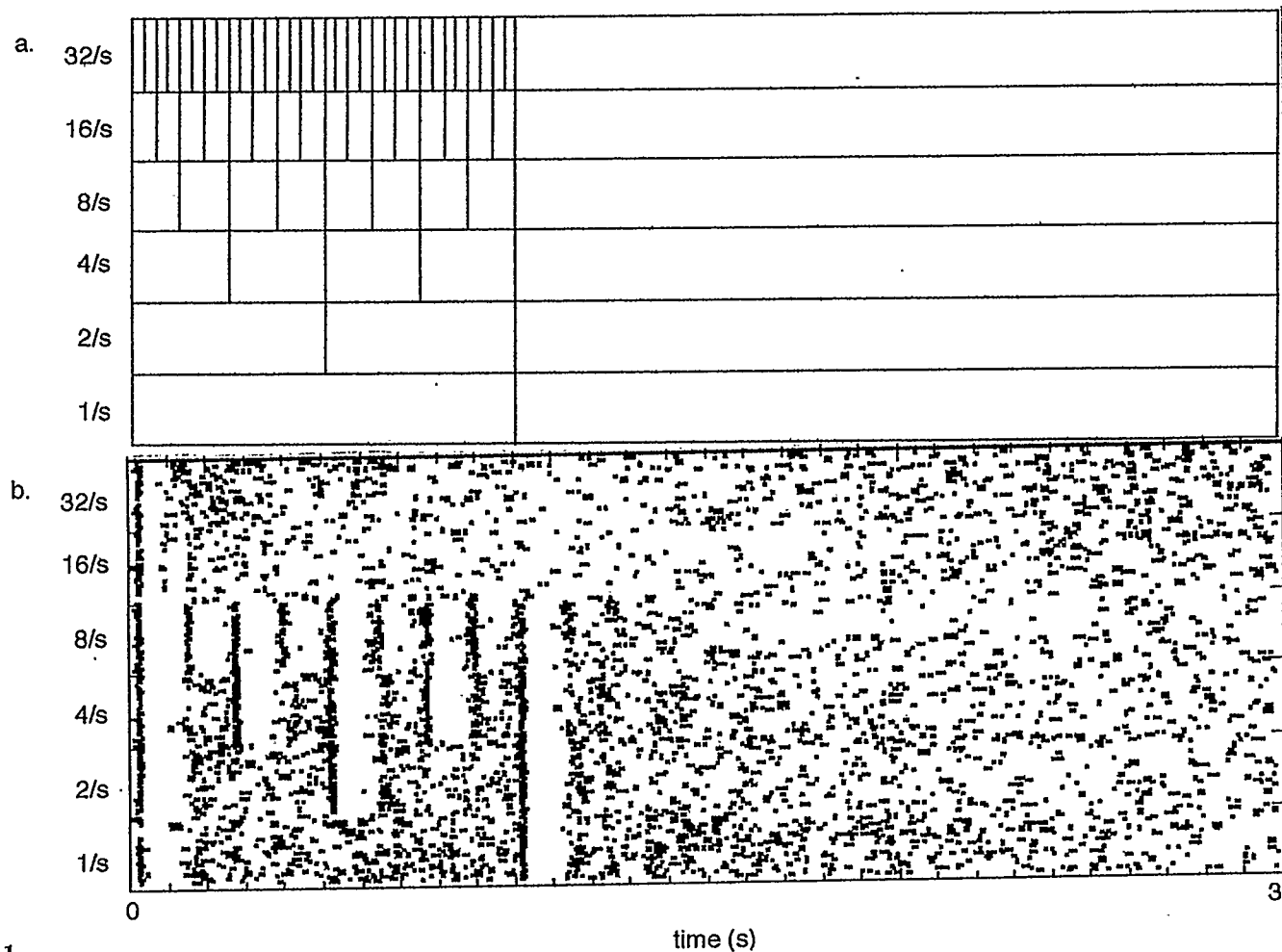


Figure 1.

Click train stimuli and a dot display of single unit firing activity during click train stimulation (first second), and following click train stimulation (last 2 seconds). a) A schematic representation of the stimulus. Click trains were presented once every 3 seconds. Clicks were presented at 6 different rates ranging from 1 to 32 Hz and each train was presented 50 times. b) A dot display of single unit firing activity. Time is represented on the x-axis, and stimulus set (click rate) on the y-axis.

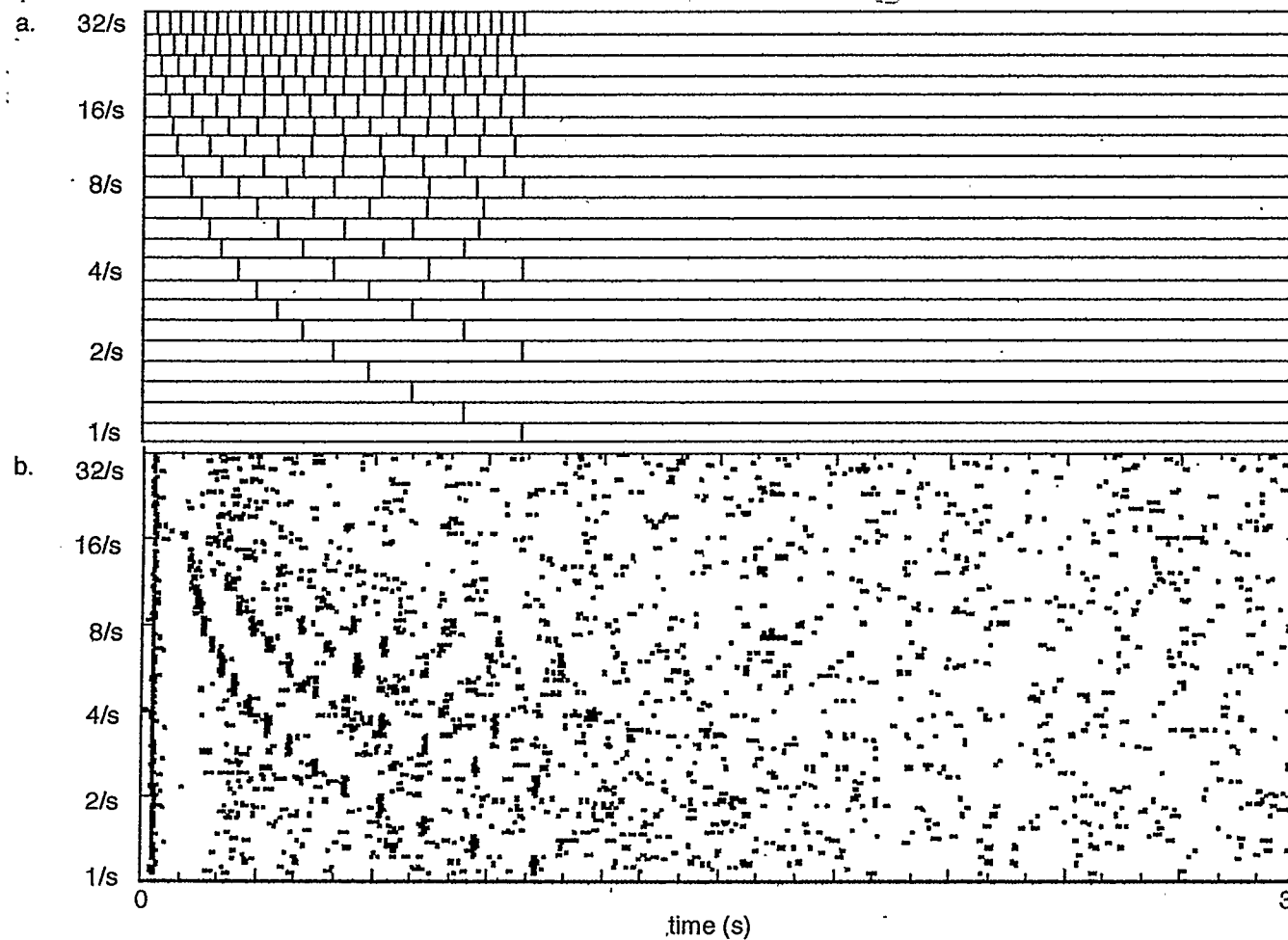


Figure 2.

Click train stimuli and a dot display of single unit firing activity during click train stimulation (first second), and following click train stimulation (last 2 seconds). a) A schematic representation of the stimulus. Click trains were presented once every 3 seconds. Clicks were presented at 21 different rates ranging from 1 to 32 Hz (4 rates per octave), and each train was presented 10 times. b) A dot display of single unit firing activity. Time is represented on the x-axis, and stimulus set (click rate) on the y-axis.

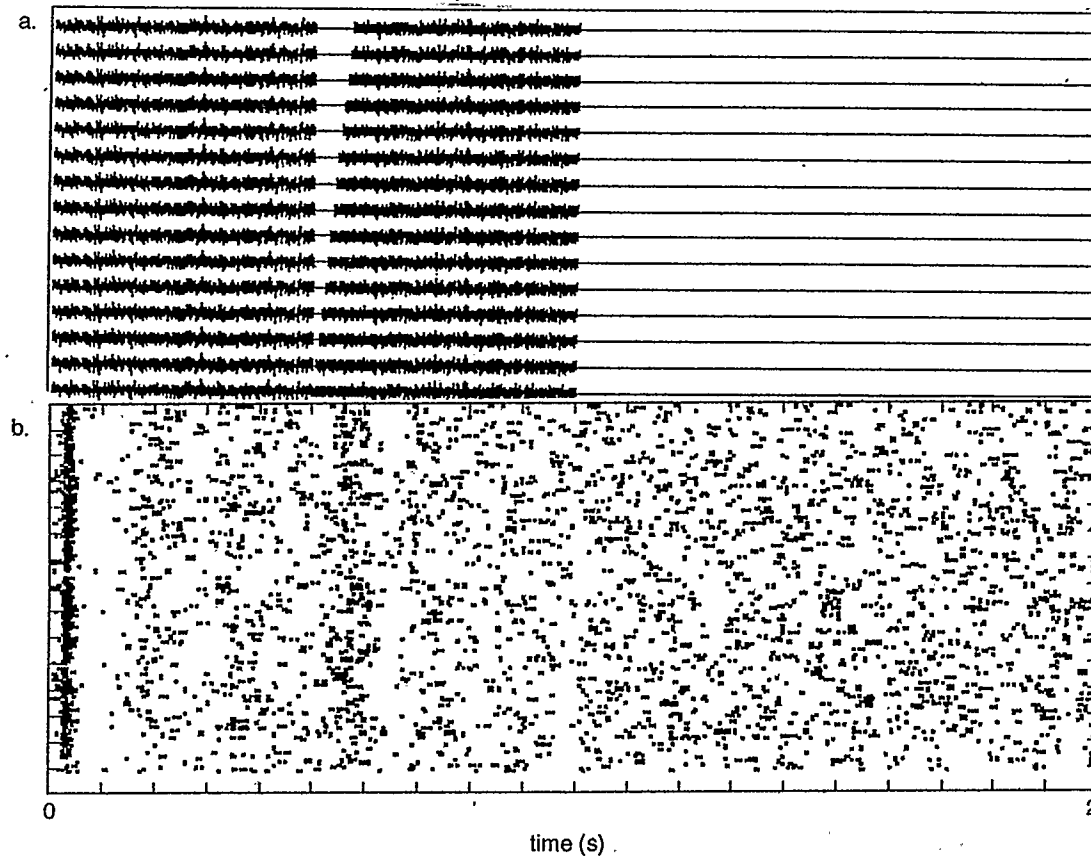


Figure 3.

Broad band noise stimuli and a dot display of single unit firing activity during noise stimulation (first second), and following noise stimulation (last second). Only noise onset responses (≤ 100 ms after noise onset) and the post noise stimulation responses (≥ 500 ms after noise stimulation) are examined in this study. a) A schematic representation of the noise stimulus. The gap in the noise burst and its effect on firing activity was not used in this study. Noise stimuli lasted for a total period of 1 second and were presented once every 2 seconds. Each stimulus was presented 20 times. b) A dot display of single unit firing activity. Time is represented on the x-axis, and stimulus set (noise stimuli) on the y-axis.

Recording Procedure

After defining the boundaries of the primary auditory cortex (AI) electrophysiologically, two tungsten microelectrodes (Micro Probe Inc.) with impedances between 1.0 and 2.5 M Ω were independently advanced perpendicular to the AI surface using remotely controlled motorized hydraulic microdrives (Trent-Wells Mark III). The signals recorded on the electrodes were amplified using extracellular preamplifiers (Dagan 2400) and filtered to remove evoked field potentials between 200 Hz (Kemo VBF8, high pass, 24 dB/oct) and 3 kHz (6 dB/oct, Dagan roll-off). The electrode signals were sampled through 12 bit A/D converters (Data Translation, DT 2752) and together with a timing signal from two Schmitt-triggers were fed into a PDP 11/53 microcomputer. In most cases, the signal on each electrode contained activity from more than one unit. These multi-unit signals were separated into single-unit spike trains using a maximum variance sorting algorithm (Eggermont, 1991). Spikes separated into a number of distinct classes were assumed to represent a particular neuron and were coded for display. Only units which had a high quality sorting (very little variability in spike waveforms within a class) were utilized in the present study. The unit code and the time of spike occurrence were sent to a Microvax II computer which presented an online color coded multi-unit dot display on either a Vectrix graphics processor or a MacIntosh II, and the unit code and time of spike occurrence were stored. Dot displays were organized per stimulus set (see Figures 1 - 3 a). Single unit recordings were obtained at a variety of cortical depths ranging from 100 to 2000 μm . Recording files of individual units must have contained a minimum of 200 spikes before being considered for further analysis.

Data Analysis

Auto-correlations and Higher order Interval Histograms

Recordings of spontaneous activity were made from 99 single units in the primary auditory cortex of 19 juvenile and adult cats (30 to 240 days). To quantify the temporal structure of spontaneous bursts the auto-correlation function and higher order interval histograms were calculated for each unit over 50 ms time lags for each 900 second recording of spontaneous activity. Interval histograms represent the distribution of time intervals between a reference spike and another spike in the spike train. First order intervals represent the time between each spike and the first successive spike in a spike train (the 'standard' interspike interval histogram). Second order intervals represent the distribution of time between all spikes and the second successive spike in the spike train. The sum of all order interval histograms for a particular unit represents the auto-correlation of that unit's spike train for time lags up to 50 ms (Figure 4). The auto-correlation function $R_{xx}(T)$ is defined by the equation:

$$R_{xx}(T) = \sum_{n=1}^N x(t_n) x(t_n + T)$$

$$\{x_n\}, n = 1, 2, \dots, N$$

where T is the lag, and t_n is the time associated with data point x_n . The auto-correlation is an even or symmetrical function, therefore calculations are done only for positive lag values. In order to remove the large central peak that occurs at a lag time of 0 (which represents the total spike count for a given unit), only lag times of greater than 0.01 ms are utilized when generating the auto-correlation function for a particular unit. Interval histograms of orders 1 to 10 (representing bursts containing 2-11 spikes), and auto-correlations contain 1 ms bin widths or intervals on their ordinate, and either counts or normalized counts on their abscissa.

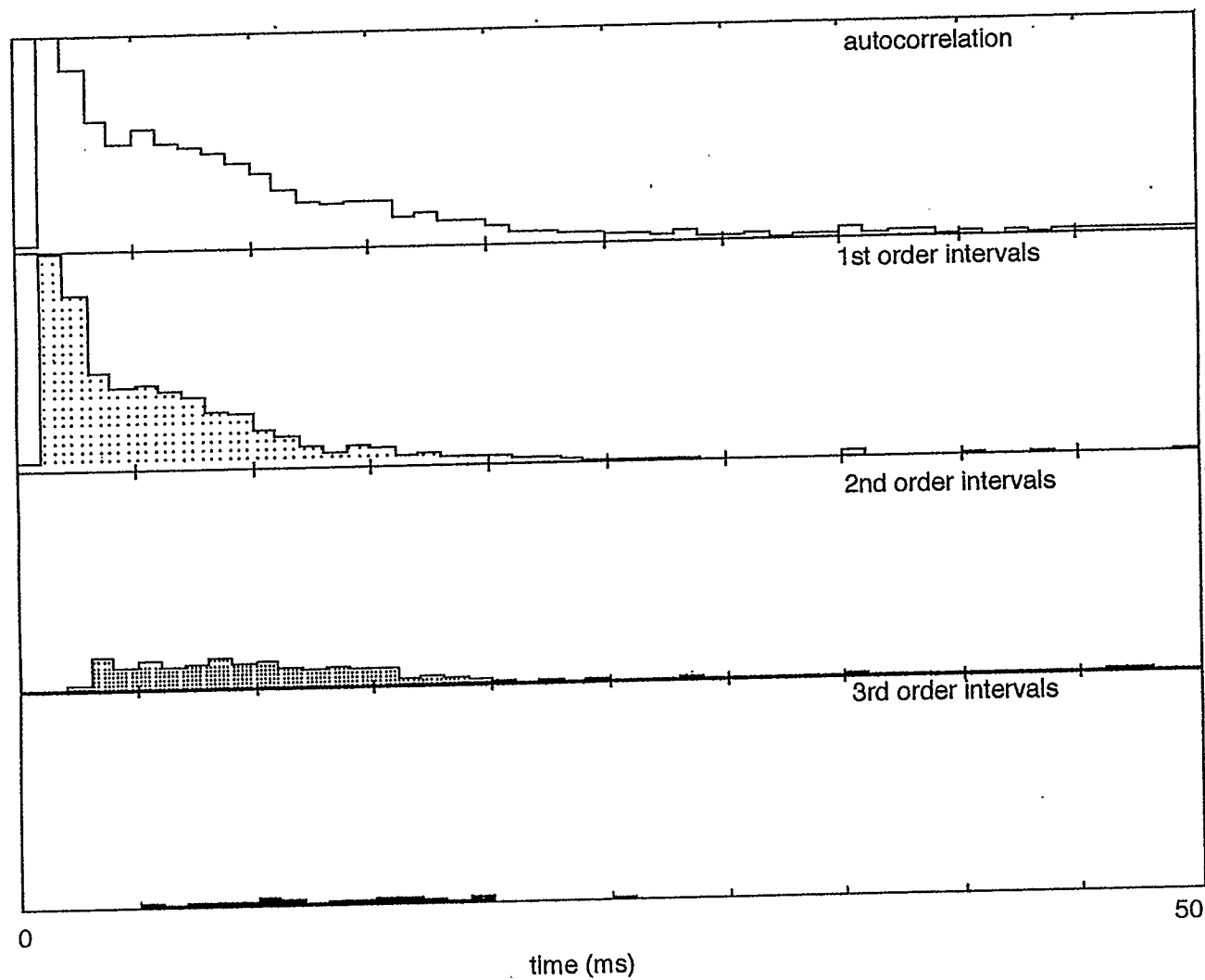


Figure 4. Auto-correlogram and interval histograms of a single unit spike train. The auto-correlation function (a) is well approximated by the sum of the first, second, and third order interval histograms (b-d, respectively).

Conditional Auto-correlations and Interval Histograms

Recordings of neural activity during periods of stimulation and in between periods of stimulation were also obtained from the same 99 units utilized in the spontaneous condition. A total of 69 units were recorded from during click train stimulation, and 30 units during broad band noise stimulus onset. Conditional auto-correlations and higher order interval histograms were calculated to examine the temporal structure of bursts during periods of stimulation. The conditional auto-correlation represents the sum of all order interval histograms conditional upon both the onset of the stimulus and the occurrence of at least 2 spikes within 100 ms of the stimulus onset. Thus, the first order conditional interval refers to the time period between the first spike after the stimulus and the next successive spike in the spike train. Higher order conditional interval histograms of orders 1 to 6 (representing bursts containing 2-7 spikes) were calculated for 50 ms time lags following the occurrence of two spikes in the 100 ms post click and post noise onset time windows (stimulation condition). However, conditional auto-correlations and interval histograms were only calculated for a subset of clicks (representing rates of 1-4/s) where the response demonstrated periodic stationarity. Auto-correlation functions and interval histograms represent counts summed over the entire period of stimulation. To examine the potential after effects of stimulation, conditional auto-correlation functions and interval histograms were also calculated for each unit in the starting 500 ms after the stimulus ended (post stimulation condition). The last click in a train is presented at a time of 1 s and trains are presented at 3 second intervals. Therefore, in the post click stimulus condition, auto-correlations and interval histograms were calculated for 50 ms lags during the last 1.5 s after each click train presentation. Interval counts were summed over the entire post stimulation period (Figures 1b & 2b). Broad band noise is presented at 2 second intervals, and the duration of each stimulus is 1 s. Thus, in the post noise stimulus condition, auto-correlations and interval histograms were calculated for 50 ms

time lags in the last 500 ms silent period after each stimulus set and summed over the whole post noise stimulation period (Figure 3b).

Normalization

Data files collected during periods of silence and stimulation are of different duration. Prior to any comparison between burst firing in the spontaneous and stimulated conditions, all distributions are normalized in one of two ways. The first normalization accounts for changes in mean firing rate between stimulus conditions by dividing the auto-correlation and higher order interval distributions or counts by the total spike count for a given unit, over the entire analysis time period. The resulting distribution values are the proportion of all spikes that are isolated spikes or bursts (proportion of singlets, pairs, triplets etc.) for a given unit. To compare whether the rate of occurrence of single spikes, pairs, triplets etc. changes as a function of stimulus condition, the raw counts of particular bursts derived from the auto-correlation and higher order interval histograms were divided by the total stimulus duration, yielding a burst rate measure that was comparable across stimulus conditions.

Comparing Burst Occurrence Across Stimulus Conditions

Counts obtained from the various order interval histograms were utilized to calculate the number of spike pairs, triplets, quadruplets etc. in the single unit recordings. The incidence of bursts calculated from higher order interval histograms over estimate the number of 'short bursts' (i.e. pairs, triplets etc.) because higher order or 'long bursts' contain lower order bursts. For example, in a 5 spike burst, there are 2 quadruplets, 3 triplets, 4 pairs and 5 single spikes. Therefore, it was necessary to correct for the contribution of higher order bursts to the lower order burst count. In an iterative way, starting with the highest order or longest burst, the count of higher order bursts (i.e.

number of 5-plets) was subtracted from the count of lower order bursts (i.e. uncorrected count of 4-plets, triplets etc. which included higher order bursts) to arrive at a count that reflected the actual number of single spikes, pairs, triplets etc. found in a 50 ms window for each unit. To examine the effect of stimulation on burst occurrence, the proportion and rate of single spikes, pairs, triplets, etc. are compared for the stimulation, post stimulation, and spontaneous conditions for each unit with a dependent t-test (Statview 4.1). The null hypothesis is that both the proportion of the response consisting of bursts and the rate of burst occurrence is the same in all three conditions.

Histogram Comparison

Interspike interval distribution differences are tested by subtracting normalized auto-correlations and interval histograms under spontaneous conditions from normalized auto-correlation functions and interval histograms in the stimulus and post stimulus conditions (Figure 4). The resultant normalized difference histograms are tested for significance on the basis of the interval distribution of the spontaneous histogram (the expectation histogram). In a 0 - 1 bin filling Poisson process the standard deviation of the expectation is equal to the square root of the expectation. In order to calculate the standard deviation of the normalized expectation histogram, it is necessary to divide the standard deviation of the expectation by the total number of spikes emitted by a given unit over the entire analysis time period. Under the assumption that the histogram obtained during periods of stimulation (test histogram) and the spontaneous histogram are identically distributed, the standard deviation of the normalized stimulated histogram can likewise be estimated from the spontaneous histogram. However, if the recordings are of different lengths, then the estimated variance of the test histogram is weighted according to its length in reference to the spontaneous recording. The difference histogram represents the combination of two random variables, the normalized expectation and test

histograms. Thus, the variance of the difference histogram is the sum of the variance of the expectation histogram and the variance of the test histogram. In the present study, a difference between the interspike interval distributions of two histograms is only considered significant if it is greater than 2.0 times the estimated standard deviation for the difference histogram over three or more consecutive bins ($p \leq .01$ per histogram).

Second Order Auto-correlations.

The serial dependence of interspike intervals was examined by modifying the Joint Post Stimulus Time Histogram (JPSTH) procedure for plotting the firing pattern of two neurons relative to the onset of a stimulus (Gerstein and Perkel, 1972). The JPSTH consists of a scatter plot of coincident firings of two units during and following the presentation of a stimulus or some other defined reference, where the density (or coincidence count) of the scatter plot is estimated by defining bins with a Cartesian grid. Abeles et al. (1993) modified the JPSTH procedure to detect compound or multi-unit firing patterns in frontal cortex by substituting the firing times of a reference unit as the stimulus, and plotting the delayed firings of a second unit relative to the 'pseudo stimulus' on the x- axis of the histogram, and the delayed firing pattern of a third unit on the y axis of the histogram. In the modified procedure the marginal histogram on the x-axis represents the pair wise correlation of firing between the reference unit and a second unit, and the marginal histogram on the y-axis represents the pair wise correlation between the second and third unit firings. The x-y plane or modified JPSTH represents the 3-fold correlation among the firings of the three units. The researchers employed a 3 ms bin width in the histograms to allow for a ± 1 ms jitter in coincident firings. The probability of observing a particular coincidence count by chance is estimated by comparing the observed count to a predicted count based on the distribution of possible JPSTH values for a given bin in a histogram (Palm, Aertsen, & Gerstein, 1988). The

marginal histograms (which represent the conditional and time dependent firing frequencies of the two units) are utilized to estimate the firing probabilities of each individual unit. The probability density and the cumulative distribution of the coincident count is calculated from the estimated firing probabilities of the two units (Palm et al., 1988). Under the assumption of independence, the observed coincident count should be completely accounted for by the marginal histograms, and have a correspondingly high probability of occurrence. A *surprise* value (Palm et al., 1988), or the negative natural logarithm of the probability of finding the observed coincident count in the predictor, can be calculated for each bin in the histogram.

In the present study, the JPSTH plotting and significance calculation procedures were modified to test for the occurrence of preferred firing intervals in the spike trains emitted by single units during periods of stimulation. Only units which emitted significant excess of short intervals or bursts during periods of stimulation (see histogram comparison procedure) were examined with the modified JPSTH procedure. In this study each spike emitted by a single unit served as a 'pseudo stimulus' or reference from which the delayed incidence of all first order spikes, second order spikes, third order spikes etc., in the same spike train are calculated on the margin of the x-axis. This marginal histogram represents the auto-correlation of the spike train for a particular unit for lag times up to 50 ms. To examine whether particular intervals in a given spike train have a tendency to co-occur, the distribution of firing times are again used as a reference for the delayed incidence of all first, second and third order spikes on the y-axis. Thus, the marginal histogram on the y-axis also represents the sum of all order intervals or the auto-correlation for a particular unit, and the x-y plane represents the co-occurrence of particular intervals in the spike train or the second order auto-correlation (see Figures 17-19). To allow for a jitter of ± 1 ms, histograms were divided into ~ 3 ms bins (50 ms/17bins). Therefore, both the x and y axes consisted of 17 time intervals or bins. The

procedure outlined above and described by Abeles et al. (1993) was utilized in the construction of the histograms, and the same calculation was performed to determine coincident probabilities and surprise values. To control for histogram wise type I error rate (the probability of rejecting the null hypothesis when it is in fact true) a Bonferroni adjustment is employed in the analysis. This adjustment is based on the number of significance tests performed on each histogram, as prescribed by Harris (1975). This adjustment is derived from the Bonferroni inequality which states:

$$\alpha_{\text{set}} \leq \sum_{i=1}^b \alpha_i = b\alpha \text{ if all } \alpha_i = \alpha$$

where α_i is the Type I error rate for the test of the i th of a set of b null hypotheses, and α_{set} is the probability that one or more of the b null hypotheses will be rejected given that all null hypotheses in the set are true. Therefore, to insure α_{set} or the histogram wise error rate remains at $p \leq .01$, the sum of α_i or the sum of the type I probabilities associated with each bin tested must be $\leq .01$. To guarantee this value is not exceeded, the histogram wise error rate of $p \leq .01$ must be divided by the number of bin wise significance tests performed in each histogram. No apriori assumptions are made about which intervals may be 'preferred' or have high coincidence counts, therefore in essence every orthogonal bin in the histogram is tested for significance. It follows that the number of significance tests performed is equal to the number of orthogonal bins in the histogram. In the case of the second order auto-correlation the bins on the diagonal represent the squared auto-correlation at lagtimes of 0, and are therefore not of interest (Figures 16-19). The second order auto correlation histogram is also symmetrical about the diagonal, thus one half of the bins in the histogram contain redundant information. In this study, each second order auto-correlation histogram contains 289 bins in total (the square of the bin count for a given axis). However, 17 of these bins are on the diagonal, and 136 bins contain redundant information. Therefore, only 136 bins are considered for

significance testing. To maintain a histogram wise type 1 error rate of $p \leq .01$, the count found in an individual bin will only be considered to deviate significantly from the predictor when the probability value is less than or equal to .0000735 (.01/136) or a surprise value greater than 9.5 ($-\ln(.0000735)$).

To examine whether the second order auto-correlation is sensitive to the recurrence of particular spike patterns a modified Poisson distributed spike train was run through the second order auto-correlation and surprise calculation procedures. The modified Poisson spike train was composed of 10 triplet patterns consisting of a 10 ms interval followed by a 20 ms interval randomly added to a Poisson distributed spike train file, with a 4 per second spike rate and 1600 spikes in total.

III. Results

Burst Firing in Single Unit Spike Trains During Stimulation and Periods of Spontaneous Activity

Figures 5a and 6a illustrate the response of a single unit in the time period immediately following click presentation and noise onset, respectively. Each dot display has time (in seconds) on the x-axis and stimulus set plotted on the y-axis (see Methods section, Figures 1 & 3). The stimulus locked response consists of a brief elevation in firing rate followed by a period of suppression for both stimuli. The suppression period following a click (~100 ms) is longer than the suppression period following noise onset (~50 ms). Note the time scale difference between the click and noise displays.

Brief duration bursts (< 50 ms) are clearly visible in the spike train of a single unit as horizontal streaks in a raster display, where individual dots are joined in a single line, or as a cluster of dots in a single row (Figures 5 & 6). Short duration bursts occur in the period immediately following stimulus presentation (a), in the post stimulation period (b), and during periods of spontaneous activity (c) in the responses to both click (Figure 5) and broad band noise stimuli (Figure 6).

In the post click condition (Figure 5b) there is a section of elevated activity following the presentation of lower rate clicks, as indicated by the higher density of dots in the bottom left corner of the raster display. Prolonged periods of elevated activity, or dense sections of the dot display, are not present during periods of spontaneous activity for the same unit (Figure 5 c), or in the 500 ms post noise period (Figure 6b). The density or distribution of dots in the post noise condition is similar to the dot distribution in the display representing a period of spontaneous activity of the same duration for the same unit (6c).

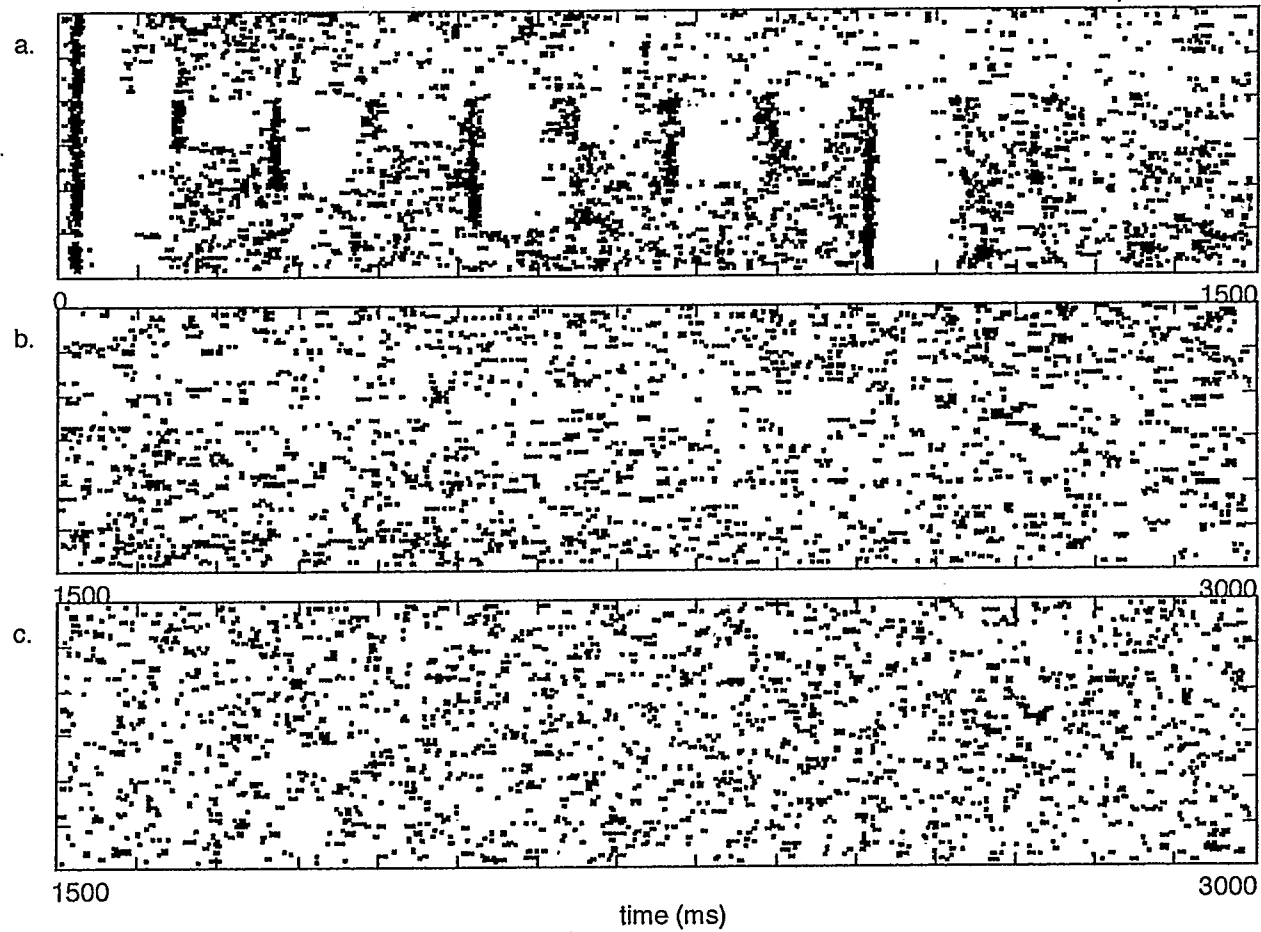


Figure 5.

Dot display of single unit firing behavior during click stimulation (a), 0.5 to 1.5 s post click train stimulation (b), and during periods of spontaneous activity (c). See figure 1 for schematic representation of stimulus. Burst-firing, shown as horizontal streaks or clusters of dots in the display, was evident in all three response periods. Note the period of elevated firing following stimulation with low rate click trains (b, bottom left corner), and the duration of the suppression period following the initial response to each click, ~ 100 ms (a).

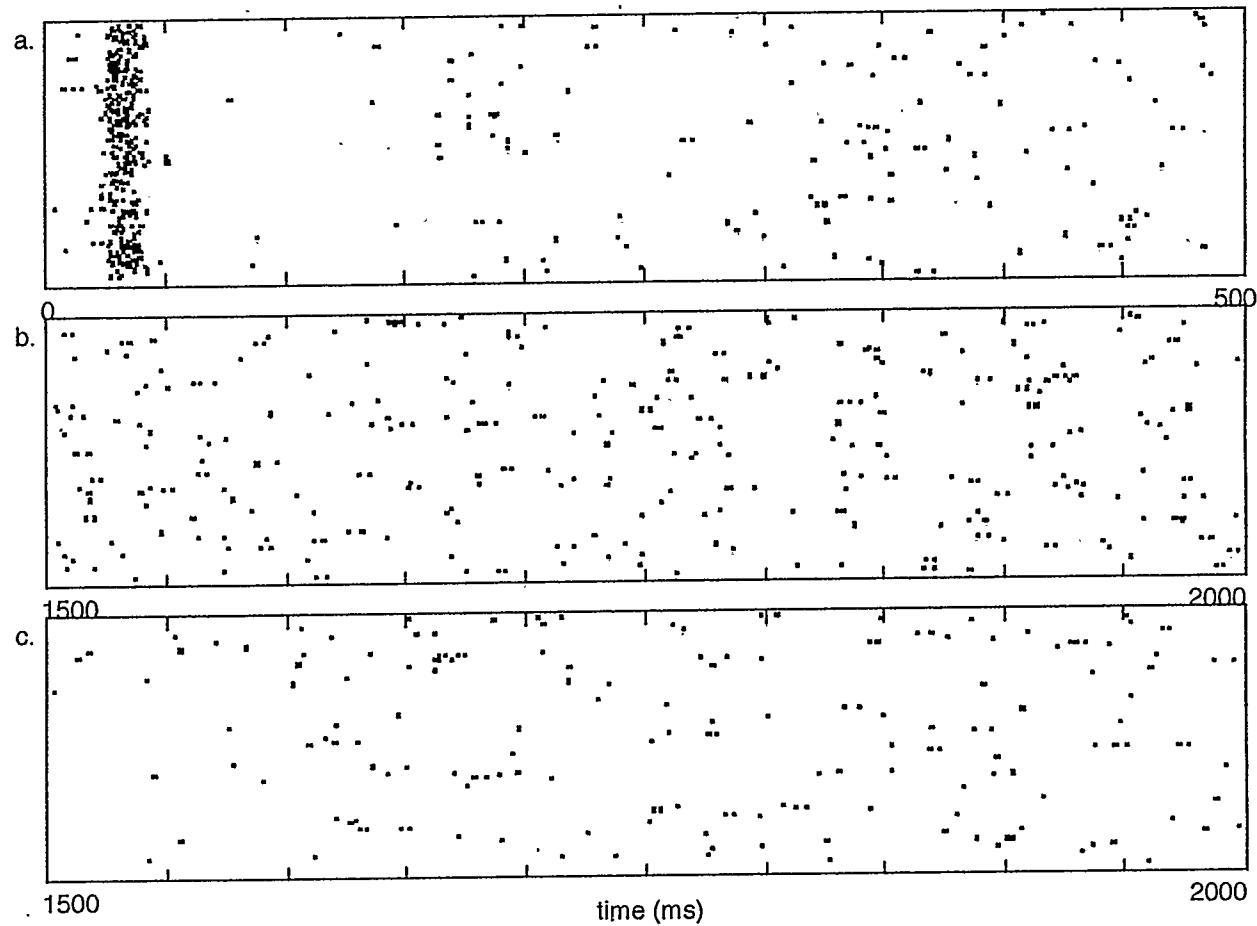


Figure 6.

Dot display of single unit firing behavior during noise onset (a), 0.5 to 1.0 s post noise stimulation (b), and during periods of spontaneous activity (c). Burst-firing, was again evident in all three response periods. For schematic representation of stimulus see figure 3. The incidence of burst firing in the post noise stimulation period and spontaneous period was similar. Note the length of the suppression period following the noise onset response, ~ 50 ms (a).

Dot displays of single unit responses to clicks and noise are further decomposed into an isolated or single spike response component and burst components. A burst is composed of two or more spikes occurring within ± 30 ms of one another. A spike is considered 'isolated' if it is not preceded or followed by another spike within a 60 ms time window. Figure 7a illustrates the total response of a single unit to clicks over a 900 s recording period. Figures 7b through 7e show isolated spike responses, and burst responses with 2 or more, 3 or more, and 4 or more spikes, respectively. A greater proportion of the response consist of bursts of two or more spikes than single spikes (7b,c), especially in regions outside of the onset responses. Single spikes and short bursts (pairs and triplets) more frequently occur in conjunction with click presentation (Figures 7 b-d) where as longer bursts (4-plets and up) are dominantly observed in the post click spontaneous response periods (7 e). Periods of elevated activity after the presentation of low rate click trains (1-4/s), shown in figures 5b and 7a, are also evident in figures 7 c-e indicating that this elevated period of activity is mainly composed of bursts of 2 or more action potentials.

The firing activity of a single unit during the onset of broad band noise is shown in the first 500 ms of figure 8 a. Single spikes are plotted in figure 8 b and bursts consisting of two or more, three or more and four or more spikes are shown in figures 8 c-e, respectively. The noise onset response is composed of both single spikes and bursts. In contrast to the click response, the noise onset response frequently contains bursts of 4 or more spikes.

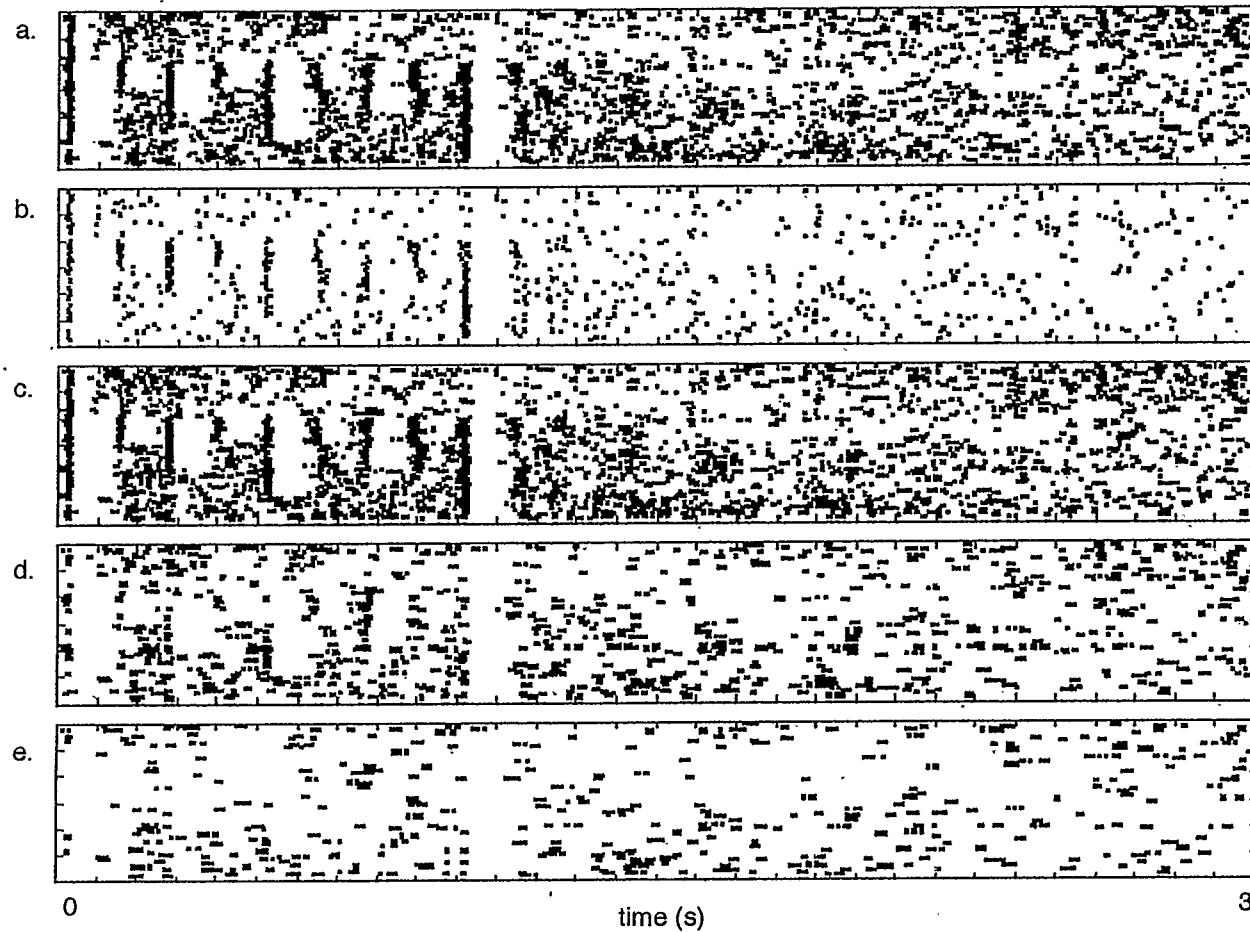


Figure 7.

Dot displays of single unit firing behavior during click train stimulation (first 1000 ms), and following stimulation (last 2000 ms). a) Isolated spikes and bursts (2 or more spikes at time lags ≤ 60 ms). b) Isolated spikes. c) Bursts consisting of 2 or more spikes. d) Bursts consisting of 3 or more spikes. e) Bursts consisting of 4 or more spikes. Isolated spike and short burst responses (pairs & triplets) were more commonly observed during click train stimulation (b-d), where as long bursts were more commonly observed in the post stimulation period (e). Periods of elevated burst firing were present 0.5s to 1.0s following the presentation of low rate click trains (c-e).

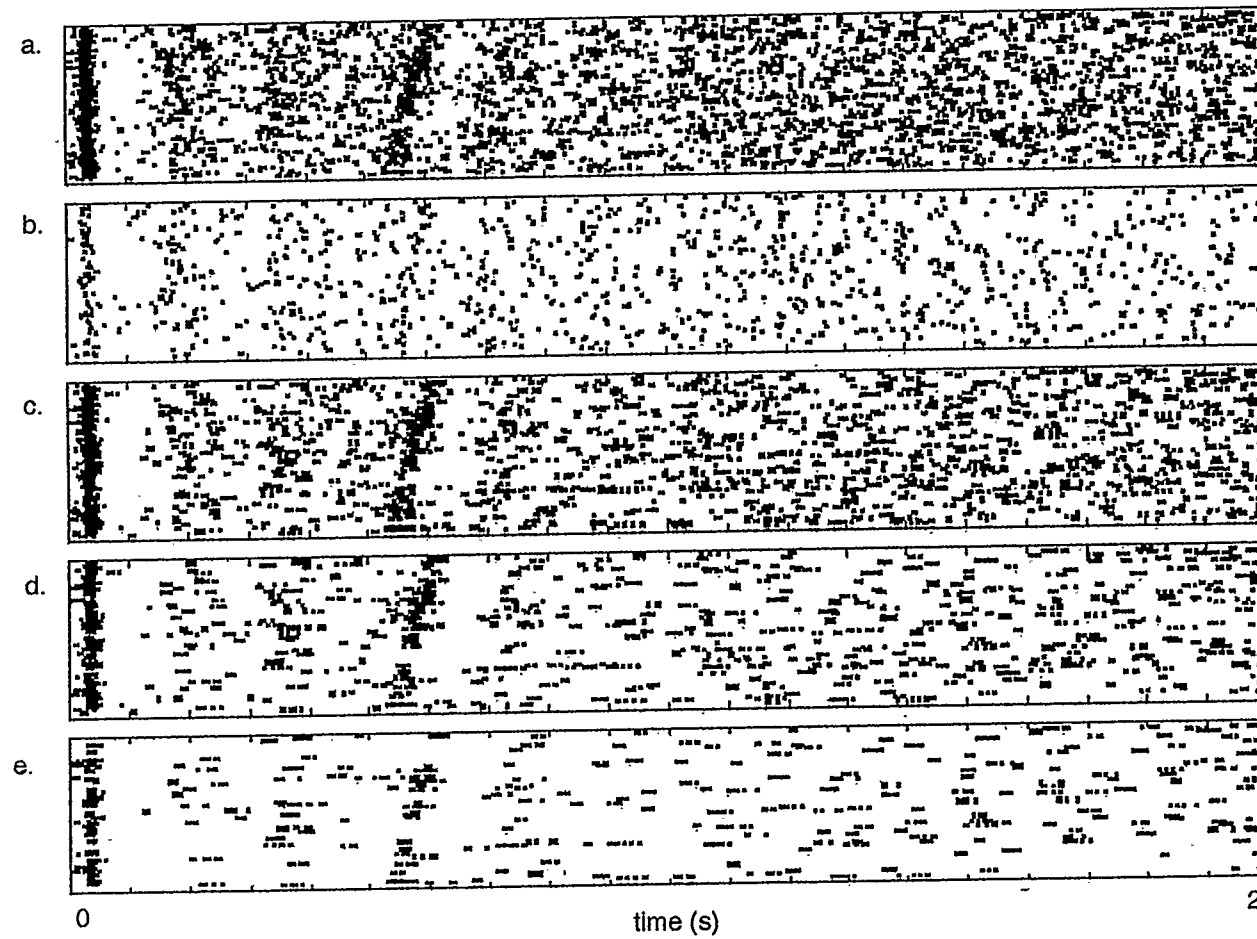


Figure 8.

Dot displays of single unit firing behavior during noise stimulation (first 1000 ms), and following stimulation (last 1000 ms). a) Isolated spikes and bursts (2 or more spikes at time lags ≤ 60 ms). b) Isolated spikes. c) Bursts consisting of 2 or more spikes. d) Bursts consisting of 3 or more spikes. e) Bursts consisting of 4 or more spikes. Unlike click responses, noise onset responses were often composed of bursts of 4 or more spikes (e).

Effect of Stimulation on Burst Occurrence

The proportion of all spikes consisting of singlets, pairs etc. emitted by a single unit are compared for three stimulus conditions: following stimulus onset (stimulation condition); starting 500 ms following stimulus offset (post stimulation condition); and for a 900s period of spontaneous activity (spontaneous condition), for both stimuli.

Proportion of Burst Responses - Click Trains

There was no significant difference between the proportion of single spikes pairs, triplets...6-plets in the spontaneous and post-stimulation response periods of 69 single units. Table 1 summarizes the results of the dependent t-test comparing the proportion of single spikes and bursts in the click stimulation and spontaneous conditions. There is a significantly larger proportion of single spikes in the responses of individual units during click stimulation than there is during periods of

Table 1. Comparison of Burst Proportion For Click Stimulation and Spontaneous Conditions

Burst Comparison (Stim.- Spon.)	Mean Difference	DF	t-Value	p
Singlets	.129	68	6.021	<.0001
Pairs	-.065	68	- 4.308	<.0001
Triplets	-.044	68	- 6.391	<.0001
4-plets	-.013	68	- 3.644	.0005
5-plets	-.004	68	- 3.338	.0014
6-plets	-.001	68	- 5.050	<.0001

spontaneous activity ($t = 6.021$, $p \leq .0001$). Periods of spontaneous activity contain a significantly greater proportion of bursts (pairs to 6-plets), than periods of stimulation.

Table 2 outlines the results of the dependent t-test comparing the proportion of single spike and burst responses in the click stimulation and post click stimulation conditions. Responses during click train stimulation are composed of a greater proportion of singlets than post stimulation responses ($t = -7.921$, $p < .0001$). However, the single unit responses in the post stimulation condition contain a significantly larger proportion of bursts composed of 2 to 6 spikes, than responses during click stimulation.

Table 2. Comparison of Burst Proportion For Click Stimulation and Post Click Stimulation Conditions

Burst Comparison (Stim.- Post. Stim.)	Mean Difference	DF	t-Value	p
Singlets	.135	68	7.921	<.0001
Pairs	-.068	68	- 5.634	<.0001
Triplets	-.046	68	- 7.076	<.0001
4-plets	-.011	68	- 3.682	.0005
5-plets	-.004	68	- 2.706	.0086
6-plets	-.002	68	- 3.573	.0007

Proportion of Burst Responses - Broad Band Noise

Table 3 summarizes the differences in the proportion of single spikes and bursts in the post noise stimulation and spontaneous response periods for 30 single units. There is no

significant difference in the proportion of single spikes, pairs, 5-plets and 6-plets in post stimulation and spontaneous responses. However, the spontaneous responses contain a higher proportion of triplets and 4-plets than the post stimulus responses ($t = -6.738$, $p \leq .0001$ & $t = -3.936$, $p \leq .0005$, respectively).

Table 3. Comparison of Burst Proportion For Post Noise Stimulation and Spontaneous Conditions

Burst Comparison (post. Stim.- Spon.)	Mean Difference	DF	t-Value	p
Singlets	- .015	29	- 0.692	.4946
pairs	.012	29	0.875	.3889
Triplets	- .040	29	- 6.738	< .0001
4-plets	- .009	29	- 3.936	.0005
5-plets	.003	29	1.427	.1644
6-plets	.0005	29	0.684	.4994

A significantly greater proportion of the noise stimulation responses are composed of single spikes when compared to the post stimulation and spontaneous responses (Tables 4 & 5). However, the post stimulus and spontaneous conditions contain a greater proportion of short bursts (pairs and triplets) than the noise stimulation condition.

Table 4. Comparison of Burst Proportion For Noise Stimulation and Spontaneous Conditions

Burst Comparison (Stim.- Spon.)	Mean Difference	DF	t-Value	p
Singlets	.111	29	6.021	.0002
pairs	- .066	29	- 4.308	.0013
Triplets	- .035	29	- 6.391	.0001
4-plets	- .007	29	- 3.644	.0526
5-plets	- .002	29	- 3.338	.4843
6-plets	- .001	29	- 5.050	.1741

Table 5. Comparison of Burst Proportion For Noise Stimulation and Post Noise Stimulation Conditions

Burst Comparison (50 ms Stim.- Post Stim.)	Mean Difference	DF	t-Value	p
Singlets	.126	29	7.921	<.0001
pairs	- .078	29	- 5.634	<.0001
Triplets	.005	29	- 7.076	.3893
4-plets	.116	29	- 3.682	.5914
5-plets	- .004	29	- 2.706	.1929
6-plets	- .001	29	- 3.573	.1695

Burst Rate Comparison - Clicks

Tables 6 and 7 outline the results of the dependent t comparison of single spike and burst rate in the click stimulation, post click stimulation, and spontaneous conditions. There was no significant difference between the single spike or burst rate in the spontaneous and post click stimulation response periods.

The single spike rate is significantly higher in the click responses than in the post-click responses (Table 7). A similar difference exists between the click stimulation and spontaneous conditions, however this difference only approaches significance at a $p \leq .01$ level (Table 6). The rate of long bursts (triplets and up) is significantly lower in the click stimulation response period than in the post click stimulation and spontaneous response periods.

Table 6. Click Stimulation and Spontaneous Single Spike and Burst Rate Comparison

Burst Comparison (Stim.- Spon.)	Mean Difference	DF	t-Value	p
Singlets	.462	68	2.190	.0391
pairs	- .132	68	- 1.681	.0974
Triplets	- .137	68	- 6.534	<.0001
4-plets	- .027	68	- 3.753	.0004
5-plets	- .011	68	- 3.907	.0002
6-plets	- .003	68	- 2.998	.0038

Table 7. Click Stimulation and Post Click Stimulation Single Spike and Burst Rate Comparison

Burst Comparison (Stim.- Post Stim.)	Mean Difference	DF	t-Value	p
Singlets	.547	68	7.921	.0083
pairs	- .111	68	- 5.634	.1700
Triplets	- .133	68	- 7.076	<.0001
4-plets	- .021	68	- 3.682	<.0001
5-plets	- .015	68	- 2.706	.0018
6-plets	- .005	68	- 3.573	.0139

Burst Rate Comparison - Broad Band Noise

Tables 8 and 9 summarize the differences in the rate of occurrence of single spikes and bursts in the three stimulus conditions for responses to noise stimuli. There was no significant difference in single spike and burst rate in the post noise stimulation and spontaneous conditions. The rate of occurrence of single spikes and pairs is significantly higher during periods of noise stimulation, than it is following stimulation and during periods of spontaneous activity. There is not a significant difference in the rate of occurrence for longer bursts (triplets and up) in the three stimulus conditions.

Table 8. Noise Stimulation and Spontaneous Single Spike and Burst Rate Comparison

Burst Comparison (Stim.- Spon.)	Mean Difference	DF	t-Value	p
Singlets	5.629	29	2.775	.0096
pairs	.726	29	2.904	.0070
Triplets	.256	29	1.728	.0945
4-plets	.118	29	1.494	.1460
5-plets	.037	29	1.434	.1622
6-plets	.014	29	1.737	.0931

Table 9. Noise Stimulation and Post Noise Stimulation Single Spike and Burst Rate Comparison

Burst Comparison (Stim.- Post. Stim.)	Mean Difference	DF	t-Value	p
Singlets	5.664	29	2.801	.0090
pairs	.725	29	3.114	.0041
Triplets	.254	29	1.814	.0801
4-plets	.114	29	1.565	.1285
5-plets	.029	29	1.372	.1806
6-plets	.012	29	1.724	.0953

Auto-correlation and Higher Order Interval Histogram Comparison

Comparison of Post Click Stimulation and Spontaneous Interval Distributions

An examination of 69 difference histograms comparing the spontaneous condition to the post click condition revealed that 20% of the auto-correlation difference histograms contained significant peaks ($p \leq .01$), indicating that for these units the distribution of interspike intervals in the post click stimulation response period was different than the interspike interval distribution during spontaneous activity. In 12 out of these 14 cases where significant deviations were observed, the difference was positive, indicating an excess of short intervals (< 50 ms) in the post-stimulus auto-correlation function (Figures 9a). These differences are also present in the higher order interval histograms, where positive differences reflect an excess of short first, second and third order intervals in the post click response period (Figure 9b-d). The differences present in the auto-correlation and higher order interval histograms indicate that the interval distribution of spontaneous activity following stimulation is significantly different from spontaneous activity during extended silent periods for a subgroup of units following click train stimulation. These differences could not be accounted for by differences in the age of the animals or the depth at which the recording was made. In cases where there is a significant difference between the post stimulation and silence spontaneous conditions, the data obtained in the silence condition serves as the spontaneous baseline to which the stimulation condition will be compared, in the rest of the cases the post click period serves as the spontaneous base line.

Comparison of Click Stimulation and Spontaneous Interval Distributions

A comparison of the auto-correlation difference histograms of 69 single units in the click stimulation and spontaneous response period indicated that 39% of the difference histograms contained significant deviations. 17 out of these 27 difference histograms

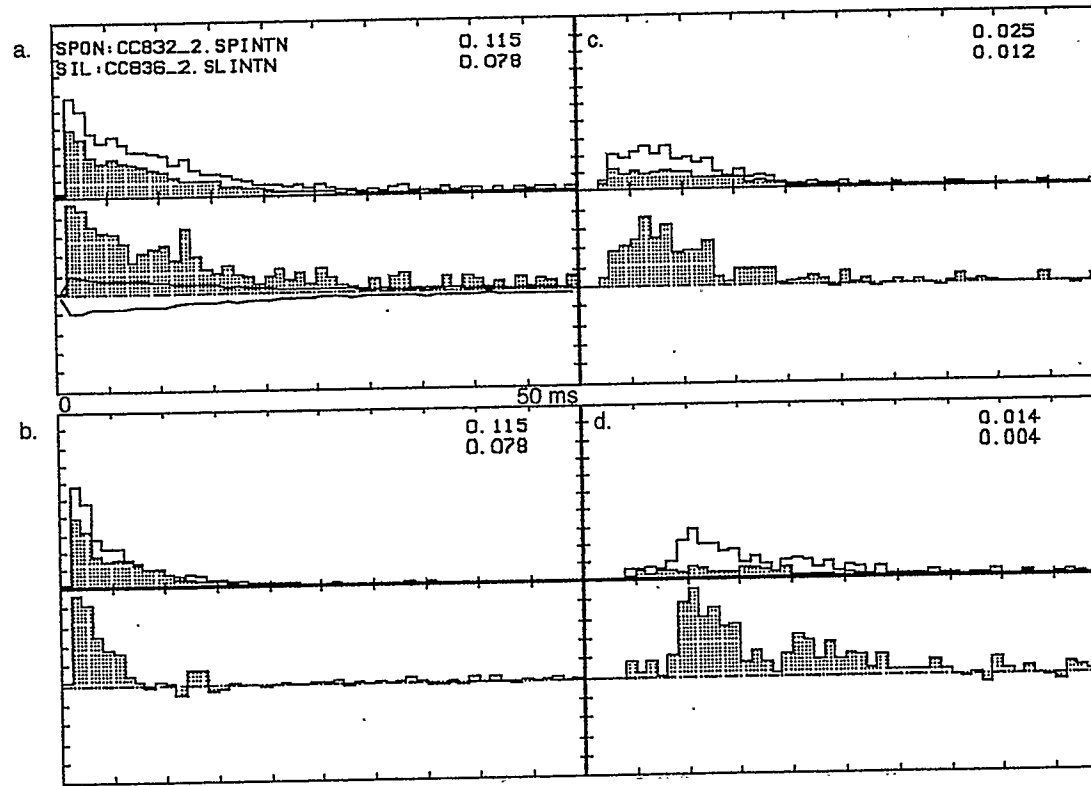


Figure 9.

Auto-correlograms (a) and higher order interval histograms (b-d) comparing the interval distribution (lags of ≤ 50 ms) of single unit spike trains in the post click train stimulation (unfilled) and spontaneous conditions (filled). a) Upper panel shows the auto-correlograms, note the excess of interval counts in the unfilled histogram relative to the filled. Lower panel shows the difference histogram, obtained by subtracting the post stimulation auto-correlogram from the spontaneous auto-correlogram. Solid lines in difference histogram (a, lower panel) represent ± 2 times the estimated standard deviation of the difference histogram, under the null hypothesis that the difference is zero. Differences in the interval distribution of the single unit spike trains in the post click train stimulation and spontaneous conditions are significant if 3 or more consecutive bins in the difference histogram fall outside the range of standard deviation values indicated by the solid lines ($p \leq .01$). Positive peaks in the auto-correlation difference histogram (a) were also present in the first (b) second (c) and third order (d) interval difference histograms (all shown in lower panels). Peak maximums are shown in right corner of a.

contained significant positive peaks (Figure 10), 9 out of 27 difference histograms contained negative peaks (Figure 11), and 1 histogram contained both a significant positive and a significant negative peak (Figure 12). In most cases where there was a significant excess of short intervals in the click stimulation responses, positive peaks were only present in the first order interval difference histogram, and usually occurred within the first 25 ms of the difference histogram (Figure 10b), although occasionally the peak occurred at a later point in the histogram (Figure 12b, 37 ms). Difference histograms containing a negative peak, indicating a shortage of brief intervals in the auto-correlations of the click responses, were present in the higher order interval comparisons (Figures 11 & 12 b). Interval shortages were most frequently observed in the tail of the auto-correlation difference histograms.

Comparison of Post Noise Stimulation and Spontaneous Interval Distributions

The difference histograms comparing the post noise response period to the silence (or spontaneous) response period contained significant deviations ($p \leq .01$) in 5 cases. In 3 out of the 5 instances where significant deviations were observed, the difference was a positive value, indicating an excess of short intervals (< 50 ms) in the post-noise stimulation auto-correlation functions (Figure 13a). In 2 of the 5 cases where significant deviations are present, the peaks in the difference histogram are negative, indicating that less short intervals are present in the post noise responses than in the spontaneous responses (Figure 14a). Both positive and negative differences are present in the higher order interval histogram comparisons (Figure 13 & 14 b-d). Again, differences in the post-noise stimulation and spontaneous histograms could not be accounted for by differences in the age of the animals or the depth at which the recording was made. In the cases where there is a significant difference in the interval distributions of the post noise and spontaneous responses, the spontaneous activity sample obtained during

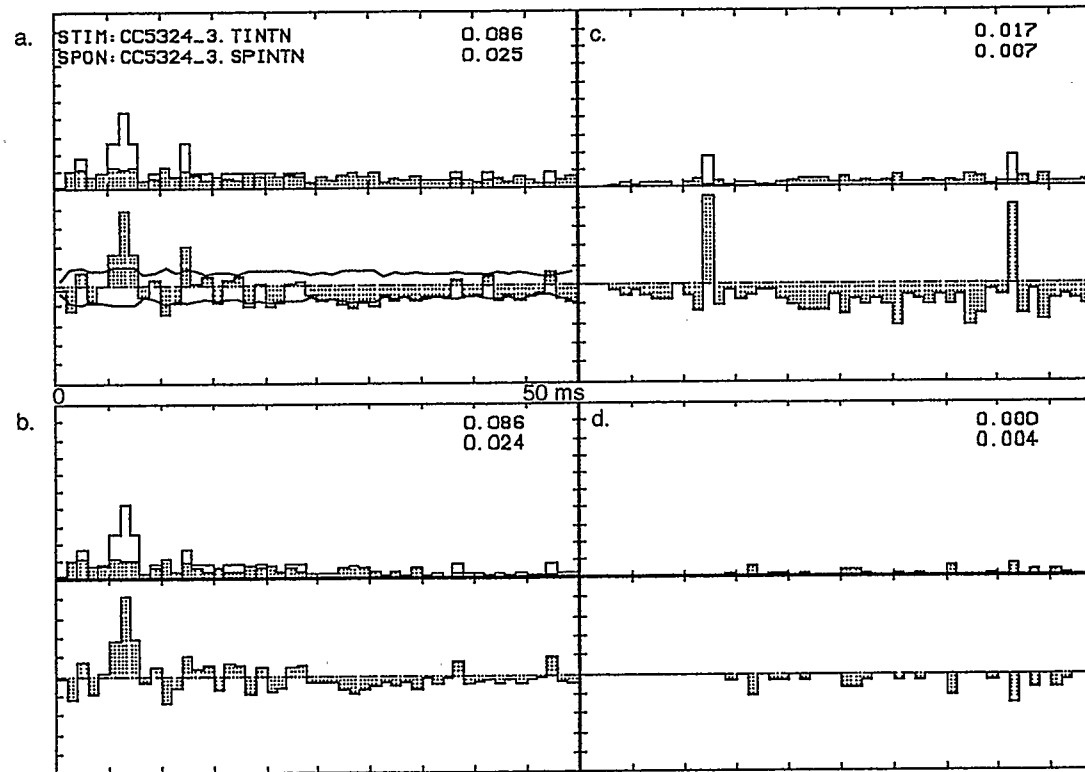


Figure 10.

Auto-correlograms (a) and higher order interval histograms (b-d) comparing the interval distribution (lags of ≤ 50 ms) of single unit spike trains in the click train stimulation (unfilled) and spontaneous conditions (filled). a) Upper panel shows the auto-correlograms, note the positive peak at short lag times in the unfilled histogram relative to the filled. Lower panel shows the difference histogram, obtained by subtracting the stimulation auto-correlogram from the spontaneous auto-correlogram. Solid lines in difference histogram (a, lower panel) represent ± 2 times the estimated standard deviation of the difference histogram, under the null hypothesis that the difference is zero. A significant three bin peak in the auto-correlation difference histogram (a) was also present in the first order interval difference histogram (b, lower panel). Note the shortage of long intervals (≥ 25 ms) in the auto-correlogram (a) and higher order interval histograms (b-d) in the stimulation condition, relative to the spontaneous baseline. Peak maximums are shown in right corner of a.

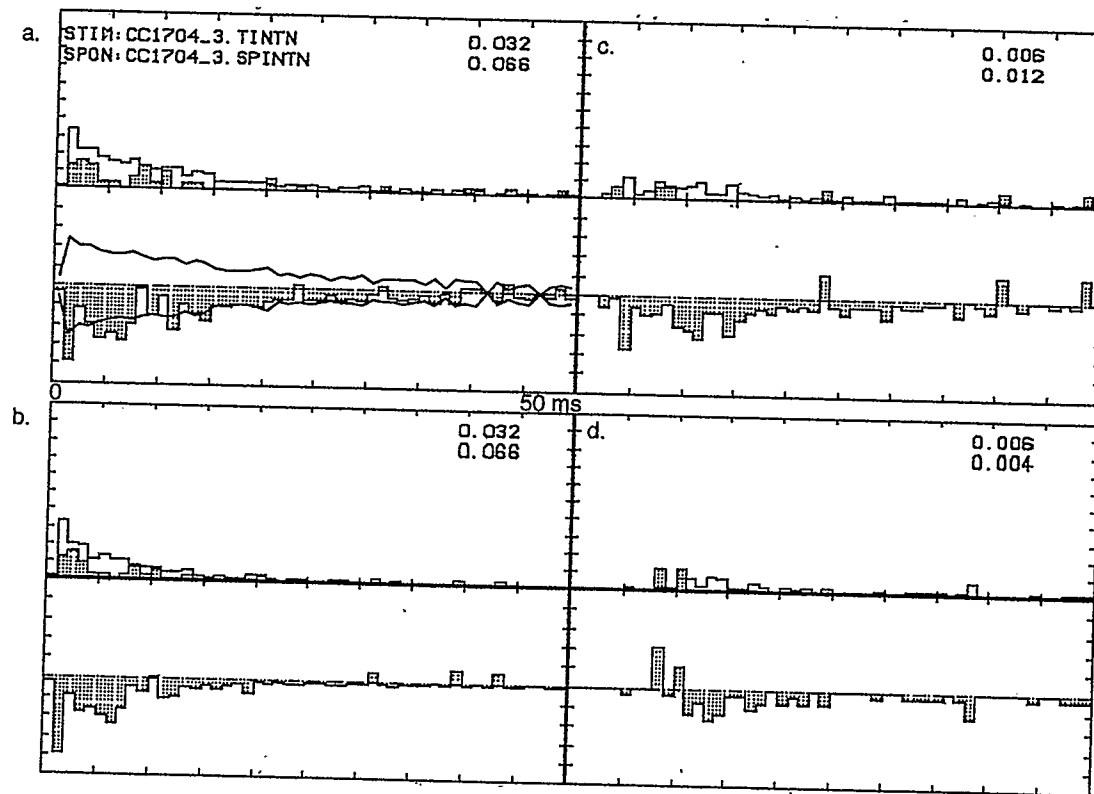


Figure 11.

Auto-correlograms (a) and higher order interval histograms (b-d) comparing the interval distribution (lags of ≤ 50 ms) of single unit spike trains in the click train stimulation (filled) and spontaneous conditions (unfilled). a) Upper panel shows the auto-correlograms, note the shortage of intervals at short and longer lag times in the filled histogram relative to the unfilled. The significant negative peaks in the auto-correlation difference histogram (a) were also present in the first, second, and third order interval difference histograms (b-d, lower panels). Peak maximums are shown in right corner of a.

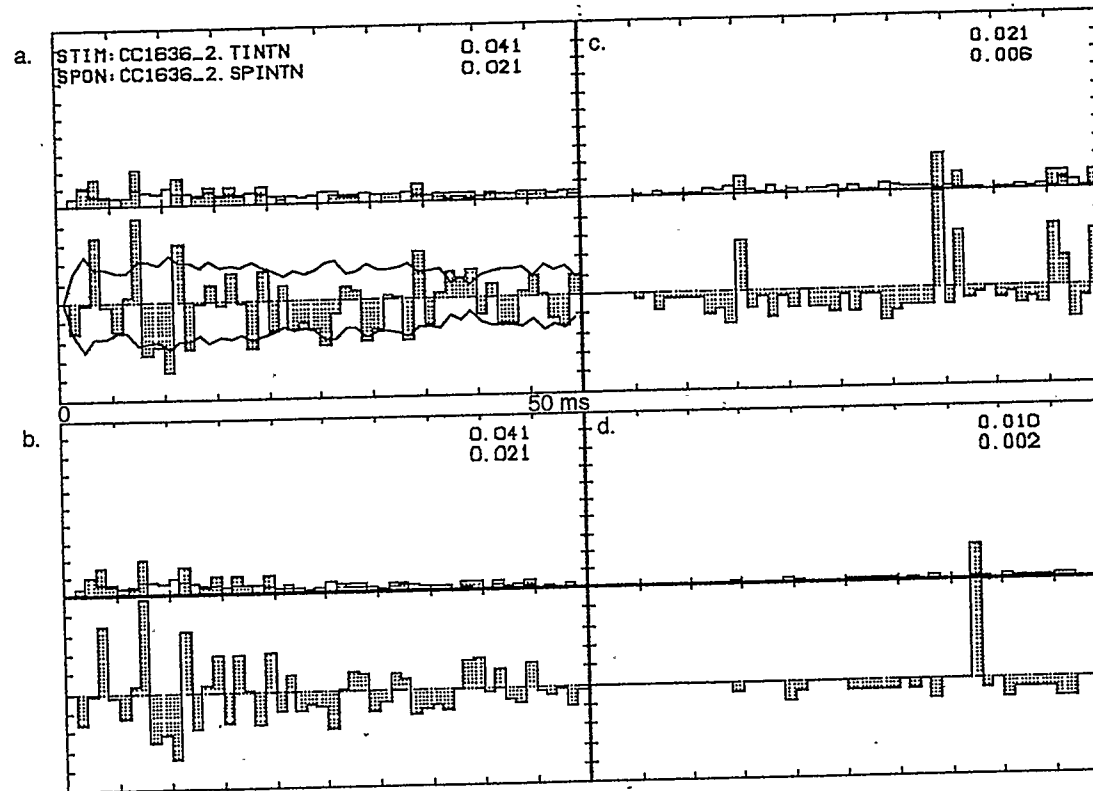


Figure 12.

Auto-correlograms (a) and higher order interval histograms (b-d) comparing the interval distribution (lags of ≤ 50 ms) of single unit spike trains in the click train stimulation (filled) and spontaneous conditions (unfilled). a) Upper panel shows the auto-correlograms, note both the shortage and excess of intervals at short and longer lag times in the filled histogram relative to the unfilled. The significant peaks in the auto-correlation difference histogram (a) were also present in the first, second, and third order interval difference histograms (b-d, lower panels). Peak maximums are shown in right corner of a.

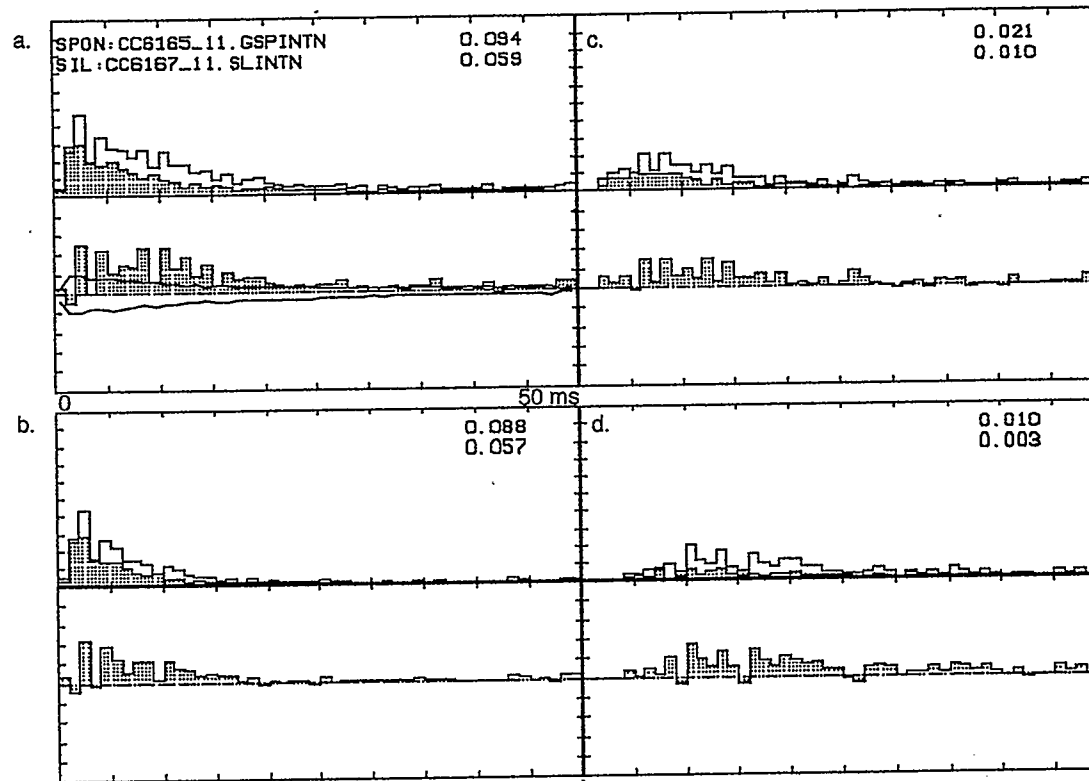


Figure 13.

Auto-correlograms (a) and higher order interval histograms (b-d) comparing the interval distribution (lags of ≤ 50 ms) of single unit spike trains in the post noise stimulation (unfilled) and spontaneous conditions (filled). a) Upper panel shows the auto-correlograms, note the excess of interval counts in the unfilled histogram relative to the filled. Lower panel shows the difference histogram, obtained by subtracting the post stimulation correlogram from the spontaneous auto-correlogram. Solid lines in difference histogram (a, lower panel) represent ± 2 times the estimated standard deviation of the difference histogram, under the null hypothesis that the difference is zero. Differences in the interval distribution of the single unit spike trains in the post noise stimulation and spontaneous conditions are significant if 3 or more consecutive bins in the difference histogram fall outside the range of standard deviation values indicated by the solid lines ($p \leq .01$). Positive peaks in the auto-correlation difference histogram (a) were also present in the first (b) second (c) and third order (d) interval difference histograms (all shown in lower panels). Peak maximums are shown in right corner of a.

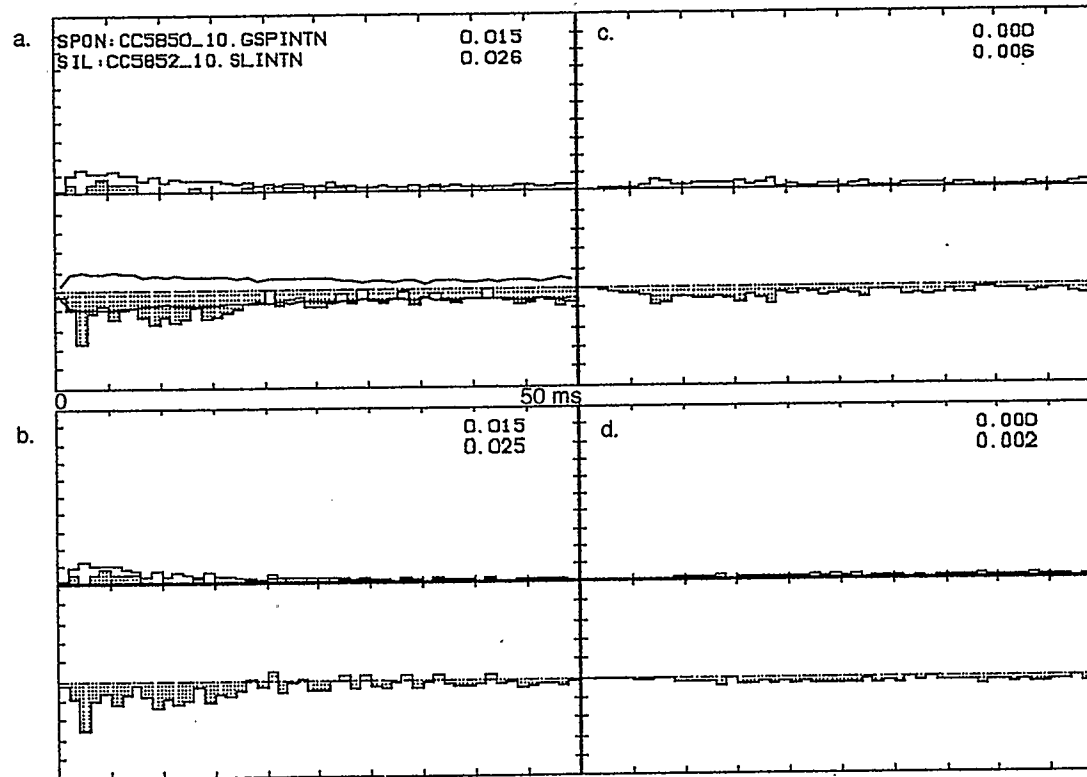


Figure 14.

Auto-correlograms (a) and higher order interval histograms (b-d) comparing the interval distribution (lags of ≤ 50 ms) of single unit spike trains in the post noise stimulation (filled) and spontaneous conditions (unfilled). a) Upper panel shows the auto-correlograms, note the excess of interval counts in the unfilled histogram relative to the filled. Negative peaks in the auto-correlation difference histogram (a) were also present in the first (b) second (c) and third order (d) interval difference histograms (all shown in lower panels). Peak maximums are shown in right corner of a.

prolonged periods of silence serves as the spontaneous baseline to which the interspike interval distributions of the noise stimulation responses are compared. In all other cases the post noise spontaneous condition serves as the spontaneous baseline.

Comparison of Noise Stimulation and Spontaneous Interval Distributions

A comparison of the auto-correlation difference histograms of 30 single units in the noise stimulation and spontaneous conditions indicated that 10% of the difference histograms contained significant peaks. All of the significant difference histograms contained positive peaks (Figure 15a). positive peaks were present in each of the higher order interval difference histograms and occurred within the first 25 ms, indicating an excess of short first, second, and third order intervals in the spike trains during noise stimulation (Figure 15b-d, respectively).

Test for Serial Dependence of Interspike Intervals

Second order auto-correlations were calculated for lag times of up to 50 ms for the spike trains of 35 single units which had a significant excess of particular interspike intervals in their stimulation or post stimulation difference histograms. Surprise values were calculated for a total of 20 units in the stimulation condition, and 15 units in the post stimulation condition, for both stimuli. The axes of the second order auto-correlation histograms were divided into 17 bins to allow for an interspike interval jitter of ~ 1 ms (see Methods section). None of the second order auto-correlation histograms calculated from the interspike interval distributions of single units during periods of stimulation contained significant bins (surprise ≥ 9.5 , per histogram error rate $p \leq .01$) (Figure 16 shows 2 typical examples). Significant bins are shown in black, non-significant are shown in shades of grey. In contrast, 3 of the post click and post noise stimulation second order auto correlation histograms contained several significant bins (Figure 17

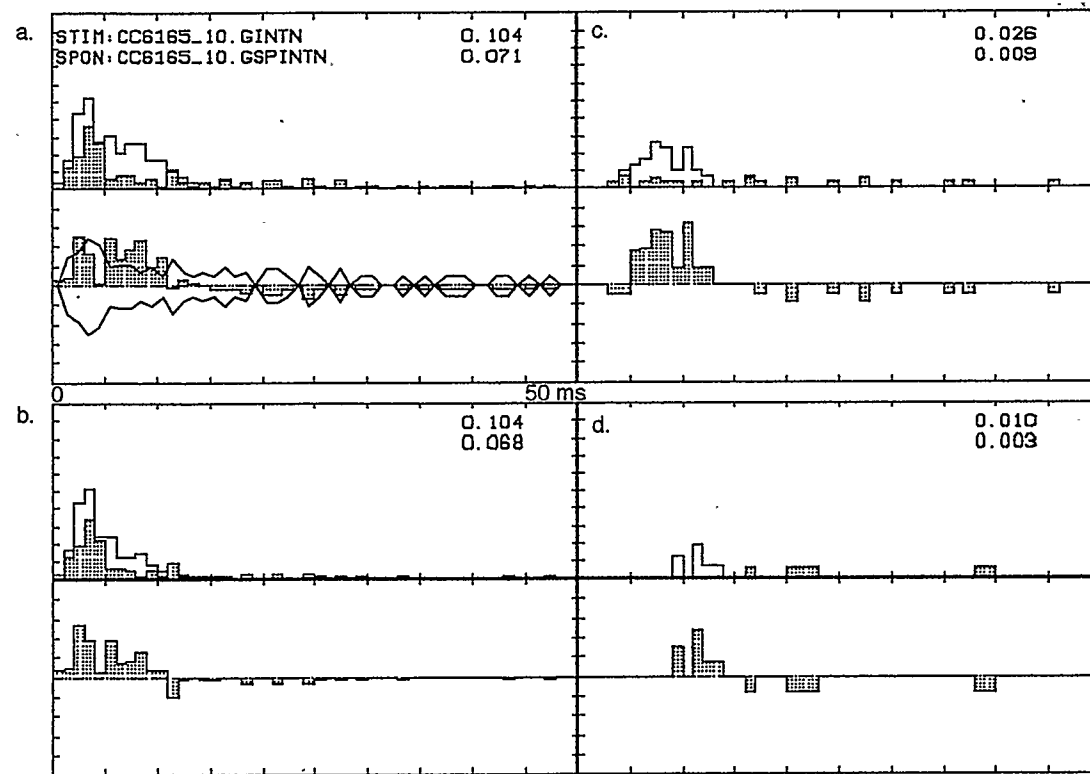


Figure 15.

Auto-correlograms (a) and higher order interval histograms (b-d) comparing the interval distribution (lags of ≤ 50 ms) of single unit spike trains in the noise stimulation (unfilled) and spontaneous conditions (filled). a) Upper panel shows the auto-correlograms, note the positive peak at short lag times in the unfilled histogram relative to the filled. Lower panel shows the difference histogram, obtained by subtracting the noise auto-correlogram from the spontaneous auto-correlogram. Solid lines in difference histogram (a, lower panel) represent ± 2 times the estimated standard deviation of the difference histogram, under the null hypothesis that the difference is zero. The significant peak in the auto-correlation difference histogram (a) was also present in the first order, second, and third order interval difference histograms (b-d, lower panels). Note the shortage of long intervals (≥ 20 ms) in the auto-correlogram (a) and higher order interval histograms (b-d) in the stimulation condition, relative to the spontaneous baseline. Peak maximums are shown in right corner of a.

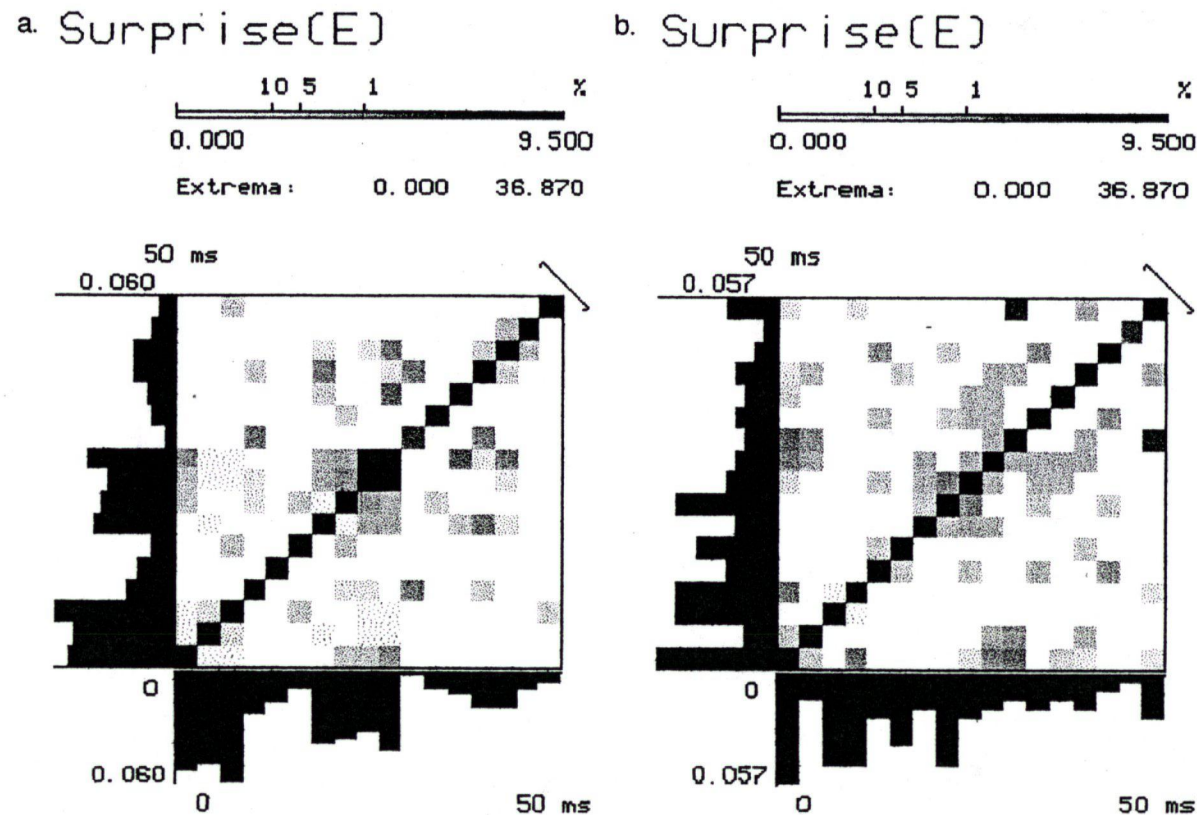
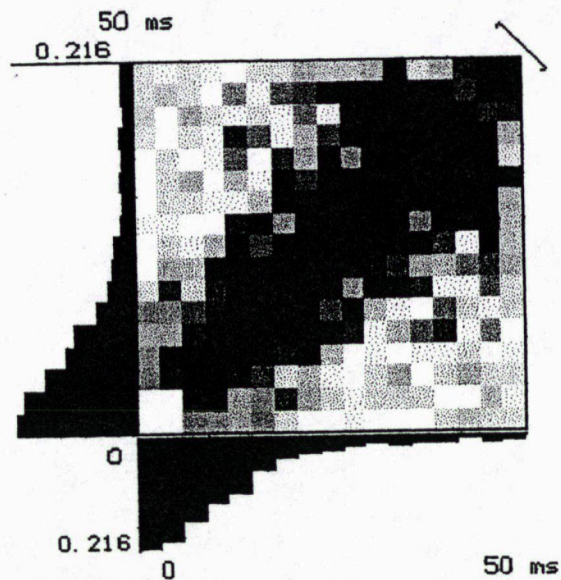
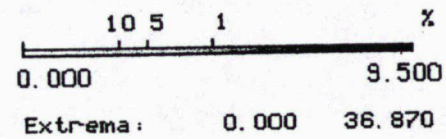


Figure 16.

Second order auto-correlation histograms of two single unit spike trains during periods of stimulation. Diagonals represent the squared second order auto-correlation, and are not of interest for this study. Histograms are symmetrical about the diagonal. Auto-correlograms of single unit spike trains at lags of ≤ 50 ms are shown in the x and y margins. Note that the auto-correlogram and second order auto-correlogram bins are ~ 3 ms. None of the off-diagonal bins in either of the second order auto-correlation histograms are significant (a,b) (surprise ≥ 9.5 , shown in black), although one bin approaches significance (b). Grey scale legends are shown at the top of each histogram.

a. Surprise(E)



b. Surprise(E)

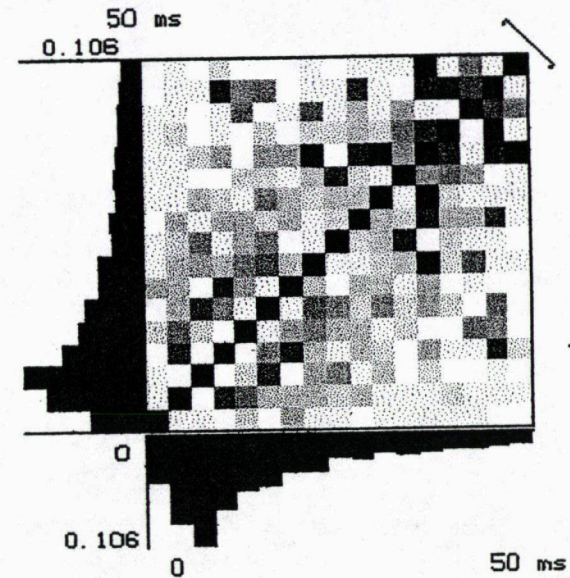
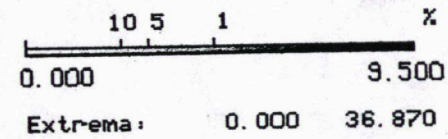


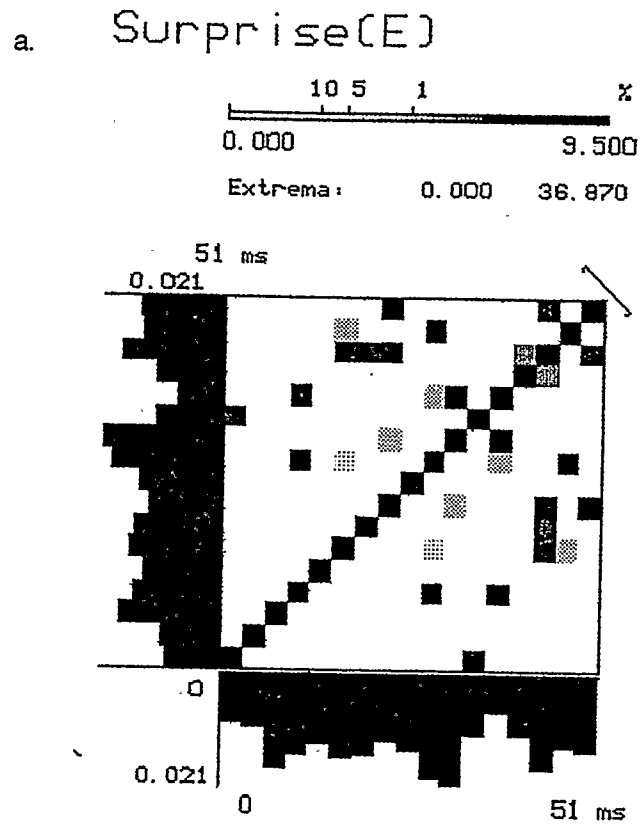
Figure 17.

Second order auto-correlation histograms of two single unit spike trains in post stimulation periods (lag times of ≤ 50 ms). a) Many significant bins are present just off the diagonal of the histogram (surprise ≥ 9.5 , shown in black) for one unit. b) A few significant bins are also present some distance from the diagonal for the second unit.

shows 2 examples). The post click second order auto-correlation histograms contained coincident counts with surprise values as large as 36.2. Most of the significant bins in these histograms were found close to the diagonal of the histogram.

To check whether the second order auto-correlation could adequately detect repeating patterns randomly distributed over a short time window, the second order auto-correlation was calculated for lag times of up to 51 ms for a modified poisson distributed spike train (a poisson distributed spike train in which a particular pattern was inserted; see Methods section). The spike pattern consisted of a 10 ms interval followed by a 20 ms interval, and was randomly placed at 10 different locations in the poisson distributed spike train (Figure 18b). Figure 18a shows the distribution of significant bins (surprise ≥ 9.5 , shown in black) in the modified poisson spike train second order auto-correlation histogram. The values on the x and y axes represent the time between each spike in the modified poisson spike train and all, first, second, third....n order spikes or the modified poisson spike train auto-correlation. The time interval between the first and second spike in the pattern is 10 ms, and the time between the first and the third spike in the pattern is 30 ms, therefore in the xy plane of the histogram the pattern is shown in position 10,30 (or 30,10). The surprise value of the bin associated with this pattern is 20.9. Several other significant bins are also present in the histogram of the modified poisson distributed spike train. Therefore, although the second order auto-correlation can detect a repeating pattern in a poisson distributed spike train, it also detects a variety of other spurious 'patterns'.

To examine the distribution of significant bins in the modified poisson spike train second order auto-correlation, a 10,000 bin histogram was constructed from the auto-correlation between a click and all first and higher order spikes for time lags of up to 300 ms (Figure 19). The 10,000 bin histogram contained many significant bins (surprise ≥ 13.1 , per histogram error rate $p \leq .01$). The distribution of surprise values for this matrix



b.

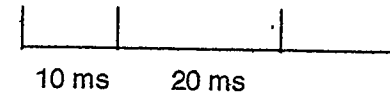


Figure 18.

a) Second order auto-correlation histogram of a modified Poisson distributed spike train at lags of ≤ 51 ms. b) A spike pattern consisting of a 10 ms interval followed by a 20 ms interval was inserted at 10 different places in the spike train. The bin containing the pattern is shown in positions 10,30 and 30,10 of the second order auto-correlation. The coincident count of the pattern was assigned a surprise value of 20.9. Several other spurious significant bins were present in the off diagonal regions of the histogram (surprise ≥ 9.5 , shown in black).

Surprise(E)

10.5 1 %
 0.000 13.100
 Extrema: 0.000 36.870

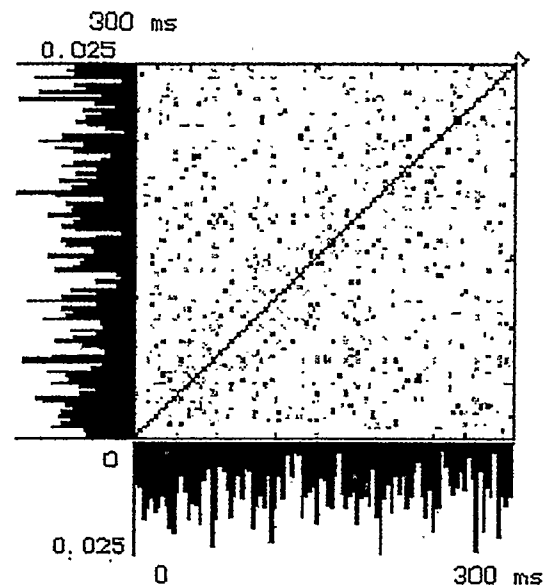


Figure 19.

a) Second order auto-correlation histogram of the same modified Poisson distributed spike train at lags of ≤ 300 ms. The bin containing the pattern is still shown in positions 10,30 and 30,10 of the histogram (surprise = 20.9). Many other spurious significant bins were present in the histogram (surprise ≥ 13.1 , shown in black).

is shown in figure 20. The surprise value of the 'pattern' contributes a two counts at 20.9 (marked with asterisk). There are, however, 16 bins in the histogram that contain spurious surprise values greater than the surprise value of the bin associated with the pattern.

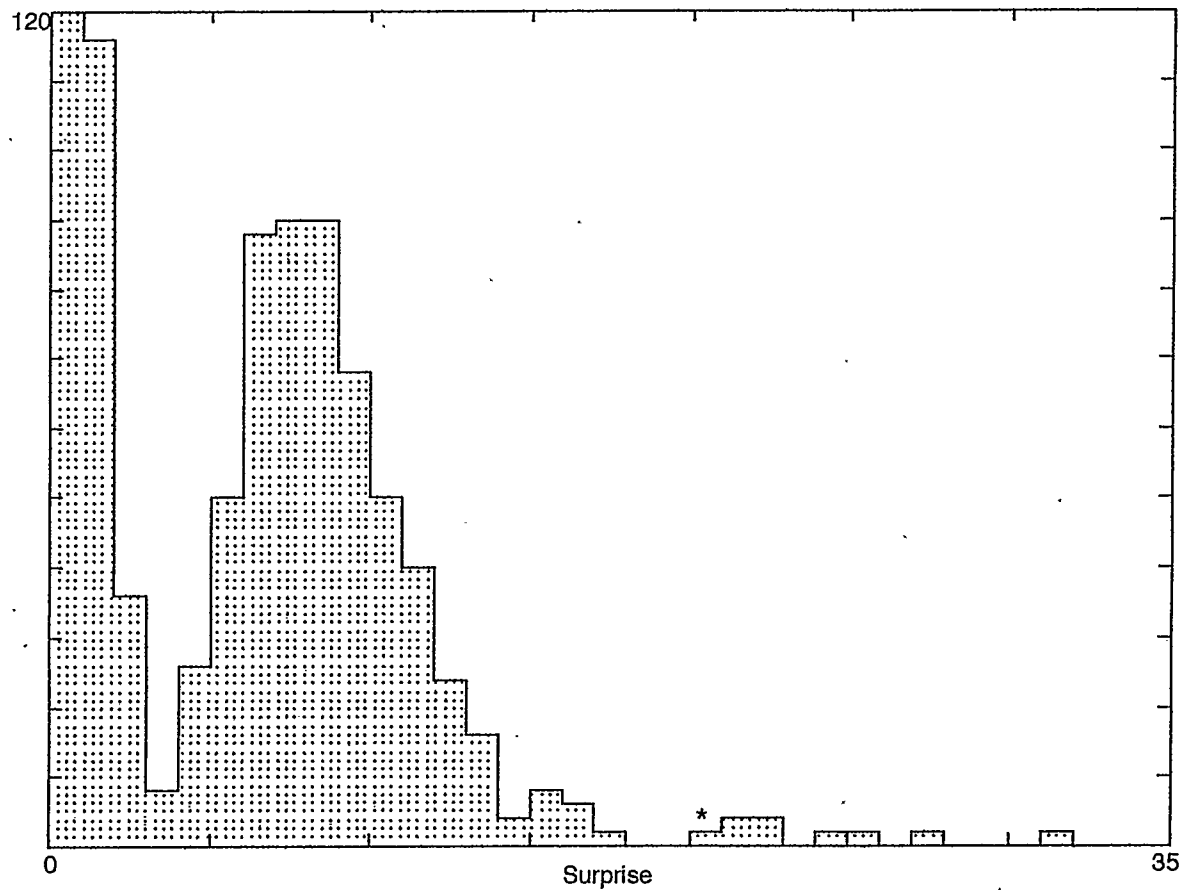


Figure 20.

The distribution of surprise values for the modified Poisson distributed spike train at lags of ≤ 300 ms with diagonal removed. The distribution contains a total of 4900 bins. The pattern was contained in 2 bins and had a surprise value of 20.9 (indicated by an *). There were many spurious significant bins in the second order auto-correlation (surprise ≥ 13.1), and 16 bins contained surprise values greater than that assigned to the pattern. Two bins were assigned surprise values > 30 .

IV. Discussion

The aim of the present study was to describe the effect of auditory stimulation with clicks and broad band noise on the occurrence, spike count and temporal structure of short time scale bursts in primary auditory cortex. In order to delineate the short term and long term effects of stimulation on burst firing, bursts in the first 100 ms following stimulus presentation were compared to bursts occurring 500 to 1500 ms after stimulus presentation, and to spontaneous bursts, for each single unit. Serial dependence of interspike intervals was tested by constructing second order auto-correlation histograms from single unit spike trains for lag times of up to 50 ms during periods of stimulation.

Generally, the incidence of burst firing was lower during periods of stimulation than it was in post stimulation and spontaneous periods. Spike trains emitted by single auditory cortical units contain a smaller proportion of bursts during click and noise stimulation than in periods of spontaneous activity. Responses during periods of noise stimulation had a smaller proportion of two spike bursts or pairs than the post noise responses. In contrast, click responses had a smaller proportion of all bursts than post click train responses. The proportion of triplets and 4-plets was significantly smaller in the post noise condition than it was in the spontaneous condition. The present study has also shown that the single spike rate is significantly higher during periods of stimulation than it is following stimulation or during periods of spontaneous activity for both stimuli. During click train stimulation, burst firing rate is lower than it is in post stimulation and spontaneous periods. There is no significant difference in burst rate for bursts of 3 or more spikes in the noise, post noise and spontaneous conditions. These findings indicate that the single unit responses to click train or noise stimulation are mainly composed of single spikes.

Comparisons of the interspike interval distribution of spike trains during stimulation, following stimulation, and in spontaneous periods indicate that auditory stimulation has

both short term and long term effects on the temporal structure and length of short time scale bursts. Stimulation generally increases the number of short first order or interspike intervals (< 25 ms) in a burst (Figures 10 & 15). Click stimulation also significantly decreased the number of long higher order intervals (> 30 ms) relative to a spontaneous baseline, whereas noise stimulation did not (although negative peaks were also present in the difference histograms during noise stimulation) (Figures 11 & 15, respectively). The spike trains of a subset of single units contained an excess of short first, second and third order intervals in post click train stimulation periods relative to a spontaneous baseline, indicating that burst firing may be higher 0.5 to 1.5 s following stimulation than it is during stimulation or periods of spontaneous activity (Figure 9). No significant serial dependence of short interspike intervals was found during periods of stimulation. Taken together, occurrence and interval distribution indices of burst firing suggest that during stimulation the incidence of burst firing is either lower than or the same as the incidence of burst firing during periods of spontaneous activity.

Mechanisms Underlying Single Unit Response Properties of Auditory Cortical Neurons

Cortical burst firing may be attributed to the intrinsic membrane properties of cortical neurons, or to synaptic inputs from other cortical neurons or the thalamus. The bursts observed during periods of stimulation and spontaneous activity in this study are similar in length (usually 2 to 5 spikes), and time scale (50 ms) to intrinsically bursting cells in layers IV and V of sensorimotor cortex (Chagnac-Amatai & Connors, 1989; Connors & Gutnik, 1990). However, short time scale bursts in this study were observed at a variety of electrode depths including superficial and deep layers of primary auditory cortex. Other researchers have indicated that many neurons in other cortical regions are able to generate rebound Ca^{++} dependent bursts following a brief hyperpolarizing pulse (i.e.

Friedman & Gutnik, 1987). Such a mechanism may account for the late rebound following the suppression period during click train stimulation (Figures 5 & 7).

Cortical neurons are part of a large neural network and therefore receive many excitatory and inhibitory synaptic inputs (DeRibaupierre et al., 1972, Douglas & Martin, 1990; Douglas & Martin, 1991). These synaptic inputs can alter the membrane properties of neocortical neurons *in vivo*, and thus make *in vitro* and *in vivo* comparisons of burst firing difficult. One extrinsic source of common input to cortical neurons that can influence or drive cortical burst firing is the rhythmic activity of thalamic relay neurons. However, as stated earlier, Eggermont et al. (1993) observed that auto-correlograms derived from bursting sections within the spike trains of spontaneously active auditory cortical neurons demonstrated no greater periodicity than the correlograms of isolated spike sections. This observation suggests that burst firing and rhythmic firing are not necessarily controlled by the same mechanisms in auditory cortex. Time dependent auto- and cross-correlograms of pairs of units show that some of the most rhythmically firing units in their study demonstrate an independence of burst firing on short time scales (20-30 ms). In the present study, the spike trains of single units on the same electrode or two different electrodes recorded at the same time and under the same stimulus conditions, may have different interspike interval distributions over a short time scale (< 50 ms), and a different proportion of bursts and single spikes in their spike trains. The difference in size, duration and interspike interval distribution of bursts generated by pairs of units suggest that burst occurrence and structure are not controlled by an input common to both units. Likely, mechanisms that control firing within a burst arise from the intrinsic properties of individual units or from local network properties of primary auditory cortex.

Dot displays of single unit responses to auditory stimulation clearly showed a post activation suppression period following click and noise onset responses (Figures 5a & 6a). The suppression period following click presentation (~100 ms) generally lasted for a

longer period of time than the suppression period following noise onset (~50 ms). Intracellular and extracellular studies examining the responses of auditory cortical neurons to click train and noise burst stimulation indicate that such activation suppression sequences may be attributed to a short latency evoked EPSP (9.6 ms) followed by a short latency (11.5 ms) evoked IPSP that lasts up to 4 times longer than the EPSP (50 to 160 ms) (De Ribaupierre, Goldstein, & Yeni-Komshian, 1972). A similar EPSP-IPSP response sequence was also observed in intracellular recordings of single visual cortical neurons during electric pulse stimulation, where evoked EPSPs and IPSPs occur almost simultaneously, and periods of excitation are followed by sustained periods of hyperpolarization (Douglas & Martin, 1991). Differences in the duration of the suppression period following click train and noise stimulation may be explained in terms of the patterns of excitation and inhibition evoked by the two stimuli. Clicks are transient stimuli, and likely evoke the EPSP-IPSP response sequence described by De Ribaupierre et al. (1972). The broad band noise stimulus is continuous and may therefore still evoke EPSPs in the time period following the noise onset response, even if evoked IPSPs are present.

Differences in the occurrence, temporal structure and length of bursts observed during click train and noise stimulation, and the post stimulation and spontaneous conditions may also be attributed to differences in the evoked and spontaneous EPSP-IPSP duration and sequence. The occurrence of short time scale bursts consisting of 2 or more spikes was lower during click stimulation than it was following click train stimulation and during periods of spontaneous activity. De Ribaupierre et al. (1972) observed that click evoked IPSPs occur shortly after evoked EPSPs and last for a period of time that is much longer than spontaneous IPSPs. Prolonged periods of hyperpolarization were not observed following spontaneous EPSPs. Instead, spontaneous EPSPs were usually followed by IPSPs of equal duration but of opposite polarity. The occurrence of a

prolonged IPSP shortly after the click onset response could effectively reduce the occurrence of successive spikes in the later half of both the post click and post noise onset response time windows used in the present study, and may account for the prolonged suppression period following both click and noise onset responses. Differences in the distribution of interspike intervals at longer time lags in the auto-correlograms in the stimulated and spontaneous conditions observed in this study provide compelling support for such a hypothesis. Auto-correlation and higher order interval histograms of single unit spike trains during periods of stimulation contained fewer long higher order intervals than spontaneous auto-correlations and interval histograms, indicating that the occurrence of short time scale bursts is lower during stimulation, especially if successive spikes occur at time lags greater than 25 ms. The later lags may correspond to the sustained hyperpolarization period (Figures 11 & 15). Increases in the proportion of single spike responses and single spike rate during stimulation in the present study likely reflect transient increases in firing rate due to stimulus induced synchronization of excitatory post synaptic potentials.

The interval distributions observed during click train and noise stimulation are also similar to the 'truncated' interspike interval distributions of visual cells in the superior colliculus during visual stimulation (Mandl, 1993). Mandl suggests that the truncation of the interspike interval distribution is indicative of a stimulus induced decrease in long interspike intervals emitted by single collicular neurons.

The findings of the present study have also shown that the spike trains of a subset of units contain an excess of short intervals 0.5-1.5 s following click train stimulation, relative to a spontaneous baseline. Long lasting effects of stimulation on single unit firing have been observed after the post-activation suppression period following click train stimulation in primary auditory cortex (Eggermont, 1991). However, most of these rebounds occur 100 - 200 ms after the suppression period. Elevated periods of burst

firing in the post stimulation responses in this study were observed ~ 300 to 1000 ms following stimulation (Figure 7). Therefore, the post activation suppression rebound cannot completely account for the differences observed in the interval distribution of spike trains in the post click train stimulation and spontaneous conditions.

Effect of Anesthesia on Burst Firing

The data in the present study was obtained from preparations where anesthesia was induced using a combination of Sodium pentobarbital and Ketamine during surgery, and Ketamine alone to maintain light anesthesia while recording. Sodium pentobarbital anesthesia produces spindling in the EEG and rhythmic firing in neocortex (Steriade & Llinàs, 1988; Abeles 1982). Barbiturate anesthesia also significantly reduces levels of spontaneous activity in cat primary auditory cortex (Phillips et al., 1989). Most of the data utilized in the present study were recorded several hours after the animals received injections of Sodium pentobarbital, and spontaneous activity levels did not vary over extended recording periods (Figures 5 & 6, see also Eggermont, 1991). Ketamine may also induce rhythmic firing behavior in the cortex. Ketamine anesthetic is thought to induce a light sleep-like state in animals. Sleep has been shown to induce correlated firing activity between cortical units in cats (Abeles, 1982). However, other studies have shown that rhythmic firing and short time scale burst firing are likely generated by different mechanisms in the primary auditory cortex of the cat (Eggermont et al., 1993). Furthermore, differences in the temporal structure, occurrence and length of short time scale bursts generated by pairs of units under the same experimental conditions and on the same electrode, observed in the present study, indicate that short time scale burst responses of single cortical units cannot be completely attributed to a common source of input. Ketamine is also known to act as an NMDA blocker and its use in this study may

have reduced NMDA mediated burst firing and rhythmic activity (Kobayashi et al. 1993; Silva et al, 1991).

Proposed Functions of the Burst Discharge

There is a high incidence of short time scale burst firing during periods of stimulation and spontaneous activity in the cortex (i.e. Dayhoff & Gerstein, 1983 b; Connors & Gutnik, 1990; Phillips & Sark, 1991; Douglas, Martin, & Whitteridge, 1991; Eggermont et al., 1993). However, the function of the short time scale burst in cortical information transfer and coding has not been clearly established. It has been suggested that short time scale bursts serve an important function in a variety of cortical processes including impulse propagation, encoding of sensory information, and synaptic stabilization. The present study addresses the question of functionality of the short time scale burst discharge in the primary auditory cortex by comparing the incidence and structure of the single unit burst discharge during periods of auditory stimulation and spontaneous activity.

Burst Firing and Information Transfer in the Cortex

Traub and Miles (1991) posit that burst firing may play an important role in impulse propagation in weakly connected neural networks, where multiple spikes emitted within a brief time period may serve to amplify the post-synaptic neural response and ensure the contiguous activation of the pre- and post-synaptic cell. Phillips and Sark (1991) similarly suggest that the generation of bursts in response to an optimal transient auditory stimulus may provide a salient neural signal in the midst of ongoing spontaneous activity in cat primary auditory cortex. Cortical burst firing in this context represents a mechanism for emphasizing or amplifying a particular stimulus related response. Burst

firing, however, is also prevalent in the spontaneous discharges of primary auditory cortical neurons (Eggermont et al., 1993).

In the present study, the proportion of short time scale bursts (pairs...6-plets) emitted during periods of noise or click train stimulation was significantly lower than the proportion of bursts emitted in the post stimulation period, and periods of spontaneous activity for individual auditory cortical units. Moreover, the rate of burst discharge during click train stimulation was significantly lower than during post click train stimulation and spontaneous periods of activity. There was no significant difference in the burst discharge rate of longer bursts (triplets and up) in the noise stimulation, post noise stimulation, and spontaneous conditions. These findings indicate that stimulation generally reduces the incidence of short time scale bursts in the spike trains of individual auditory cortical neurons, especially when the stimulus is transient. Therefore, it is unlikely that short time scale bursts could serve to amplify a particular stimulus related response in the midst of ongoing spontaneous activity if the incidence of burst firing during stimulation is actually lower or equal to the incidence of burst firing during periods of spontaneous activity.

Burst Firing as a Neural Code

As stated earlier, the term 'neural code' is not uniquely defined. In one context a neural code can refer to alterations in the mean firing rate of a single unit under particular experimental conditions. The interspike intervals in the spike train of such a 'rate' coding neuron are independent or uncorrelated. There is experimental evidence to support the existence of such 'rate codes' in the cortex (i.e. Mountcastle, 1957; Hubel & Wiesel, 1968), however, recent findings indicate that the timing of spikes emitted by single neurons may also play a significant role in neural processing (see Cariani, 1994; Vaadia & Aertsen, 1992 for review). The temporal pattern of spikes in a spike train emitted by a

single unit may also constitute a neural code for a particular stimulus or stimulus parameter in the cortex (Dayhoff & Gerstein, 1983 a,b; Middlebrooks, Clock, Xu & Green, 1994). The interspike intervals within a 'pattern' would be serially dependent, and the pattern would repeat under similar stimulus conditions (Dayhoff & Gerstein, 1983 a,b).

The short time scale bursts observed in the spontaneous and post stimulus conditions in the present study are of a similar length (3 to 7 spikes) and duration (< 52 ms) as "favored" spike patterns observed in cat striate cortex during visual stimulation, and the clustered discharges of cortical units in the ectosylvian gyrus that are thought to code for sound localization (Dayhoff & Gerstein, 1983b; Middlebrooks et al., 1994). Cattaneo et al. (1981) found that complex cells in the striate cortex regularly emit brief bursts (≤ 50 ms) of action potentials in response to a visual stimulus, but only rarely emit bursts spontaneously. Bursts generated by complex cells were also tuned to the spatial frequency, velocity, and orientation of a sine wave grating, where as isolated spikes were not.

In contrast to these findings, the present study has shown that click train and noise stimulation generally reduces the proportion of bursts of two or more spikes in the single unit responses of cat auditory cortical units, and increases the proportion and rate of occurrence of single spikes, relative to a spontaneous baseline. In most cases, during stimulation there was an excess of brief (< 25 ms) first order intervals and a shortage of long (> 25 ms) higher order intervals in the auto-correlograms and higher order interval histograms of single unit spike trains, relative to a spontaneous baseline. Mandl similarly noted an enhancement in the occurrence of short first order interspike intervals of single cells in the superior colliculus during visual stimulation. The findings of the present study indicate that the most salient effect of stimulation on firing behavior is to increase the occurrence of single spikes and in some instances, pairs of spikes in the time period

immediately following a click or noise onset. At longer time lags, stimulation generally decreases the occurrence of successive spikes in a burst. Therefore, most single auditory cortical units do not emit an excess of short time scale bursts of 3 or more spikes in response to clicks or noise stimulation, relative to a spontaneous baseline. The decrease in the occurrence of bursts of 3 or more spikes in single unit spike trains during periods of stimulation suggests that if bursts represent a stimulus related neural code or favored pattern, than the occurrence of the pattern is a relatively rare event. Although the effect of intensity on burst firing was not examined in this study, other researchers have indicated that suprathreshold increases in transient stimulus intensity delete successive spikes in a burst (Phillips & Sark, 1991). Therefore, short time scale bursts would also not likely serve as a robust stimulus intensity code in the auditory cortex.

Second order auto-correlation tests of serial dependence of interspike intervals within a burst did not contain any significant off diagonal bins or coincidence counts, indicating intraburst intervals were not serially dependent during stimulation. This finding suggests that short time scale bursts do not serve as stimulus related neural 'patterns' in the time period immediately following noise onset or click presentation in the primary auditory cortex.

The second order auto-correlation histogram and surprise calculation procedures are clearly sensitive to the repeated occurrence of particular spike patterns inserted into a randomly distributed spike train (Figures 18 - 20). However, the surprise calculation procedure also assigned high significance values to a variety of other spurious 'patterns' in the randomly distributed spike train. The difficulties associated with the liberal assignment of significance levels to particular bins in the histogram was an unexpected finding, and makes the interpretation of significance in the second order auto-correlation and other related procedures quite tenuous.

Burst Firing and Synaptic Stabilization

As stated earlier, burst firing is an efficient and reliable way to propagate impulses in neural networks with low connection strengths (Traub & Miles, 1991). A burst in a presynaptic cell will illicit a series of EPSPs that summate effectively in the post-synaptic cell it innervates. Consequently, even subthreshold EPSPs can evoke spiking or bursting in the post-synaptic cell (Traub & Miles, 1991). The contiguous activation of a pre and post-synaptic cell and the depolarization of the post-synaptic cell above a critical threshold are thought to be key components of Hebbian synaptic modification (Singer, 1985). Thus, burst firing may have an important role in the formation and stabilization of synaptic connections in the neocortex during development. Eggermont et al. (1993), observed an age dependence of spontaneous burst occurrence in single auditory cortical units of kittens and adult cats. In particular, the investigators noted that the incidence of burst firing was significantly higher in kittens than adult cats when age related differences in firing rate were taken into account. In this study, the age of an animal did not have a substantial influence on burst occurrence. The differences in the observations made in the Eggermont et al. (1993) study and the present study may be attributed to differences in the age of the animals utilized in the two studies. Data in this study was obtained from cats 30 to 240 days old, where as the other study included younger kittens ranging in age from 10 to 52 days.

Prolonged Effects of Stimulation on Burst Firing

Auditory stimulation had a long term effect on the firing activity of a subset of single units in cat primary auditory cortex. Periods of elevated burst firing were evident in the dot displays of single unit spike trains 0.5 s to 1 s after the presentation of the last click in a train at low presentation rates (Figure 7). In the post click stimulation condition, auto-correlograms and higher order interval histograms of a subset of units contained an

excess of short first, second, and third order intervals, relative to a spontaneous baseline. Single units which generate a substantial number of bursts following stimulation also generate click locked responses during click train stimulation and exhibit a post-activation suppression period and a late rebound (Figure 1). These units also tend to have a higher mean burst rate during stimulation (.506 bursts/sec), than units which do not show such prolonged stimulation related effects (mean burst rate .236 bursts/sec). As stated earlier, other studies have noted incidents of elevated firing in rebound periods following click stimulation in auditory cortex (Eggermont, et al., 1991). However, the elevated burst firing period observed in the present study extends well beyond this rebound period. Periods of elevated burst firing have been also observed hours after passive avoidance training in the chick forebrain (Mason & Rose, 1987). Substantial increases in neuronal burst firing were observed 3 to 7 hours following passive avoidance training (Mason & Rose, 1987; Gigg, Patterson & Rose, 1993 & 1994). The authors suggest that such time dependent increases in burst firing may be associated with long-term memory consolidation for the task (Gigg et al., 1994).

V. Summary and Conclusions

Short time scale bursts were present in the spike trains of single auditory cortical units during stimulation, following stimulation, and during periods of spontaneous activity. Generally, the incidence of burst firing is higher in post stimulation and spontaneous periods than during stimulation, especially during click train stimulation. During stimulation, spike trains contain an excess of brief first order intervals, and a shortage of long higher order interspike intervals, relative to a spontaneous baseline. Noise stimulation enhances the occurrence of short first, second and third order intervals. Variations in burst firing activity under different stimulus conditions observed in this study may be attributed to the sequence and duration of evoked and spontaneous post synaptic potentials observed in intracellular recordings of neocortical neurons (DeRibaupierre et al., 1972; Douglas and Martin, 1991).

The low incidence of burst firing during stimulation opposes the view that bursts serve as a mechanism to emphasize or amplify particular stimulus related responses in the presence of ongoing spontaneous activity in the primary auditory cortex. Moreover, there is little evidence to support the notion that brief bursts of 3 or more spikes occasionally emitted by single auditory cortical units during stimulation represent sparse patterns or neural codes, as intraburst intervals are not serially dependent. Difficulties encountered with testing for serial dependence of interspike intervals with the second order auto-correlation and related procedures was an unexpected finding of this study, and is presently the subject of ongoing investigation.

Periods of elevated burst firing observed in single unit spike trains 0.5-1.0 s after click stimulation indicate that stimulation may have prolonged effects on burst firing in the primary auditory cortex. Although a few studies have noted elevated periods of firing activity in the neocortex following stimulation (i.e. Eggermont, 1991), the firing behavior of single units in post stimulation periods has not been well described. A detailed

investigation of time dependent variations in burst firing following stimulation might provide a better understanding of the functional value of burst firing in the neocortex.

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