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SYNCHRONY, CONNECTIVITY, AND FUNCTIONAL SIMILARITY IN AUDITORY MIDBRAIN LOCAL CIRCUITS

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Abstract—The central nucleus of the inferior colliculus (ICC) contains a laminar structure that functions as an organizing substrate of ascending inputs and local processing. While topographic distributions of ICC response parameters within and across laminae have been reported, the functional micro-organization of the ICC is less well understood. For pairs of neighboring ICC neurons, we examined the nature of functional connectivity and receptive field preferences to gain a better understanding of the structure and function of local circuits. By recording from pairs of adjacent neurons and presenting pure-tone and dynamic broad-band stimulation, we estimated functional connectivity and local differences in frequency response areas (FRAs), spectrotemporal receptive fields (STRFs), nonlinear input/output functions, and single-spike information. From the cross-covariance functions we identified putative unidirectional as well as bidirectional excitatory/inhibitory interactions. STRFs of neighboring neurons strongly conserve best frequency, and moderately agree in STRF similarity, bandwidth, temporal response type, best modulation frequency, nonlinearity structure, and degree of information processing. Excitatory connectivity was stronger and temporally more precise than for inhibitory connections. Neither connection strength nor degree of synchrony correlated with receptive field parameters. The functional similarity of local pairs of ICC neurons was substantially less than for local pairs in the granular layers of primary auditory cortex (AI). These results imply that while the ICC is an obligatory nexus of ascending information, local neurons are comparatively weakly connected and exhibit considerable receptive field variability, potentially reflecting the heterogeneity of converging inputs to ICC functional zones.

Key words: inferior colliculus, STRF, information, microcircuits, fine-scale networks.

INTRODUCTION

The central nucleus of the inferior colliculus (ICC) is the main lemniscal station in the auditory midbrain, yet relatively little is known about the functional processing in ICC local networks, which are the main arbiters of information convergence, integration and conversion. Characterizing these networks is necessary because the ICC is an obligatory processing hub: the ascending inputs from several brainstem nuclei converge and interact in the ICC, and the ICC is the main source of input to the auditory thalamus (Adams, 1979; Brunso-Bechtold et al., 1981; Aitkin and Phillips, 1984). The ICC is highly structured; it contains fibrodendritic laminae (Oliver and Morest, 1984; Malmierca et al., 1995) that consist of neurons with different synaptic domains or functional zones associated with various converging brainstem inputs (Loftus et al., 2004, 2010; Malmierca et al., 2005). Synaptic domains are thought to contain groups of adjacent ICC neurons that share similar patterns of inputs (Loftus et al., 2004, 2010). Knowledge of the local connectivity and synaptic organization is essential for discovering the principles of intranuclear processing that shape the functional transformation of the converging inputs in different functional zones.

Each fibrodendritic lamina contains neurons that preferentially respond to a restricted frequency range of ~1/3 octave (Schreiner and Langner, 1997; Malmierca et al., 2008). While each layer responds best to a preferential range of frequencies, the set of layers covers the whole frequency range in tonotopic fashion, so that frequency preference strongly and systematically varies orthogonally to ICC laminae (Merzenich and Reid, 1974). Further, individual ICC laminae contain a range of basic acoustic parameters and response properties, such as bandwidth, latency, and modulation characteristics, with some of them showing topographic organization (Schreiner and Langner, 1988; Langner et al., 2002; Rodriguez et al., 2010; Schnupp et al., 2015). Thus, the intricate functional organization of the ICC provides a prime opportunity for exploring how auditory information is integrated and processed in the auditory midbrain.

The ICC's functional organization is a reflection of the spatial distribution of the anatomical inputs that it

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Abbreviations: AI, primary auditory cortex; ASI, asymmetry index; bTMFs, best temporal modulation frequencies; CCC, cross-correlation coefficient; CF, characteristic frequency; DMR, dynamic moving ripple; FRAs, frequency response areas; ICC, central nucleus of the inferior colliculus; ISIs, inter-spike intervals; LSO, lateral superior olive; MSO, medial superior olive; PSTH, post-stimulus time histogram; PTI, Phasic-Tonic Index; RPI, response precision index; STRFs, spectrotemporal receptive fields.

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receives. Inputs from the medial (MSO) and lateral superior olive (LSO), as well as the cochlear nucleus, preferentially target restricted regions of the ICC (Spangler et al., 1985; Oliver, 1987; Shneiderman and Henkel, 1987; Oliver et al., 1997). Thus, the ICC contains a highly organized global pattern of receptive field parameters and anatomical inputs (Loftus et al., 2010). Despite this, the functional utility of the input patterns has not been recovered. The segregated inputs may be a way for the ICC to organize ascending information before packaging it for subsequent auditory stations. The ICC likely also performs further processing on the inputs by imposing specific computations (Ehret, 1997). These two options are not mutually exclusive, although if the ICC's laminar structure is used merely as a consolidation point, local ICC neurons may remain heterogeneous in their response properties. In contrast, if neighboring ICC neurons share similar processing principles, then this may indicate that ICC neurons can perform new computations that further refine and potentially transform ascending information.

Few studies have targeted the micro-organization of the ICC. When tones were presented, neighboring neurons had similar characteristic frequencies (CFs) (Syka et al., 1981; Seshagiri and Delgutte, 2007). Yet, other tone response properties, such as bandwidth, threshold, and latency, appeared to be more divergent between local neurons. Complex sound reverse-correlation analysis also found that CF was highly similar between neighboring neurons (Chen et al., 2012). Other acoustic feature preferences, such as temporal and spectral modulation preferences, and receptive field similarity, were less similar, even for neighboring neurons, with spatial distance being a major determinant of receptive field and spike train correlation strength (Chen et al., 2012).

Our goal was to provide a more detailed picture of several aspects of micro-processing in the ICC for very closely spaced neurons while taking into account the type of local interaction. Previous studies did not scrutinize the relationship between STRF parameters and functional connectivity, nor did they assess how different temporal interaction types are related to functional processing. We addressed this by assessing the functional connectivity of neurons recorded from the same electrode contact and by distinguishing between excitatory and inhibitory interactions, as well as their unilateral or bilateral directionality. Based on these distinctions, we compared local differences in tonal responses, spectrotemporal receptive field (STRFs), nonlinear input/output functions, and information processing. By comprehensively analyzing local pairs of ICC neurons, we were able to quantify characteristics of receptive field processing between pairs of neurons from a circuit perspective. Additionally, we compared the ICC results to similar observations in the input layers of the primary auditory cortex (AI) (Atencio and Schreiner, 2013) to determine whether joint processing in highly local circuits shares characteristics across different stations in the lemniscal pathway.

EXPERIMENTAL PROCEDURES

Surgical procedures, stimulation, and recording

The experimental procedures used in this study have been previously described (Atencio et al., 2012), and were similar to previous reports (Schreiner and Langner, 1997; Escabi and Schreiner, 2002). Three young female adult cats were given an initial dose of ketamine (22 mg/kg) and acepromazine (0.11 mg/kg), and anesthesia was maintained with pentobarbital sodium (Nembutal, 15–30 mg/kg) during the surgical procedure. The animal's temperature was maintained with a thermostatic heating pad. A custom head holder was used to stabilize the head. Bupivacaine was applied to incision points. Surgery consisted of a tracheotomy, reflection of the soft tissues of the scalp, craniotomy over cortex, and durotomy. The cortex posterior to auditory cortex, and above the inferior colliculus, was then aspirated, which allowed for direct visualization of the inferior colliculus and recording access using a lateral-medial approach (Schreiner and Langner, 1997). The tentorium overlaying the inferior colliculus was not removed, which likely allowed full access to most regions of the ICC, though there may have been possible under-sampling of the caudal ICC. After surgery, the animal was maintained in an areflexic state with a continuous infusion of ketamine/diazepam (2–10 mg/kg/h ketamine, 0.05–0.2 mg/kg/h diazepam in lactated Ringer solution). All procedures were in strict accordance with, and were administered under an experimental protocol approved by, the University of California, San Francisco Committee for Animal Research under protocol AN086113.

With the animal inside a sound-shielded anechoic chamber (IAC, Bronx, NY, USA), stimuli were delivered via a closed speaker system to the ear contralateral to the ICC that was recorded from (electrostatic diaphragms from Stax, Japan). Extracellular recordings were made using multi-channel silicon recording probes, which were provided by the University of Michigan Center for Neural Communication Technology. The probes contained sixteen linearly spaced recording channels, with each channel separated by 150 μm. We only used probes with channel impedances between 4 and 5 MΩ since these impedances allowed us to resolve ICC single units; lower impedances usually did not allow for adequate single-unit isolation. Probes were carefully positioned using a microdrive (David Kopf Instruments, Tujunga, CA, USA), and inserted multiple times in each subject ($N = 14$ in subject 1, $N = 27$ in subject 2, and $N = 19$ in subject 3).

Channels that were within the ICC were identified by examining pure-tone stimulation responses. The most superficial electrode contacts usually exhibited little tuning, and if tuning was present, it was very diffuse, indicating that the contacts were likely located in the dorsal cortex of the IC. At increasing depths, clear pure-tone tuning emerged along the extent of the linear electrode. Manual manipulation of a function generator during experiments allowed pure-tone response to be systematically varied, with low frequencies exciting shallower depth channels and higher frequencies