Neuroscience 150 (2007) 970–983

EARLY CORTICAL DAMAGE IN RAT SOMATOSENSORY CORTEX ALTERS ACOUSTIC FEATURE REPRESENTATION IN PRIMARY AUDITORY CORTEX

M. A. ESCABÍ,[a] N. C. HIGGINS,[b] A. M. GALABURDA,[c] G. D. ROSEN[c] AND H. L. READ[b]*

[a]*Electrical and Computer Engineering, Biomedical Engineering, University of Connecticut, Storrs, CT 06269, USA*

[b]*Psychology, Behavioral Neuroscience Division, University of Connecticut, Storrs, CT 06269, USA*

[c]*Department of Neurology, Division of Behavioral Neurology, Harvard Medical School, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, MA 02215, USA*

Abstract—Early postnatal freeze-lesions to the cortical plate result in malformations resembling human microgyria. Microgyria in primary somatosensory cortex (S1) of rats are associated with a reduced behavioral detection of rapid auditory transitions and the loss of large cells in the thalamic nucleus projecting to primary auditory cortex (A1). Detection of slow transitions in sound is intact in animals with S1 microgyria, suggesting dissociation between responding to slow versus rapid transitions and a possible dissociation between levels of auditory processing affected. We hypothesized that neuronal responses in primary auditory cortex (A1) would be differentially reduced for rapid sound repetitions but not for slow sound sequences in animals with S1 microgyria. We assessed layer IV cortical responses in primary auditory cortex (A1) to single pure-tones and periodic noise bursts (PNB) in rats with and without S1 microgyria. We found that responses to both types of acoustic stimuli were reduced in magnitude in animals with microgyria. Furthermore, spectral resolution was degraded in animals with microgyria. The cortical selectivity and temporal precision were then measured with conventional methods for PNB and tone-stimuli, but no significant changes were observed between microgyric and control animals. Surprisingly, the observed spike rate reduction was similar for rapid and slow temporal modulations of PNB stimuli. These results suggest that acoustic processing in A1 is indeed altered with early perturbations of neighboring cortex. However, the type of deficit does not affect the temporal dynamics of the cortical output. Instead, acoustic processing is altered via a systematic reduction in the driven spike rate output and spectral integration resolution in A1. This study suggests a novel form of plasticity, whereas early postnatal lesions of one sensory cortex can have a functional impact on processing in neighboring sensory cortex. Published by Elsevier Ltd on behalf of IBRO.

Key words: perinatal, plasticity, microgyria, auditory, spectral, temporal.

*Corresponding author. Tel: +1-860-486-4108; fax: +1-860-486-2760.
E-mail address: heather.read@uconn.edu (H. L. Read).

Abbreviations: A1, primary auditory cortex; ANOVA, analysis of variance; BF, best frequency; BW, bandwidth; CF, characteristic frequency; FRA, frequency response area; MGB, medial geniculate body; MG+, microgyria present; MG−, microgyria absent; MI, monotonicity index; MTF, modulation transfer function; MZ, multi-modal somatosensory cortex; nMTF, rate normalized modulation transfer function; PNB, periodic noise burst; PSTH, post-stimulus time histogram; P1, postnatal day 1; RLC, rate-level curve; rMTF, rate modulation transfer function; SLI, specific language impairment; sMTF, synchrony modulation transfer function; SPL, sound pressure level; S1, primary somatosensory cortex; T, response threshold; VB, ventrobasal thalamus; VS, vector strength.

0306-4522/07$32.00+0.00 Published by Elsevier Ltd on behalf of IBRO.
doi:10.1016/j.neuroscience.2007.07.054

Auditory processing deficits are coincident with cortical migration anomalies in humans with dyslexia and specific language impairment (SLI); however the relationship between these clinical phenotypes has not been determined. Postmortem examinations of the brains of developmental dyslexics have revealed neocortical malformations including heterotopias, dysplasias, and microgyria (Galaburda and Kemper, 1979; Galaburda et al., 1985; Humphreys et al., 1991). Dyslexics with SLI have difficulty processing rapid transitions in sounds (Tallal and Piercy, 1974; Tallal et al., 1993). Paradoxically, the microgyria are not confined to auditory cortex as one might predict based on the acoustic processing deficits; however, there is a loss of large neurons in the medial geniculate body (MGB) that is the primary source of thalamic input to auditory cortex. Furthermore, the degree of auditory impairment appears to change as a function of cortical location of the anomaly (de Vasconcelos Hage et al., 2006).

Neocortical malformations resembling human polymicrogyria can be induced by focal ischemia (via a freeze-lesion) in the cortical plate of postnatal day 1 (P1) rats (Dvorak et al., 1978; Humphreys et al., 1991; Ferrer et al., 1993). The freeze-lesion causes the loss of layers VI and V neurons, which have already migrated to the cortical plate, and abnormal development of layer III, which matures following P1. Behavioral detection and auditory cortical field potential responses to rapid tone sequences are suppressed in rodents with genetic or freeze-lesion-induced cortical dysplasias (Fitch et al., 1994; Frenkel et al., 2000; Peiffer et al., 2001, 2002). The microgyric rats appear to have a specific temporal processing deficit, as they readily detect sound transitions presented every 200 ms but fail to detect the same transitions if they occur in shorter time windows (Tallal et al., 1993). Though other cognitive parameters are altered, acoustic processing deficits are a common outcome of genetic or traumatic cortical dysplasias.

The neural bases of the acoustic processing deficits associated with parietal cortical dysplasia are unknown. This understanding comprises a particular challenge, as in human dyslexics ectopias or microgyria are rarely confined to A1, and instead impinge on nearby cortex (Galaburda

and Kemper, 1979; Galaburda et al., 1985). In rats with experimentally induced microgyria, cortical neuron morphology and thalamic connections within the lesioned area (Giannetti et al., 1999, 2000; Rosen et al., 2000) are altered dramatically, and the immediately surrounding cortex can be rendered hyperexcitable (Jacobs et al., 1996, 1999). The number of neurons with large cell bodies in the MGB of the thalamus is reduced in animals with primary somatosensory cortex (S1) microgyria (Herman et al., 1997; Peiffer et al., 2002; Rosen et al., 2006). A loss of large thalamic neurons in the geniculate has also been observed in human dyslexics (Livingstone et al., 1991; Galaburda et al., 1994). The physiological impact of the thalamic and cortical reorganization associated with S1 microgyria on cortical sensory processing outside the microgyrus has not been described.

Primary auditory cortex (A1) is a candidate substrate for behavioral and physiologic changes associated with parietal cortical dysplasias in rodents. The loss of large MGB neurons in animals with S1 microgyria likely impacts A1 processing as MGB is the major source of subcortical input to A1. Normally, the large neurons within the medial division of MGB project to both A1 and to neighboring somatosensory cortex (Brett-Green et al., 2003). Thus, sound processing in A1 could be altered via alterations of neighboring somatosensory cortical input or via alterations of shared thalamocortical input. In the present study, we compared the spectral and temporal acoustic feature representation of A1 neurons in animals with microgyria induced by P1 freeze-lesions to the somatosensory cortex to that of controls.

EXPERIMENTAL PROCEDURES

Postnatal surgery

Animals were housed and handled according to approved guidelines by the University of Connecticut Animal Care and Use Committee. Animals were treated in accordance with guidelines set by the NIH and the American Veterinary Medical Association. All efforts were made to minimize the number of animals in the study and their suffering. Microgyria were induced following previously published procedures (Humphreys et al., 1991). Three experimental groups were generated including: 1) freeze lesion group with induced bilateral microgyria, 2) sham surgery group, and 3) a naïve control group. In brief, pregnant Wistar rats were obtained from Charles River Laboratory (Wilmington, MA, USA) in the last week of gestation. The pregnant females were singly housed under a 12-h light/dark cycle and were provided with food and water *ad libitum*. On P1, male and female pups were randomly assigned either to receive bilateral freezing injury to the parietal cortex, a sham operation or no operation. Subjects were anesthetized by placement on ice for 2 min. A small incision on the scalp was made midsagittally. For those subjects receiving freezing lesions, a cooled (−70 °C) probe was placed over the presumptive parietal cortex (centered directly in line with bregma, approximately 2 mm lateral to the sagittal suture) for 5 s. The procedure was repeated on the opposite hemisphere with a second cooled probe. Animals receiving sham surgery were treated identically, with the exception that the probe was at room temperature. The incision was sutured, ink was injected into the footpads for identification, and the pups were warmed before being returned to their mother.

Experimental groups

Experimental groups comparisons for pure-tone responses included nine rats with bilateral microgyria (MG+) and eight control rats with no dysplasia (MG−). Multi-way analysis of variance (ANOVA) analysis found no differences between the rate-level dependencies of sham and naïve surgical controls between experimental group comparisons ($F_{1,621}=2.5$, NS). Thus, sham-operated and naïve experimental groups were combined and considered as a single control group for all analysis (MG− group). The control MG− group included four male and four female rats. The MG+ group contained six male and three female rats. Multi-way ANOVA analysis found no significant sex differences in this sample set. Multi-way ANOVA comparisons for MG+ and MG− populations were used to assess differences between these two groups while accounting for potential effects of unit type (single versus multiunit) and SPL. All statistical analysis was performed with MATLAB® statistics toolbox (The MathWorks Inc., Natick, MA, USA). Recordings were carried out in ventral auditory field in a subset of the male animals in this study and will be examined elsewhere.

Surgery and recording in adult rats

Anesthesia was induced with sodium pentobarbital (<40 mg/kg, i.p.) for surgical procedures and supplemented for unit recording in young adult male and female (50 to 80-day-old) rats. Heart rate, body temperature, breathing rate and reflexes were monitored to judge health and anesthetic level. Tracheotomy was performed to minimize breathing sounds and ensure adequate ventilation. The cisterna magna was drained to minimize cerebral edema. Bone and dura were removed to expose a 7×7 mm area of temporal cortex. No recordings were made if large abnormal vessels associated with the microgyria were found in temporal auditory cortex following craniotomy. Sterile saline was periodically applied to the cortical surface to keep it moist. The topography for pure-tone frequency response was measured with unit and intrinsic optically imaged activity to identify the tonotopic fields in temporal auditory cortex. Continuous intrinsic optical imaging techniques were the same as described previously by Kalatsky et al. (2005) and analysis of imaging data will be described in a separate manuscript. The location of A1 was also confirmed by position relative to bregma and the midline as well as by frequency reversals observed in the optical and unit frequency maps (not shown). A1 units were also determined based on short latency (7–25 ms) responses. Thick epoxy-insulated low impedance (1–2 Ω) tungsten electrodes were positioned in AI at a depth corresponding to layer IV (550 μm). Single and multiunit neuronal spike activity was measured extracellularly. Data were collected from approximately 15 sites per rat. Multiple stimulus conditions and sound types were used to characterize response properties hence recording required approximately 2 h per site and 24 h total recording time per animal.

Histology

After a 24 h recording time animals were given a lethal dose of sodium pentobarbital (>100 mg/kg, i.p.) and were perfused with 0.1 M phosphate buffer followed by 4% paraformaldehyde buffered fixative solution. Brains were removed from the skull and a photo was taken of the whole brain to document the location of the microgyria (Fig. 1A). Brains were blocked, sectioned into two 5 mm blocks and cut in the coronal plane at 60 μm on a vibratome. In five rats brain blocks were paraffin embedded to allow for 8 μm sectioning on a microtome. Sections were mounted on charged or gelatinized slides, processed for Nissl staining and coverslipped. Microgyria identified as described previously (Herman et al., 1997) were found predominantly within the parietal cortex and often had spurs that radiated dorsal and anterior to auditory cortex but in no