Hearing Research 311 (2014) 49–62

Contents lists available at ScienceDirect

Hearing Research

journal homepage: www.elsevier.com/locate/heares

Review

Manganese enhanced magnetic resonance imaging (MEMRI): A powerful new imaging method to study tinnitus

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ARTICLE INFO

Article history:
Received 15 October 2013
Received in revised form
5 February 2014
Accepted 10 February 2014
Available online 26 February 2014

ABSTRACT

Manganese enhanced magnetic resonance imaging (MEMRI) is a method used primarily in basic science experiments to advance the understanding of information processing in central nervous system pathways. With this mechanistic approach, manganese (Mn^{2+}) acts as a calcium surrogate, whereby voltage-gated calcium channels allow for activity driven entry of Mn^{2+} into neurons. The detection and quantification of neuronal activity via Mn^{2+} accumulation is facilitated by "hemodynamic-independent contrast" using high resolution MRI scans. This review emphasizes initial efforts to-date in the development and application of MEMRI for evaluating tinnitus (the perception of sound in the absence of overt acoustic stimulation). Perspectives from leaders in the field highlight MEMRI related studies by comparing and contrasting this technique when tinnitus is induced by high-level noise exposure and salicylate administration. Together, these studies underscore the considerable potential of MEMRI for advancing the field of auditory neuroscience in general and tinnitus research in particular. Because of the technical and functional gaps that are filled by this method and the prospect that human studies are on the near horizon, MEMRI should be of considerable interest to the auditory research community.

This article is part of a Special Issue entitled <Annual Reviews 2014>.

1. Overview

Manganese enhanced magnetic resonance imaging (MEMRI) is a relatively new imaging method that is not dependent upon blood flow. This methodology has unique capabilities for identifying cerebral architecture, mapping neuronal pathways, and objectively evaluating the physiologic extent and spatial locations of cerebral function (Pautler, 2004, 2006; Boretius and Frahm, 2011). Although manganese (Mn^{2+}) can act as a tract tracer via microtubule based axonal transport (Pautler, 2004; Lee et al., 2007), our focus here is on using Mn^{2+} as a probe of neuronal function. Specifically, Mn^{2+} ions enter active cells primarily through voltage-gated calcium channels and accumulate inside neurons. As a paramagnetic contrast agent, Mn^{2+} shortens T_1 relaxation times and provides contrast enhancement of T_1-weighted images in those brain areas

Abbreviations: AC, auditory cortex; AMYG, amygdala; BBB, blood brain barrier; CIC, central nucleus of the interior colliculus; CNS, central nervous system; dB, decibels; D-AP5, (D(−)-2-Amino-5-phosphonopentanoic acid; DCN, dorsal cochlear nucleus; FDA, Food and Drug Administration; IC, inferior colliculus; IP, intraperitoneal; IV, intravenous; KCNQ, voltage-gated potassium channel; LTCC, L-type calcium channels; Mn^{2+}, manganese; MRI, magnetic resonance imaging; MEMRI, manganese enhanced magnetic resonance imaging; MGB, medial geniculate body; MPRAGE, magnetization prepared rapid acquisition gradient echo; NAD^+, nicotinamide adenine dinucleotide; NMDA, *N*-methyl-D-aspartate; PFL, parafolloculus lobe of the cerebellum; PPI, prepulse inhibition; ROI, region-of-interest; SPL, sound pressure level; SC, subcutaneous; VCN, ventral cochlear nucleus

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http://dx.doi.org/10.1016/j.heares.2014.02.003
0378-5955/

where manganese ions have accumulated.[1] Thus, increased neuronal activity, either stimulus driven or endogenously generated, results in more Mn^{2+} being present in cells which in turn allows for spatial localization and quantification of neuronal activity to specific regions of the brain by MRI (e.g., Koretsky and Silva, 2004; Pautler, 2006; Silva et al., 2004; Silva and Bock, 2008).

In the short time since MEMRI has been introduced, it has been applied in many diverse areas, including: intra-retinal ionic regulation (Berkowitz et al., 2007b), mapping studies of visual pathways (Yamada et al., 2008; Bock et al., 2009; Bissig and Berkowitz, 2009), evaluation and differentiation of laminar structure in somatosensory cortex (Silva et al., 2008) and other brain areas (olfactory bulb, hippocampus, cerebellum) (Watanabe et al., 2013), characterization of central odorant, olfactory, nociceptive, and motor pathways (Chuang et al., 2009; Eschenko et al., 2010; Yang et al., 2011; Lehallier et al., 2012), examination of neuroplasticity (Tindemans et al., 2003; Van der Linden et al., 2004; Immonen et al., 2008), assessment of ischemia, gliosis, and neuronal injury (Aoki et al., 2003, 2004; Kawai et al., 2010; Inoue et al., 2010; Bade et al., 2013), phenotyping models of psychiatric disease such as schizophrenia and bipolar disorder (Lutkenhoff et al., 2012; Hattori et al., 2013), evaluating stress circuits in the brain by distinctive induction methods (Bangasser et al., 2013), evaluating cognitive function via the retrieval of taste-aversion memory, localizing fundamental processes associated with memory consolidation, assessing the calcium hypothesis of aging in rat hippocampus (Inui-Yamamoto et al., 2010; Chen et al., 2013; Bissig and Berkowitz, 2013) and, acting as a biomarker for epileptogenesis in the kainic acid induced status epilepticus (KASE) rat model of mesial temporal lobe epilepsy (Dedeurwaerdere et al., 2013), to name a few.

Hearing scientists were among the first to capitalize on this methodology and have been instrumental in applying this technique to basic research topics related to developmental neurobiology of the auditory system, including the organization and/or reorganization of tonotopic maps under conditions of normal and altered development (Yu et al., 2005, 2007), in neuronal tract tracing and functional activity mapping of frequency and intensity coding in auditory pathways (Yu et al., 2008; Jin et al., 2013; Lee et al., 2007, 2012), elaborating on stimulus driven circuits of the lateral lemniscus and superior olivary complex (Watanabe et al., 2008), in evaluating changes in central auditory pathways resulting from temporary and permanent noise induced threshold shifts (Gröschel et al., 2011), in phenotyping specific genetic anomalies which focus on central neurological manifestations of inner hair cell dysfunction in Bassoon mutant mice where, moderate hearing loss and seizures are manifest as part of the disease expression (Altrock et al., 2003; Angenstein et al., 2007), in phenotyping central auditory defects in fibroblast growth factor 17 mutant mice (Yu et al., 2011), and more recently, to the area of tinnitus.

Experimental evidence showing that MEMRI can be used to localize endogenously generated neural hyperactivity in rats having behavioral evidence of tinnitus induced by noise exposure and salicylate administration opens up a whole new research domain for studying phantom-like perceptions in an objective manner (Brozoski et al., 2007b, 2013; Holt et al., 2010). Indeed, it is anticipated that application of MEMRI to tinnitus research will yield enormous benefits for understanding underlying mechanisms and in developing new treatment options for this condition.

The use of MEMRI offers unique features that distinguish it from other imaging methodologies like positron emission tomography (PET), single photon emission tomography (SPECT), and functional magnetic resonance imaging (*f*MRI) based on the blood oxygenation level dependent (BOLD) response. In imaging studies using small laboratory animals, spatial resolution is an important issue. Consider that MEMRI of the brain can provide functional information with ~100 micrometer (um) resolution *in vivo*; whereas PET studies are limited by much lower spatial resolution in the range of millimeters (mm's) (see Malison et al., 1995; Tai et al., 2005; Paul et al., 2009). This constraint is particularly evident when attempting to characterize neuronal activity in small but functionally distinct regions of the auditory brainstem such as subdivisions of the cochlear nucleus (CN) in the rat. The importance of this distinction relates to the observation that the CN complex has been identified as playing a distinct role in tinnitus (Kaltenbach, 2006; Kaltenbach et al., 2004). The CN of the rat presents a challenge for image capture because of its very small dimensions (anteroventral nucleus, 0.32 mm; posteroventral nucleus, 0.96 mm, and dorsal nucleus, 1.20 mm, in the rostro–caudal plane). Other areas-of-interest within the CN, such as the molecular, fusiform, and deep layers are located 370 μm in the ventral plane.[2] Thus, the high resolution of MEMRI has clear advantages over other methodologies used for tinnitus research.

Functional MRI has improved spatial and temporal resolution in comparison to PET. However, the most widely used and fully-developed *f*MRI methods rely on functional activations in response to some type of external stimulation (i.e., image capture implemented inside the magnet must be synchronized [triggered] to an *external* stimulus/event driving brain activity) (see Cacace et al., 2000 for a review), although instances where *internally* generated *on* and *off* states that can be controlled by the individual, like gaze-evoked, gaze-modulated, and cutaneous-evoked tinnitus are the exceptions (e.g., Cacace et al., 1994a, b; 1999, Cacace, 1999; Giraud et al., 1999; Lockwood et al., 2001; van Gendt et al., 2012). Nevertheless, when considering conventional *f*MRI, the assumption that tinnitus may be differentially affected depending upon the acoustic stimulus or that auditory processing may be divergent in tinnitus patients compared to non-tinnitus patients, is reasonable. For example, Melcher et al. (2000) have shown that IC evoked activity contralateral to lateralized tinnitus was depressed (Gu et al., 2010; Levine et al., 2007; Roberts et al., 2010). This was interpreted as a ceiling effect deriving from elevated spontaneous activity associated with tinnitus. Using a different *f*MRI method (sparse-imaging), de Kleine et al. (2007) and Lanting et al. (2009) documented somewhat different results, showing moderately elevated evoked activity in the IC and significantly elevated activity in the cerebellum of patients with normal hearing and tinnitus. These human *f*MRI data are in agreement with animal studies implicating both the IC and cerebellum in tinnitus (Bauer et al., 2013a, b; Brozoski et al., 2013; Bauer et al., 2008; Holt et al., 2010). Despite its somewhat higher resolution, some of the same interpretive limitations apply to *f*MRI as they do to PET. In conventional *f*MRI, there is the obvious burden of having to extrapolate from stimulus driven activity to the more clinically relevant "steady-state" aspect of tinnitus; i.e., continuous "ringing or buzzing in the ears." In comparison to standard stimulus driven *f*MRI techniques, the less widely used resting-state *f*MRI (RS-*f*MRI) methods do not require externally synchronized stimuli for

[1] Contrast between tissue components in MRI is usually based on the differential rates of relaxation which subsume the transition from transverse magnetization back to longitudinal magnetization. T_1 and T_2 are independent relaxation time constants. Based on the imaging parameters chosen for the MRI scan, images can be biased towards being either T_1 or T_2-weighted and thereby vary the contrast between gray matter, white matter, cerebrospinal fluid, and skull.

[2] Measurements courtesy of Dr. Avril Genene Holt.