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Research report

Acoustic tone or medial geniculate stimulation cue training in the rat is associated with neocortical neuroplasticity and reduced akinesia under haloperidol challenge

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ABSTRACT

Sensory cues can improve movement deficits in Parkinson's disease, but little is known about the mechanisms involved. To investigate neuroplastic changes following sensorimotor cue training, rats were shaped to respond to acoustic tone or medial geniculate stimulation cues by retrieving a food reward. Neuroplasticity associated with training was assessed by changes in auditory neocortical evoked field potentials and dendritic morphology. Stimulation cue training was associated with changes in dendritic arbour length and complexity in auditory and motor neocortices, but was without effect on evoked electrophysiological responses. Tone cue training was associated with a significant increase in peak height of the evoked auditory response and then under haloperidol challenge, demonstrated reduced akinesia. Results indicate that cue-training induces neuroplastic changes that may be related to improved sensorimotor function under dopaminergic antagonism.

1. Introduction

Core hypokinetic symptoms in Parkinson's disease present as difficulty in the initiation and poverty and slowness in the execution of movement. It has long been known that PD patients, despite severe hypokinesia, are able to perform movements in response to external sensory cues with greater velocity, force, and accuracy than they would otherwise be able to voluntarily [1,2]. This "paradoxical kinesia" in PD suggests that while motor function capacity is preserved, movement deficits occur as a result of impaired motor control [3]. In recent years, renewed interest in cued movement facilitation has focused on developing novel rehabilitation therapies that employ auditory cues as adjunctive therapies to pharmacotherapy [4,5].

Little is known about how auditory cues can bypass faulty internal cue and pre-movement set related activity of the basal ganglia in PD [6], but their understanding is of great clinical interest in order to focus and maximize the effects of rehabilitative therapies. Rat models provide an excellent substrate in which to answer these questions by providing unparalleled flexibility and amenability to numerous experimental interventions compared to human studies [7,12]. The auditory [8,9] and motor [10,11] neocortices of the rat have shown to be highly malleable even in adulthood, demonstrating both anatomical and physiological changes with experiential training and learning in a task-dependant manner.

Acoustic cues or stimulation of extra-basal ganglia structures have been shown to facilitate release from catalepsy and reinstate previously lost behaviour in rats [12,13]. These findings resemble auditory cue facilitation of movement in PD [14], but whether sensorimotor training induces neocortical plasticity is unknown. This study presents a behavioral model to assess auditory-stimulation induced cortical plasticity in the rat. Rats were trained to respond to a single auditory tone or a brief train of stimulation to the medial geniculate nucleus by initiating movement to collect a sucrose pellet reward in an open recording chamber. Following successful training, changes in evoked auditory neocortical responses and dendritic morphology in auditory and sensorimotor neocortex were assessed. To determine whether prior acoustic tone cue training can facilitate movement under antagonism of dopaminergic systems, performance in a

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probe cueing test was assessed under haloperidol cataleptic challenge.

2. Methods

2.1. Rats

A total of 27 adult male Long-Evans rats were used in this study. All rats received a chronic electrode implantation in the medial geniculate body (MGB) of the auditory thalamus and weighed 254–392 g at the time of implantation. Rats were obtained from the University of Calgary Breeding Colony and housed individually in clear plastic cages in a colony room maintained on a 12 h light/dark cycle (lights on at 07:15) at 21 °C. They were provided free access to food and water throughout the duration of their housing except for being food restricted to 90% of their implantation body weight at electrode implantation during behavioural training. All procedures strictly adhered to the guidelines of the Canadian Council on Animal care and were approved by the Institutional Animal Care committee of the University of Calgary. All efforts were made to adhere to the principles of reduction, refinement, and replacement in experimental design [15], with every attempt made to limit the number of subjects and minimize animal suffering.

2.2. Experimental groups and procedures

Rats were randomly assigned into four groups: tone cue trained ($n = 8$) with yoked controls ($n = 8$) and MGB stimulation cue trained ($n = 6$) with yoked controls ($n = 5$). Reported sample sizes were unequal between groups due to surgical and head cap losses ($n = 2$ for stimulation cue trained, $n = 3$ for nonstimulation cue trained). Seven days following implantation surgery, baseline electrophysiological responses were taken for each rat. Rats then underwent behavioural training and follow-up electrophysiological and anatomical records were obtained.

2.3. Chronic electrode implantation

Rats were anaesthetized with isoflurane (4% induction, 1.5% maintenance; VIP-3000 Vaporizer, Matrix, Orchard Park, NY) and placed in a stereotaxic frame with the incisor bar set to skull flat. Lidocaine (2%) was administered subcutaneously at the incision site and the scalp incised. Twisted-wire bipolar recording and stimulating electrodes were constructed from Teflon-coated stainless steel wire 178 μm in diameter (A-M Systems, Everett, WA). Electrode terminals were connected to gold-plated male amphenol pins and the two uninsulated poles for implantation were separated by 0.5 mm.

Three bipolar electrodes were chronically implanted in the right hemisphere according to the stereotaxic coordinates of Paxinos and Watson [16] and nomenclature of Zilles [17] at the following coordinates relative to bregma: primary auditory field (Te1; AP −5.8, ML +6.0, V −4.3 mm), primary sensorimotor cortex (Par1; AP +1.0, ML +4.0, V −2.5 mm), and the ventral division of the medial geniculate body (MGB; AP −5.8, ML +3.7, V −5.8 mm). The ventral division of the MGB was chosen as the stimulation site as it is the sole division of the medial geniculate that comprises the lemniscal pathway conveying unimodal auditory information to the primary auditory field [18]. The caudal region of the primary auditory field was chosen for the recording site as low frequencies are represented in this area [19,20] and a lower frequency, 1 kHz tone was utilized in the experiment. Sensorimotor recording coordinates were chosen as they corresponded to the output layer of the forelimb region of the primary motor cortex [21,22].

Electrophysiological monitoring was performed during surgery and dorsal-ventral placements of the electrodes adjusted to maximize the amplitude of the evoked responses. Electrode placement verification was confirmed by a positive evoked MGB response, and by visual inspection of post-mortem tissue. The amphenol pins connected to the electrodes were then inserted into a McIntyre connector plug ([23]; Ginder Science, Ottawa, ON) which was adhered to the skill with dental cement and anchored with five stainless steel screws, one of the screws serving as a ground electrode. The scalp was then sutured around a dental cement headcap and rats were given a topical application of Xylocaine jelly (2%) anaesthetic around the incision. Rats were given 7 days to recuperate prior to obtaining baseline electrophysiological records.

2.4. Evoked field potentials

Evoked responses were recorded as per Flynn and Teskey ([24]; refer for full description). Input/output records were obtained by administering pulses of increasing intensity to MGB and Te1, separately, with the resultant evoked field potentials recorded in primary auditory (MGB stimulation) and motor (Te1 stimulation) neocortical electrodes recorded. Stimulation current consisted of biphasic rectangular pulses with a width of 200 μs and a 200 μs delay between phase inversions

2.5. Evoked potential analysis

Evoked potentials obtained prior to and following cue training were examined for changes in the relative peak height of the response. Relative peak height was used as it provided a relatively unbiased quantification of the complex, polysynaptic evoked responses and was defined as the smallest, trough, value (mV) of the response subtracted from the largest, peak, value (Fig. 1). Records at a stimulation intensity of 464 μA were used for statistical analyses as this stimulation intensity was resulting in maximum amplitude of the evoked response. Any cases where a clear electrophysiological response could not be ascertained due to noise or instability in the I/O series were excluded from the analyses. For analyses, the percent change in the peak height of the response post-training to baseline was used to compare groups. Percent change in peak height was calculated as (peak height post-training − peak height at baseline)/(peak height at baseline) × 100.

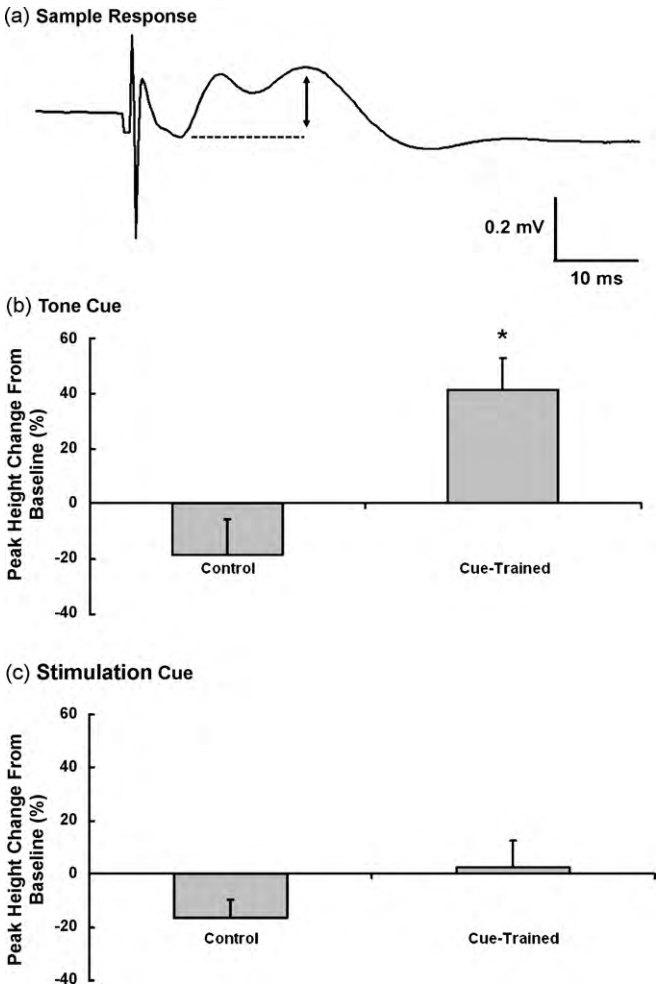

Fig. 1. (a) Sample recorded field potentials evoked with 200 μS biphasic square wave pulses at an intensity of 464 μA. Response in the primary auditory cortex (Te1) from stimulation of the ventral division of the medial geniculate (MGB). Arrows indicate peak height of the response. Percent change in relative peak height (mean ± SEM) of evoked auditory field responses in: (b) tone and, (c) MGB cue groups following cue-training relative to baseline. Peak height was calculated as the smallest trough value subtracted from the largest peak (mV). Means marked with a star are significantly different from their corresponding control mean ($p < .05$).

2.6. Behavioural shaping

Cue group rats were trained to retrieve one-gram sucrose reward pellets (Bioserve, Frenchtown, NJ) upon cue presentation in an open recording chamber. Cues were either a 5-s presentation of a 1 kHz pure tone sinusoidal waveform (tone cue; 70–80 db SPL; Audacity v1.3) or a 5-s train of biphasic stimulation of the MGB (stimulation cue). Thalamic stimulation consisted of biphasic rectangular pulse trains with a 200 μs pulse width and 200 μs delay between phase inversions at an intensity of 100 μA and a frequency of 10 Hz.

Training consisted of three distinct stages. Rats were first acclimatized to the recording chamber (32 cm × 57 cm) and provided free access to the pellet rewards placed in a 4 cm × 4 cm polystyrene disk (VWR International) for 15 min each day for 2 consecutive days. Cue group rats were slowly shaped to respond to the cue by initiating movement to retrieve the sucrose pellet placed in the weigh dish. The rat was placed at the starting location in the rear-right of chamber and the cue given. If the rat did not initiate movement to retrieve the pellet by the end of the