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High frequency repetitive sensory stimulation improves temporal discrimination in healthy subjects

Roberto Erro [a,b,*], Lorenzo Rocchi [a,c], Elena Antelmi [a,d], Raffaele Palladino [e], Michele Tinazzi [b], John Rothwell [a], Kailash P. Bhatia [a]

[a] Sobell Department of Motor Neuroscience and Movement Disorders, University College London (UCL) Institute of Neurology, London, United Kingdom
[b] Dipartimento di Scienze Neurologiche e del Movimento, University of Verona, Verona, Italy
[c] Department of Neurology and Psychiatry, Sapienza University of Rome, Rome, Italy
[d] Department of Biomedical and Neuromotor Sciences, Alma Mater Studiorum, University of Bologna, Bologna, Italy
[e] Department of Primary Care and Public Health, Imperial College London, United Kingdom

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HIGHLIGHTS

- High frequency stimulation of the skin focally improves temporal discrimination in the area of stimulation.
- The effect is reversible with temporal discrimination threshold returning to baseline values within 24 h.
- Such a protocol could potentially be used as a therapeutic intervention to ameliorate physiological decline in the elderly or in other disorders of sensorimotor integration.

ABSTRACT

Objective: High frequency electrical stimulation of an area of skin on a finger improves two-point spatial discrimination in the stimulated area, likely depending on plastic changes in the somatosensory cortex. However, it is unknown whether improvement also applies to temporal discrimination.
Methods: Twelve young and ten elderly volunteers underwent the stimulation protocol onto the palmar skin of the right index finger. Somatosensory temporal discrimination threshold (STDT) was evaluated before and immediately after stimulation as well as 2.5 h and 24 h later.
Results: There was a significant reduction in somatosensory temporal threshold only on the stimulated finger. The effect was reversible, with STDT returning to the baseline values within 24 h, and was smaller in the elderly than in the young participants.
Conclusions: High frequency stimulation of the skin focally improves temporal discrimination in the area of stimulation. Given previous suggestions that the perceptual effects rely on plastic changes in the somatosensory cortex, our results are consistent with the idea that the timing of sensory stimuli is, at least partially, encoded in the primary somatosensory cortex.
Significance: Such a protocol could potentially be used as a therapeutic intervention to ameliorate physiological decline in the elderly or in other disorders of sensorimotor integration.

1. Introduction

Accurate exploration of our environment requires that we know both the spatial location and the relative timing of sensory information. Such abilities decline with age (Evans et al., 1992; Stevens and Choo, 1996) and reflect the overall physiological, structural, and metabolic changes that occur in the elderly (Raz et al., 2005; Terry et al., 1987; Leenders et al., 1990). Therefore in recent years there has been much interest in a number of reports showing that training can improve perceptual abilities even in adults (Gilbert et al., 2001; Seitz and Dinse, 2007; Citri and Malenka, 2008).

* Corresponding author at: UCL Institute of Neurology, 33 Queen Square, London WC1N 3BG, United Kingdom.
E-mail address: erro.roberto@gmail.com (R. Erro).

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Although most training approaches involve high levels of attention, others employ a more basic physiological mechanism that can improve perception by repeated stimulation of sensory pathways. Dinse and colleagues (Dinse et al., 2006; Godde et al., 1996, 2000) have shown that high frequency repetitive sensory stimulation of cutaneous receptors (HF-RSS) protocol can improve sensory perception in the stimulated area in animal experiments and in humans. It is suggested that stimulation leads to "coactivation" of receptive fields underneath the electrodes, and that this induces lasting changes in central sensory representations. Thus, in rats, repeated high frequency coactivation of sensory inputs from a digit increases the representational area of that digit in sensory cortex and increases the receptive field size of individual cortical neurons (Godde et al., 1996). Somewhat paradoxically, the same protocol in humans enhances two-point discrimination for several hours (Dinse et al., 2006; Godde et al., 2000). As the authors pointed out, an initial expectation might be that larger receptive fields would reduce perceptual acuity. However, perceptual ability does not necessarily relate to the receptive field size of individual neurons, but instead reflects the sum total of information present in the discharge of many neurons (Dinse et al., 2006; Godde et al., 1996, 2000). Thus, increasing numbers of neurons responsive to inputs from an area of skin that have overlapping and slightly different receptive fields, can code acuity with greater precision than any single neuron alone.

Theoretically, the same argument can be applied to temporal acuity: The summed activity of greater numbers of neurons responding to an input may be capable of higher temporal resolution than any one neuron alone. However, this has never been tested formally in the context of coactivation conditioning. In fact, Godde et al. found that the response duration of sensory neurons increased after conditioning in rats (Godde et al., 1996), which could potentially reduce temporal resolution.

The present experiments were therefore designed to examine the consequences for temporal perception of repetitive coactivation of sensory inputs from a digit in human volunteers. Temporal acuity was assessed by measuring the somatosensory temporal discrimination threshold (STDT), defined as the minimum interval between two stimuli that are clearly perceived as being separate. Despite inter-subject variability, healthy individuals usually perceive two tactile stimuli as sequential when the interstimulus interval (ISI) exceeds 30–50 ms (Lacruz et al., 1991), although threshold tends to decline with age (Humes et al., 2009).

The first aim of the experiment was to test whether HF-RSS changed the STDT in healthy young volunteers. In addition, since Dinse et al. had shown that the effect of HF-RSS on spatial discrimination was larger in the elderly than in the young (Dinse et al., 2006) we asked whether any changes in STDT were larger in an elderly group of volunteers compared with the young participants.

2. Subjects and methods

2.1. Participants

Twelve healthy right-handed young subjects (seven females; aged 28–32 years – Group A) and ten healthy right-handed elderly subjects (4 females; aged 50–76 years – Group B) participated in the study after giving their written informed consent. Participants had no history of any neuropsychiatric disorders, neurosurgery, or metal or electronic implants and were not on drugs active at CNS level at the time of the experiments. All experimental procedures were approved by the local institutional review board and conducted in accordance with the Declaration of Helsinki and according to international safety guidelines.

2.2. High frequency repetitive sensory stimulation protocol

HF-RSS was performed as previously described (Schlieper and Dinse, 2012). For application of the HF-RSS, we used self-adhesive electrodes (10 mm in diameter), which were taped to the first (cathode) and third phalanx (anode) of the right index finger. The cathode electrode allowed simultaneous stimulation of the skin portions of the right index finger under it, thereby leading to "coactivation" of all receptive fields within this area (Schlieper and Dinse, 2012). Stimuli consisted of bursts of 20 Hz square-wave electrical pulses with a width of 0.2 ms, delivered every 5 s with a constant current stimulator (Digitimer DS7AH), for a duration of 45 min (total of 540 stimuli and 10,800 pulses). Coactivation stimuli were applied at maximum tolerated intensities (mean intensity: 4.9 mA in the young group and 5.45 mA in the elderly equating on average to 300% of the sensory threshold, defined as the weakest stimulus that the subject could detect).

2.3. Somatosensory temporal discrimination threshold (STDT) procedure

STDT was investigated by delivering paired stimuli starting with an ISI of 10 ms preceded by a single stimulus and progressively increasing the ISIs (in 10 ms steps) according to the experimental procedures used in previous studies (e.g., ascending STDT) (Pastor et al., 2004; Fiorio et al., 2007). To keep subjects' attention high and to minimise the risk of perseverative responses, random catch trials (single stimulus) occurred at least once in each of the ascending series (Conte et al., 2012). Each stimulus consisted of a square-wave electrical pulse with a width of 0.2 ms delivered with a constant current stimulator (Digitimer DS7AH) through surface skin electrodes (5 mm in diameter) placed on the last phalanx with the anode located 0.5 cm distally from the cathode. The procedure was performed on three different fingers: right index finger (stimulated finger); right thumb (non-stimulated contiguous finger), and the left index (non-stimulated non-contiguous finger). The stimulation intensity was defined for each subject by delivering series of stimuli at increasing intensity from 2 mA in steps of 1 mA; the intensity used for STDT was the minimal intensity perceived by the subject in 10 of 10 consecutive stimuli. Subjects were asked to report verbally whether they perceived a single stimulus or two temporally separated stimuli. The first (lowest) of three consecutive ISIs at which participants recognized the two stimuli as temporally separated was considered the STDT. Each session comprised three separate blocks. The STDT was defined as the average of three STDT values, one for each block, and was entered in the data analysis. The STDT procedure was performed before the coactivation protocol (T0), 5 min (T1), 2.5 h (T2) and 24 h (T3) after the end of the coactivation protocol in the group of young subjects to assess: (1) if the HF-RSS could lead to an improvement of STDT values; and (2) to assess the reversibility of the potential improvement over 24 h. The STDT procedure was only performed at T0 and T1 in the elderly group to see whether the improvement was any different in magnitude compared to the group of young subjects.

2.4. Data analysis and statistics

To understand which factor(s) could influence the outcomes we fitted three mixed linear models for repeated measures. Two separate models were run on each of the two groups considering "time" and "finger" as factors, and the interaction term between the two variables, including for the group of young subjects the complete set of four outcome measurements. We then fitted a general model considering "group", "time" and "finger" as covariates, as well as the interaction term between time and finger and the interaction term between time and group. To test the goodness