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The routine circular coil is reliable in paired-TMS studies

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HIGHLIGHTS

- Routine circular coils are easy to handle in TMS measurements.
- They are as reliable as figure-of-eight coils for assessment of cortical excitability.
- Their use can help TMS become a popular marker in clinical studies.

ABSTRACT

Objective: Motor cortex excitability can be measured by transcranial magnetic stimulation (TMS) using different coil types, but paired-TMS was originally devised with a figure-of-eight coil. We asked whether the most popular, circular coil was suited to the every-day assessment of cortical excitability, particularly paired-TMS indexes, and if it reduced the measurement error.
Methods: We studied 12 right-handed, healthy subjects (34 ± 7.6 years). Resting motor threshold (MT), cortical silent period (CSP), short-interval intracortical inhibition (SICI) at the 2, 3, 4 and 5 ms interstimulus intervals (ISIs) and intracortical facilitation (ICF) at the 14 and 16 ms ISIs were measured. Intrinsic variability of these indexes was evaluated in terms of Coefficients of Variation, to estimate the measurement error. This sequence was carried out both using a figure-of-eight coil over the hand motor area and a circular coil centred at the vertex. Testing was repeated 8–13 months later.
Results: On average, MT, SICI and ICF did not show any statistically significant difference ($p > 0.05$) when studied with the figure-of-eight as compared with the circular coil. CSP was significantly shorter ($p = 0.007$) with the figure-of-eight coil. Using either coil did not affect measurement variability. There was no significant session-to-session group difference at any of the variables using either coil type.
Conclusions: Except for the CSP duration, the TMS testing and retesting of cortical excitability, particularly the paired-pulse indexes, did not vary significantly as a function of the coil used.
Significance: Routine circular coils can be used reliably in paired-TMS studies designed to measure longitudinal changes in cortical excitability though they do not reduce the measurement error.

1. Introduction

Single and paired-pulse transcranial magnetic stimulation (TMS) can be used to evaluate excitatory/inhibitory intracortical circuits. They have been used extensively to study the pathophysiology of various neuropsychiatric diseases (Afra et al., 1998; Badawy et al., 2007; Bettucci et al., 1992; Bohotin et al., 2003; Brighina et al., 2002; Hamer et al., 2005; Manganotti et al., 2000; Reutens and Berkovic, 1992; Rothwell, 2007; Siniatchkin et al., 2007; van der Kamp et al., 1997; Vucic and Kiernan, 2006; Werhahn et al., 2000a,b; Ziemann, 2004a, 1998) and have also provided insights on the mechanisms of brain plasticity (Chen and Udupa, 2009; Siebner and Rothwell, 2003; Ziemann, 2004b) and neuroactive drugs (Ziemann, 2003, 2004a). Over the last 20 years an impressive growth in TMS studies of motor cortical excitability was observed including several longitudinal studies (Rossini and Rossi, 2007). This is why, it is important to establish reproducibility, and ease of performing prolonged studies on many patients several times. One of the problems that could influence this is the coil type and shape. The two most commonly used coils are either a figure-of-eight coil (either wing: 9 cm outer diameter) placed over the motor hand area or a circular coil (13.5 cm outer diameter) placed over the vertex. In the original description of the paired-pulse technique (Kujirai et al., 1993) the figure-of-eight coil at the hot-spot for the

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target muscle was used. While this is the standard technique for most labs, it is somewhat difficult to implement. Precise definition of the hot-spot itself is not always straightforward and is time-consuming. Then, subsequent inadvertent displacements of the focal device may well occur, unless mechanical constraints are applied, which happens rarely. While the earlier, circular coil centred at the vertex may stimulate a larger area of the cortex, it is much easier to be placed and held at the proper location, which can be immediately identified in subsequent sessions on the 10–20 system coordinates (Shimizu et al., 1999).

As we shall discuss, there is however no previous definite evidence for the routine, every-day use of the circular coil in paired-TMS studies. Abbruzzese et al. (1999) reported no difference between the coils, but they recorded from the *Biceps brachii* muscle (BB) in three subjects. Shimizu et al. (1999) recorded from hand muscles in a larger sample, and found a similar behaviour of the two coils, particularly at the interstimulus interval (ISI) of 2 ms, but not at ISI 5 ms.

The intrasubject, intersubject, interinvestigator and intersession variability of TMS indexes proved high in healthy subjects. However, group averages of, for instance, paired-pulse variables showed in general no significant differences on repeated sessions. Still, there is no definite conclusion on the potential influence of the coil shape on the measurement error or session-to-session repeatability (Boroojerdi et al., 2000; Maeda et al., 2002; Mills and Nithi, 1997; Orth et al., 2003).

Therefore, in the current study we explored if cortical excitability measures, particularly paired-pulse variables, are influenced by the circular versus the figure-of-eight coil, in terms of absolute values and session-to-session repeatability. Special attention was paid to the intrinsic variability of the measures obtained with either coil, which was assessed in terms of Coefficient of Variation (CV). Overall, we wanted to establish if the traditional, circular coil can be universally recommended for the simplest paired-pulse TMS applications, and if it reduces the measurement error. If so, this may promote more widespread and systematic clinical applications of TMS indexes.

2. Methods

2.1. Subjects

Twelve right-handed healthy volunteers (6 females, mean age 34 years, range 25–49 years) were included in the current study. None had history of seizures or any other neurological disorders.

The study protocols were approved by the Local Research Ethics Committee and written informed consent was obtained from all individuals.

All the TMS variables were measured with both coil types (figure-of-eight and circular) during either session. The order of which coil was used first was determined randomly for each subject. This testing protocol was then repeated for each subject 8–13 months later.

All the tests were performed early in the afternoon in a quiet laboratory room, at a standard temperature of 23 °C. Participants were asked not to take neuroactive drugs, caffeine or alcohol and to maintain normal sleep habits for at least a week before either test. Normal blood pressure, heart rate, and body temperature were ascertained before the testing started.

2.2. Transcranial magnetic stimulation

During TMS, the subjects sat in a comfortable, reclining chair. Motor evoked potentials (MEPs) were recorded by pairs of Ag–AgCl disk electrodes from the right first dorsal interosseous muscle (FDI) in a belly-tendon montage (electrode distance = 6 cm).

Data were collected, amplified, and filtered (30 Hz–3 kHz) through a CED 1902 isolated amplifier (CED, Cambridge, UK) that fed signals to an A/D converter (CED Micro 1401 Mk II, Cambridge, UK). The sampling rate was 5 kHz. Digitized signals were handled on a PC by the Signal version 2.15 program (CED, Cambridge, UK) and stored on disk for subsequent analysis. The latencies of all waveforms were measured to the onset of the first negative peak and the MEP amplitude was measured from peak to peak.

Within either TMS session, the variables described below were studied with the two coil types in a random order. The figure-of-eight Magstim focal coil (outer winding diameter 9 cm) was positioned over the "hot-spot" for the right FDI i.e. where the largest MEPs with the shortest latencies were obtained. The coil handle pointed occipitally, forming a 45°angle to the sagittal plane. The circular Magstim coil (outer diameter 13.5 cm) was centred at the vertex (Cz site of the 10–20 system, marked with indelible ink). It had an anticlockwise current flow, which was preferential for the left (dominant) motor cortex. Coils were manually held in position by the operator. Eight out the twelve participants were naïve to experiments since they did not belong to the internal staff. Four experimenters alternated in a random order for stimulation (not the senior author).

Either experimental session lasted 60–90 min and the following variables were recorded:

2.2.1. Motor threshold (MT)

Resting MT was determined using a single monophasic electromagnetic stimulator (Magstim 200, Magstim Co., Whitland, Dyfed, UK), while the subject was at rest, verified by continuous visual and auditory EMG feedback. MT was defined as the minimum stimulator intensity that evoked at least 50% of responses with an amplitude of 50 μV or more following 16 consecutive stimuli in the relaxed FDI (Rossini et al., 1994).

2.2.2. Cortical silent period (CSP)

CSP was defined as the period of suppression of the EMG activity produced by a magnetic shock (1.2 $*$ MT) in the pre-activated (20% maximum voluntary contraction) FDI. The CSP length went from the stimulus artefact to the consistent/sustained reappearing of the EMG activity, and was determined by visual inspection of 15 single-trial tracings, whose measures were averaged later on. Two experimenters carried out measurements independently, then compared their data and reached a final agreement on the actual CSP duration. This was meant to reduce subjectivity in the determination of the CSP offset (Garvey et al., 2001). Except for the strongest stimulus intensities, the silent period length is in direct proportion to the size of the preceding MEP (Cantello et al., 1992). Thus, considering the CSP tracings, we measured the average peak-to-peak MEP amplitude throughout, to control for spurious changes in the CSP length due to changes in the preceding MEP size.

2.2.3. Short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF)

This was done using the paired-pulse technique (Kujirai et al., 1993), using two stimulators coupled with a BiStim device (Magstim Co., Whitland, Dyfed, UK). All stimuli were delivered while the subjects were at rest. Tracings with an undue background EMG were discarded. The intensity of the conditioning stimulus was 0.8 $*$ MT. The intensity of the test stimulus was 1.2 $*$ MT, and was slightly adjusted to evoke MEPs sized about 1 mV peak-to-peak. Stimulation was performed at 2, 3, 4, 5, 14 and 16 ms ISIs. For each ISI, 16 control and 16 conditioned MEPs were recorded in a random order. Between each stimulus or couple of