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# Title. Effects of quadripulse stimulation on human motor cortex excitability: a replication study

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Quadripulse stimulation (QPS) is a form of repetitive transcranial magnetic stimulation (rTMS) able to induce LTP and LTD-like plasticity in humans [3,5,7]. Short intervals between pulses (e.g. 5 ms) facilitate motor evoked potentials (MEPs) for the next 30min or more, whereas longer intervals (e.g. 50ms) reduce them [3,5,7]. Preliminary evidence suggests that the response to QPS is relatively homogenous across individuals [2,7]. Thus it could be a useful additional tool in the armoury of non-invasive brain stimulation. However, all published QPS studies to date have been conducted by the same Japanese research group. The aim of this study was to evaluate QPS in a Caucasian population.

Twenty healthy subjects (10 females; mean±SD age 27 ± 4 years; no history of neurological or psychiatric disorders) visited the laboratory on two occasions separated by ≥1 week, receiving a different QPS protocol on each. Subjects were seated comfortably and TMS was performed using four monophasic stimulators (Magstim 200, The Magstim Company Ltd., UK) combined through a connecting module attached to a 70mm figure-of-eight coil maintained over the dominant representation of the first dorsal interosseous (FDI) muscle. MEPs were recorded from FDI via surface EMG. Neuronavigation (Brainsight, Rogue Resolutions Ltd., UK) ensured a consistent coil position during all sessions. Following determination of resting (RMT) and active motor threshold (AMT), three baseline blocks of 20 MEPs (B1, B2, B3), with test stimulus (TS) intensity set to produce MEPs ~0.5mV amplitude [3,5], were recorded. QPS protocols consisted of 360 trains of four monophasic pulses (total 1440 pulses) given at 0.2 Hz. Stimuli in each train were separated by intervals of 5ms (QPS-5) in one session or 50ms (QPS-50) in the other [3,5,7]. The QPS stimulus intensity for both protocols was 90% AMT [3,5,7]. Blocks of 20 MEPs were recorded immediately after QPS and every 5 min for 25 min (P0, P5…P25) using the same TS as at baseline. The order of sessions (QPS-5 and QPS-50) was randomly allocated for each participant.

There were no differences in RMT, AMT, TS or QPS intensity between the two conditions (*t*-tests: all $p > 0.15$; Fig 1B). Two-way repeated measures ANOVA was used to evaluate the effects of QPS condition and time on absolute MEP amplitudes: there were main effects of condition ($p = 0.003$) and time ($p = 0.036$), and a condition × time interaction ($p = 0.047$) (Fig 1A). One-way ANOVA was used to evaluate changes over time for each condition. There was a main effect of time for QPS-5 ($p = 0.024$), indicating facilitation of MEPs compared to baseline (Fig 1A); however, there was no effect of time for QPS-50 ($p = 0.461$), indicating there was no inhibition of MEPs (Fig 1A). Individual responses to each protocol are shown in Fig 1C and 1D.

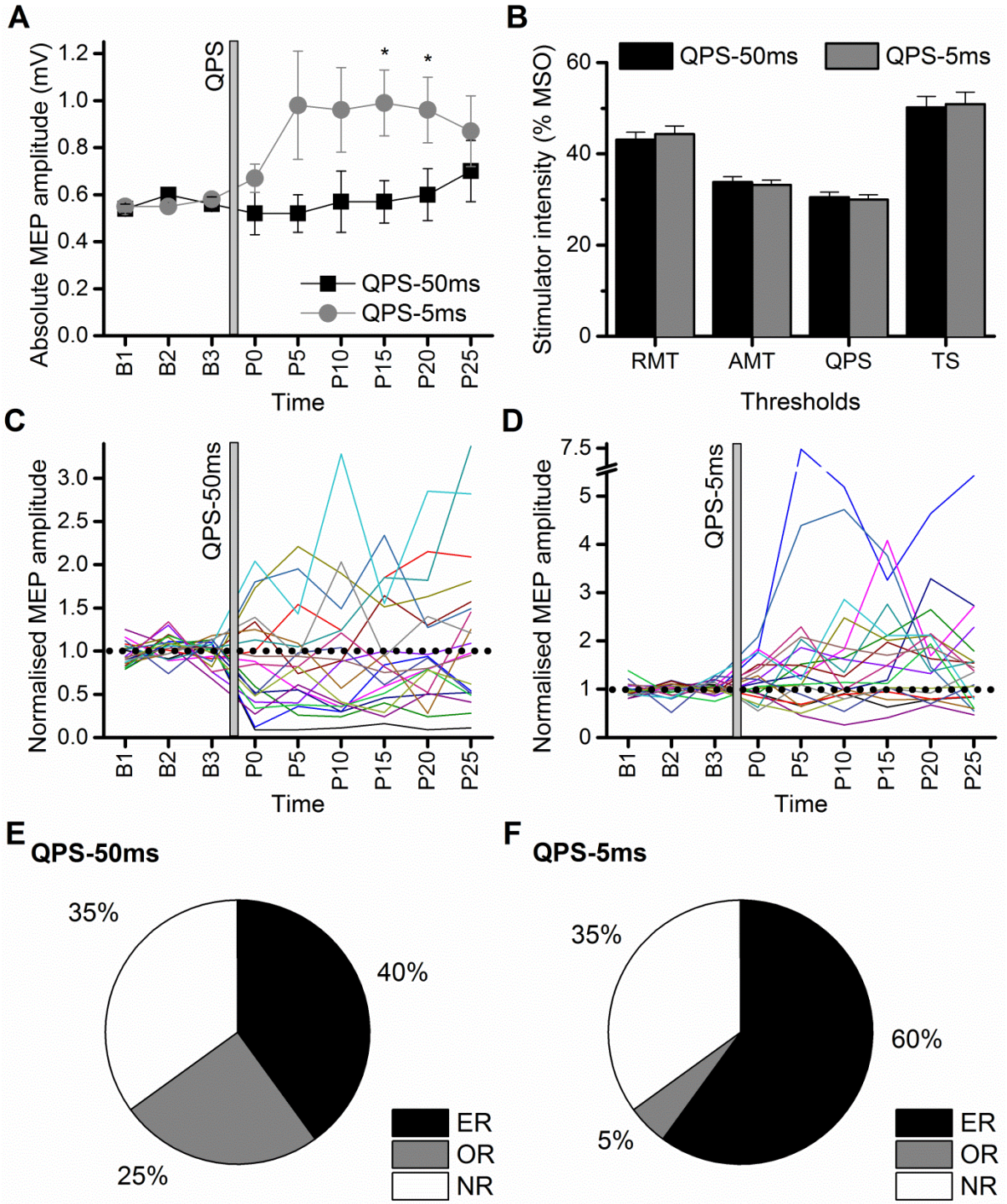


**Figure 1.** Group data showing effects of QPS-5 and QPS-50 on absolute MEP amplitude (**A**) and baseline measurements of thresholds in each session (**B**). Individual data showing effect effects of QPS-50 (**C**) and QPS-5 (**D**) on normalised MEP amplitudes. Black dotted lines indicate average normalised baseline MEP amplitude. Percentage of responders for QPS-50 (**E**) and QPS-5 (**F**) protocols based on grand average response of post-QPS time points. Group data are mean±SEM, N=20. *$P$ < 0.05 compared to mean baseline after Bonferroni correction for multiple comparisons.

The percentage of responders was calculated as follows: absolute MEP amplitudes were averaged across B1-B3 and P0-P25, respectively, for each individual in each session. The standard error of the mean (SEM) for the 20 MEPs in each of B1-B3 was calculated and averaged across B1-B3 for each individual in each session. This was then averaged across all individuals and sessions to create a grand mean SEM (±0.108). A change in post-QPS MEP amplitude compared to baseline was considered to be real when it exceeded the baseline value ± 95% confidence interval of the SEM (mean±0.212). Individuals were deemed Expected Responders (ER) when their mean post-QPS value exceeded the upper (QPS-5) or lower limit (QPS-50), Non-Responders (NR) when the value was within the limits for either condition, and Opposite Responders (OR) when values exceeded the lower (QPS-5) or upper limit (QPS-50). The percentage of ER was 40% for QPS-50 (Fig 1E) and 60% for QPS-5 (Fig 1F).

The grand mean of P0-P25 MEP amplitudes was normalised to the grand mean of B1-llB3 MEP amplitudes for each condition to evaluate the correlation between QPS-5 and QPS-50 effects with RMT, AMT, TS and QPS intensity. Responses to QPS-50 were negatively related to AMT and QPS intensity (both $r$ = -0.451, $p$ = 0.046), such that individuals with higher thresholds tended to exhibit the expected MEP suppression.

As reported by Ugawa and colleagues [2,3,5], QPS-5 induced overall facilitation of corticospinal excitability although there was no significant suppression after QPS-50. Considering the mean overall response in each individual, 60% were facilitated after QPS-5, with 40% being suppressed after QPS-50.

The facilitatory effect of QPS-5 is thought to involve changes in the synaptic efficacy of local excitatory circuits responsible for short-interval intracortical facilitation (SICF) and intracortical facilitation (ICF) [5]. The same mechanisms are thought to underlie the reported inhibitory effect of QPS-50 [2,5,7], although this was more difficult to reproduce in the present study (Fig 1C, 1E). The use of navigated TMS argues against the possibility that the results were influenced by variable coil positioning over the motor cortex. Approximately 20% of the inter-individual variability in response to QPS-50 could be explained by individual differences in AMT and QPS intensity: those with higher thresholds tended to show the expected inhibition. It's possible that the mechanisms for QPS-50 are related to corticospinal excitability or, since thresholds are also influenced by extrinsic factors such as scalp-to-cortex distance [9], are more dependent on circuits with high thresholds that are unrelated to corticospinal excitability (e.g. ICF circuits) [1]. Finally we cannot discount the possibility that racial differences between Japanese and Caucasian participants influenced the results because significant differences between Asian and Caucasian individuals have been documented for some indices of cortical excitability such as RMT (but not AMT) [10]. The

present study would therefore have benefited from a direct comparison of Caucasian and Japanese individuals.

The percentage of ER in our study (60% QPS-5; 40% QPS-50) were slightly low compared to data presented recently, where rates of ER, NR and OR were 85%, 9% and 6% for QPS5, and 67%, 30%, and 3% for QPS-50 (n=33) [2]. The discrepancy could be influenced by the small sample size in our study. The slightly lower age of participants in our study (mean ± SD: 27±4 versus 38±7 years) seems unlikely to be a factor since greater motor cortex plasticity is expected in young compared to old individuals [8]. Alternatively, differences between studies in the distribution of sexes could play a role because sex is a potential determinant of motor cortex plasticity [8], but this is speculative since the sex of participants was not reported by Enomoto et al. [2]. Notwithstanding the difference in percentage of ER between studies, the ER rates in our study appear comparable with those of other facilitatory/inhibitory plasticity protocols such as theta burst stimulation and paired-associative stimulation (40-50%) [4,6]. We therefore conclude that both forms of QPS may be useful additions to the repertoire of protocols available for non-invasively interrogating human cortical plasticity.

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**Conflict of interest:** None

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