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Title page

Comparison of Rossini–Rothwell and adaptive threshold-hunting methods on the stability of TMS induced motor evoked potentials amplitudes

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Abstract

Several methods can be used to determine the resting motor threshold (RMT) and by that recording transcranial magnetic stimulation (TMS) induced motor evoked potentials (MEPs). However, no research has compared the test retest reliability of these methods. Thus, the aim of this study was to determine intra- and inter-session reliability of Rossini–Rothwell (R-R) and parameter estimation by sequential testing (PEST) methods on TMS-induced MEPs and comparison of these two methods on RMT. Twelve healthy individuals participated in this study three times (T1, T2 and T3) over two days. TMS was applied using both R-R and PEST to estimate RMT and average of 25 MEPs were acquired at each of the three time points. The ICCs indicated high intra-session reliability in the MEP amplitudes for both methods (0.79 and 0.88, R-R and PEST respectively). The RMT and MEP amplitudes had higher inter-session reliability in both methods (0.99 and 0.998, R-R and PEST respectively; 0.84 and 0.76, R-R and PEST respectively). There was no significant difference between methods for RMT at both T1 (maximum stimulator output of R-R vs PEST, 33.7±7.7% vs. 33.8±7.6%, p = 0.75) and T3 (maximum stimulator output of R-R vs PEST, 33.5±7.3% vs 33.7±7.3%, p = 0.19). There was a significant positive correlation between the methods' estimates of RMT, with PEST requiring significantly fewer stimuli. This study shows that the R-R and PEST

methods have high intra-and inter-session reliability and the same precision, with PEST having the advantage over R-R in speed of estimation of RMT.

Key word: Healthy human; Motor Evoked Potentials; Motor cortex; Resting Motor Threshold; Transcranial Magnetic stimulation

Significance statement: The results of this study add to increasing the usage of PEST for determining resting motor threshold using TMS.

Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive neurophysiological technique that has been widely used to measure corticomotor activities in humans (Krause and Kadosh, 2013; Liu and Au-Yeung, 2014). TMS uses electrical current via a coil over the scalp to induce a magnetic field, which leads to depolarization of cortical neurons (Walsh and Pascual-Leone, 2003; Liu and Au-Yeung, 2014). When a TMS pulse is applied over the primary motor cortex (M1) the response can be recorded from the target muscle on the opposite site by surface electromyography (EMG). This response is called the motor evoked potential (MEP). These MEPs can be used to assess corticospinal excitability (CSE) in humans. CSE changes are assessed by measuring MEP amplitudes or the integration of MEP areas. In this regard, larger or smaller MEP amplitudes or areas indicate higher or lower CSE changes respectively.

Reliability of measurements for each outcome measure is a key consideration in any research (de Vet et al., 2006; Schmidt et al., 2009). A number of studies have reported good to excellent reliability for assessment of CSE (Kamen, 2004; Christie et al., 2007; Cacchio et al., 2009). Several factors can affect the reliability of CSE measurements using TMS (Chipchase et al., 2012). Evidence indicates that between-subject factors such as age (Pitcher et al., 2003; Olivveiro et al., 2006; Smith et al., 2011), gender and genotype, and within-subject factors such as caffeine use, prior activity of the target muscle and time of the day can affect MEP responses induced by TMS (Chipchase et al., 2012). In addition, some TMS features, such as coil type (Flemming et al., 2012), placement (Ngomo et al., 2012), orientation (Thomson et al., 2013), intensity of TMS pulses (Fisher et al., 2002) and inter-pulse interval (Vaseghi et al., 2012) have implications for the reliability of MEP measurements.

Determination of resting motor threshold (RMT) is an important step in determination of MEPs and therefore CSE assessment. RMT can be determined via several methods, including the relative frequency or Rossini–Rothwell (R-R) method (Rossini et al., 1994; Rothwell et al., 1999), the Mills–Nithi method (Mills and Nithi, 1997), supervised parametric estimation (Tranulis et al., 2006) and adaptive threshold hunting methods based on parameter estimation by sequential testing (PEST) (Awiszus et al., 1999; Awiszus, 2003). Of these, the R-R method is the most commonly used technique and has become the standard method for determination of RMT. However, an International Federation of Clinical Neurophysiology (IFCN) report has endorsed PEST as a valid method for determination of RMT (Groppa et al., 2012).

It has been suggested that PEST can estimate RMT more quickly and accurately than the R-R method (Silbert et al., 2013; Ah Sen et al., 2017). Silbert et al. (2013) reported that PEST is faster because compared to the need for 56 stimuli via the R-R method; it determines RMT after using 12 stimuli. However, this number of stimuli used in PEST lacks mathematical validity as a method to determine the actual RMT (Awiszus, 2012). Moreover, Ah Sen et al. (2017) reported that compared to the R-R method which requires 35 stimuli, the PEST method only requires for determination of RMT. However, these studies did not report the test–retest reliability of MEP amplitudes measured by the RMT determined by R-R or PEST methods. Indeed, to the best of our knowledge, there is no published study comparing these methods in regards to test–retest reliability. Given the interest in this area, as well as the IFCN recommendation, we aimed to assess the test–retest reliability of R-R and PEST on TMS-induced MEPs, and to assess whether there was a difference in RMT and therefore MEPs amplitudes using these two techniques. This study also aimed to assess whether PEST is faster than R-R for RMT determination. Thus, we hypothesized that PEST determines RMT which can be used for reliable assessment of TMS induced MEPs. We also hypothesized that there would be no difference in RMT and induced MEPs using these techniques within and between days. In addition, we hypothesized that the PEST method would be faster than the R-R method for determination of RMT.

Methods

Participants

Twelve healthy volunteers (7 women and 5 men) with an average age and height (± SD) of 23.9 ± 5.7 years and 1.68 ± 0.12 m were recruited. Participants were excluded if they reported any neurological, psychological, or endocrinological conditions. Prior to enrolment, all participants completed the Adult Safety Screening Questionnaire (Keel et al., 2001) to determine their suitability for TMS assessment and written informed consent was obtained according to the Declaration of Helsinki. Measurements were performed by the same examiner and conducted at the approximately same time of the day (8.00–12.00) to avoid diurnal variation. The estimated sample size was 10 to 14, based on the aim of detecting a minimum acceptable reliability of 0.60 with an alpha level of 0.05 (1-tailed) and power of 80%, using the method recommended by Portney and Watkins (2000). All study procedures were performed in accordance with the Human Research Ethics Committee at Monash University, Australia.

Experimental design

This study adopted a repeated measures design, with all participants participating in two sessions separated by at least 48 hours. After determination of RMT, the intra- and inter-session reliability of R-R and PEST methods for induction of TMS induced MEP amplitudes were assessed. For intra-session reliability, MEPs were recorded in response to 25 stimuli with an intensity of 120% RMT of the first dorsal interosseous (FDI)'s representation in M1 and average of 25 MEPs were assessed before and after 20 minutes of no intervention. The inter-session reliability was assessed by comparing the 25 recorded MEPs in day 1 and day 2, at least 48 hours apart (Figure 1).

"Please insert Figure 1 here"

TMS

In each assessment session, participants were seated comfortably with their right forearm pronated and the wrist joint in a neutral position on an armrest. A standard skin preparation of cleaning and abrading was performed for each electrode site to achieve low skin impedance of $\leqslant$ 10kΩ (Gilmore and Meyers, 1983; Groppa et al., 2012). Pre-gelled self-adhesive bipolar Ag/AgCl disposable surface EMG electrodes were placed over the belly of the FDI on the dominant hand. The ground electrode was placed ipsilaterally over the ulnar styloid process (Oh, 2003). EMG signals were recorded and amplified (x1000), with signals filtered

(bandpass: 10-500 Hz), and then processed offline using commercially available software (LabChart™ software, AD instruments, Australia) via a laboratory analogue-digital interface (The PowerLab 8/30, AD Instruments, Australia).

Participants remained seated during the TMS measurements. According to the international 10-20 system, the vertex (Cz) was measured and marked as a reference point for locating the hand representation area in the M1. Single-pulse TMS was applied over M1 using a MagPro R30 (MagOption) stimulator (MagVenture, Denmark) with a figure-of-eight coil (max. initial dB/dt 28 KT/s near the coil surface). The coil was placed tangentially on the left hemisphere about 4-7 cm lateral and 0-3 cm anterior to the vertex with the handle pointing backward at 45° from the midline sagittal plane of the skull. In this position, the induced current flowed in posterior-anterior direction (Rossini and Rossi, 1998; Mills, 1999; Schmidt et al., 2009). The TMS intensity ranging between 50% - 55% maximum stimulator output (MSO) was used as starting intensity. The intensity of 50% MSO was used for young-adults (<35 years) and 55% was used for middle-age adults (35-40 years). At starting intensity, several positions were searched for larger MEPs with three stimuli. Once the site producing largest MEPs (origin) was identified, the site was further searched in four cardinal directions (anterior, posterior, medial and lateral with three MEPs at each site, 1 cm apart). If all the sites produce larger MEPs, the intensity was reduced in 5% and repeated the procedure. When there were no any larger MEPs at any of these directions, the origin was considered as the "hotspot" for resting FDI.

The TMS intensity related to RMT was determined using R-R and PEST. Inter-stimulus interval of 10s was used during threshold estimation and recording of MEP amplitude for both R-R and PEST to avoid the hysteresis effect of short inter-trial intervals on MEP amplitude (Moller et al., 2009; Julkunen et al., 2012). Two investigators were involved in testing. The first investigator carried out both R-R and PEST, but was blinded to stimulus intensity as required during PEST. The second investigator set stimulus intensity as required during PEST and was blinded to the stimulus intensity and results of the R-R method.

Measurement of RMT by PEST method

A freeware program of TMS Motor Threshold Assessment Tool, MTAT 2.0 (http://www.clinicalresearcher.org/software.htm) (Awiszus and Borckardt, 2011), which employs a maximum-likelihood PEST strategy without prior information, was used to assess

RMT using the programs pre-determined TMS intensity. For RMT, an MEP amplitude of >50 μV was considered a successful trial. When this intensity was not observed, a new intensity displayed by the program was used until the success point was reached. The target RMT was found when it was mathematically valid and 95% confidence intervals were within accuracy limits imposed by safety guidelines (Awiszus, 2011, 2012). The number of stimuli delivered to determine RMT was recorded.

Measurement of RMT by R-R method

The Groppa modification of the "relative frequency" criterion (Groppa et al., 2012) was used to determine the RMT. Since the R-R method does not nominate a starting intensity, we chose 37% of MSO, which corresponds to the starting intensity of the PEST program. The RMT for each participant was determined by increasing by 5% and subsequently by 1–2% MSO intervals until the lowest intensity that produced MEPs of >50 μV in at least 5 out of 10 consecutive stimuli (Groppa et al., 2012) was found. The number of stimuli delivered to determine RMT was also recorded.

Data analysis

Intra- (T1 and T2) and inter-session (T1 and T3) reliability (the relative measure of reliability) for MEPs and RMT of R-R and PEST were determined using intra-class correlation coefficient (ICCs) with 95% confidence intervals based on absolute agreement, in a 2-way mixed effect model. An ICC value above 0.75 was considered to represent good reliability (Pourtney and Watkins, 2000).

Bland-Altman plots were constructed to demonstrate agreement for intra and inter-sessions of R-R and PEST. Limits of agreement (LOA) were used to evaluate variability in mean differences associated with overall mean scores included in the Bland-Altman plots. Bland-Altman plots were constructed by plotting mean differences against the average of two means of R-R and/or PEST. LOA for intra-session (between T1 and T2) and inter-session (between T1 and T3) of R-R and PEST were estimated by calculating the mean difference (*d*) and standard deviation of mean difference (SD_d) (Bland, J and Altman, D, 1986). Values of *d* approaching 0, and smaller values of SD_d, indicated better agreement within (intra) and between (inter) sessions.

A simple linear regression was calculated to predict RMT using PEST based on R-R at T1 and T3. Paired t-tests were used to compare number of stimuli, RMT between R-R and PEST methods. Correlations for RMT between R-R and PEST were assessed using ICCs, and the agreement between R-R and PEST for T1 and T3 were assessed using Bland-Altman plots.

Statistical analyses were performed using IBM SPSS statistics 22 (IBM SPSS, Armonk, NY) and $p<0.05$ was considered significant.

Results

Intra-session reliability

The intra-session reliability was only tested for TMS induced MEPs. The results of MEPs showed individual ICC values of 0.79 (95% CI: 0.26–0.94) and 0.88 (95% CI: 0.58–0.96) for R-R and PEST respectively. Bland-Altman plots for MEPs using R-R and PEST methods showed good agreement between T1 and T2 (Figure 2A,B).

"Please insert Figure 2 here"

Inter-session reliability

The inter-session reliability was performed on both TMS induced MEPs and RMT. The ICCs of MEPs for inter-session reliability (T1 and T3) were high, with values of 0.84 (95% CI: 0.44–0.95) and 0.76 (95% CI: 0.19–0.93) for R-R and PEST, respectively. ICCs for RMT using R-R and PEST were 0.99 (95% CI: 0.98–0.99) and 0.998 (95% CI: 0.99–0.99) respectively. Bland-Altman plots for MEPs and RMT using R-R and PEST also showed good agreement between T1 and T3 (Figure 2C, D, E, F).

Comparison between R-R and PEST methods

Number of stimuli

The number of stimuli required to determine RMT using R-R was significantly greater than that for PEST at T1 (41±16 vs 20.0±0.0, $p<0.001$) and T3 (42±15 vs 20.0±0.0, $p<0.001$). There were no significant differences between the group mean data for RMT for T1 and T3. There was good correlation and agreement between R-R and PEST for estimation of RMT

(Table 1 and Figure 3A, B). Regression analyses showed very high levels of shared variance between R-R and PEST estimates of RMT at T1 ($F(1,10) = 728$, $p<0.001$, $R^2 = 0.986$) and T3 ($F(1,10) = 1401$, $p<0.001$, $R^2 = 0.993$) (Figure 4 A and B).

"Please insert Table 1, Figure 3 and Figure 4 here"

Discussion

This study evaluated test–retest reliability of R-R and PEST for TMS-induced MEPs and the fastest method for determination of RMT in healthy individuals. The findings suggest that measuring MEP amplitudes using PEST produces very similar results to the R-R method, with good intra- and inter-session reliability. It also shows good inter-session reliability of RMT using both R-R and PEST. A significant main effect of participant is found for MEP amplitude while post hoc analysis revealed few of them with significant time and method effect. In addition, the results indicate that PEST can determine the RMT faster, with fewer stimuli, than the R-R method, and that RMTs measured with PEST correlate strongly with RMTs measured by R-R.

Intra- and inter-session reliability of MEPs

The findings of high intra-session reliability of TMS-elicited MEPs using both R-R and PEST methods are consistent with those of previous studies, which suggest that a stable estimates of MEPs separated by 20 min of no intervention can be achieved within a session (Christies et al., 2007; Bastani and Jaberzadeh, 2012; Vaseghi et al., 2015; Hashemirad et al., 2017). The results also suggest that MEP measurements obtained across two sessions 48 hours apart produces good reliabilities using either R-R or PEST methods. Previous studies also demonstrated good reliabilities of TMS-elicited MEPs using the same interval (Bastani and Jaberzadeh, 2012; Vaseghi et al., 2015). While previous studies concentrated mainly on correlation, the present study for the first time assessed agreement between sessions using the Bland-Altman method. The use of Bland-Altman plots further demonstrates the strength of

intra- and inter-session agreement of MEPs, and reveals additional information such as graphical representation of results that is not acquired from ICC measurements.

Reliability of RMT measurements

Good agreement was observed between PEST and R-R methods for estimation of RMT in between days. The results also showed a high inter-session reliability of RMT using both R-R and PEST methods. Interestingly, there was no significant difference between PEST and R-R methods for RMT. Thus, these findings confirm that researchers should have confidence in the PEST method for determination of RMT. Additionally, the findings confirm that PEST and R-R are targeting the same RMT values, corroborating Silbert et al.'s (2013) and Ah Sen et al.'s (2017) results.

Number of stimuli for determination of RMT (R-R vs. PEST)

This study showed that PEST was faster and used fewer stimuli than the R-R method for RMT determination. R-R method adjustments include choice of starting intensity, number of stimuli for determination of RMT, and intensity increments or decrements. In contrast, decisions about the starting intensity and subsequent values for PEST are based on mathematical and statistical concepts (Awiszus, 2011; Awiszus, 2012). This finding is similar to the results of Ah Sen et al. (2017). The relative speed and efficiency of PEST and R-R we measured are also in line with Silbert et al.'s (2013) study, although the number of stimuli required to achieve the RMT was higher in the present study. Silbert et al. acquired 12 stimuli to estimate RMT, whereas Awiszus (2012) recommended 20 stimuli to yield accurate and mathematically valid RMTs. Another study also concluded that PEST is faster than the Mills-Nithi method (Mishory et al., 2004), and recently Qi et al. (2011) demonstrated that Awisus' (2003) PEST method and a PEST variant based on Bayesian statistics are faster than the R-R method. Even though they illustrated that their new Bayesian method is effective in reducing the number of pulses to estimate the RMT, the method requires a priori information about the underlying threshold. In contrast, the method used in the present study did not require a priori information, and can be used for people naive to TMS.

Limitations

While the present study showed good reliability findings, these should be interpreted in the context of the following limitations. This study was limited to healthy young participants, so findings cannot be extrapolated to older people and patients with pathological conditions. Another critical point is that we used only one stimulus intensity (120% RMT), and it is not possible to expand our findings to higher or lower intensities. This study enrolled both male and female participants; the findings should be interpreted cautiously since the effect of hormonal levels in women at the time of testing may have influenced MEPs. This study was also limited with the small sample size (12 participants) compared to the sample size of Ah Sen et al.'s (2017) study (15 participants). This may limits the extrapolation of the findings. However, it should be noted that the sample size was calculated based on the pilot study prior the main experiment and indicated number of 12 participants are adequate for this study.

Suggestions for future studies

Future research is needed to investigate the reliability of RMT and MEPs with respect to higher vs. lower intensities, older vs. younger participants, males vs. females, during different times of the day, and active vs. rest, as these variables were held stable during the present study to minimize their effect on reliability. It is also important to investigate the test-retest reliability of AMT using these two methods.

Conclusions

In conclusion, this study showed that both the R-R and PEST methods are valid for determination of RMT, and that there is no difference between TMS-induced MEPs derived with the methods when measured on two occasions on the same day or between days. It is suggested that 20 stimuli are optimal for estimating RMT using PEST.

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Conflict of interest

None of the authors have potential conflicts of interest to be disclosed.

Author contribution

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Conceptualization,* TDD, SJ, *Methodology*, TDD, SJ, MZ, *Investigation*, TDD, *Formal Analysis*, MF, GE, *Writing- Original draft*, TDD, *Writing – Review & Editing*, SJ, MZ, MF, GE, *Supervision*, SJ.

Figure legends

Figure 1. Experimental set-up, TMS was delivered on first dorsal interosseous (FDI) hotspot and 30 MEPs were recorded during two-session experiments with at least 48 hours apart.; R-R, Rossini-Rothwell; PEST, adaptive threshold-hunting methods based on parameter estimation by sequential testing; MT, motor threshold; MEPs, motor evoked potentials; FDI, first dorsal interosseous T1, time 1; T2, time 2; T3, time 3

Figure 2. Bland-Altman plots for intra- and intersession MEPs, (A) intra-session R-R (T1vs T2), (B) intra-session PEST (T1 vs T2), (C) intersession R-R (T1 vs T3), (D) inter-session PEST (T1 vs T3)

Figure 3. Bland-Altman plots for R-R vs PEST on RMT (A) at T1, (B) at T3,

Figure 4. Scatter plot and regression line of MT estimated with the R-R vs. PEST (A). At T1, (B) at T3

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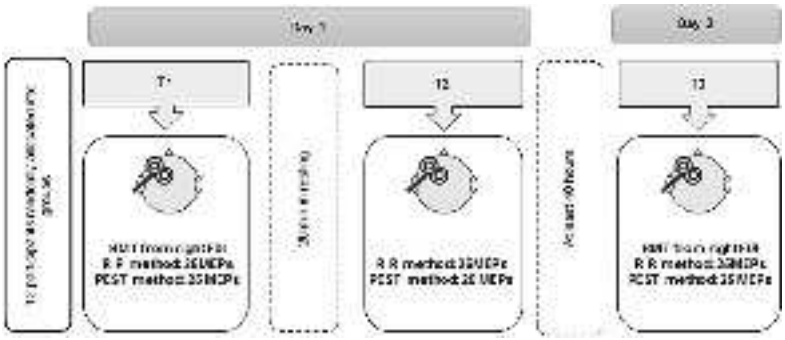
Table 1. ICC values and paired t-test results on R-R vs PEST

	Time	R-R Mean (SD)	PEST Mean (SD)	P value	ICC (95% CI)
RMT (% MSO)	T1	33.7 (7.7%)	33.8 (7.6%)	0.75	0.99 (0.98-0.99)



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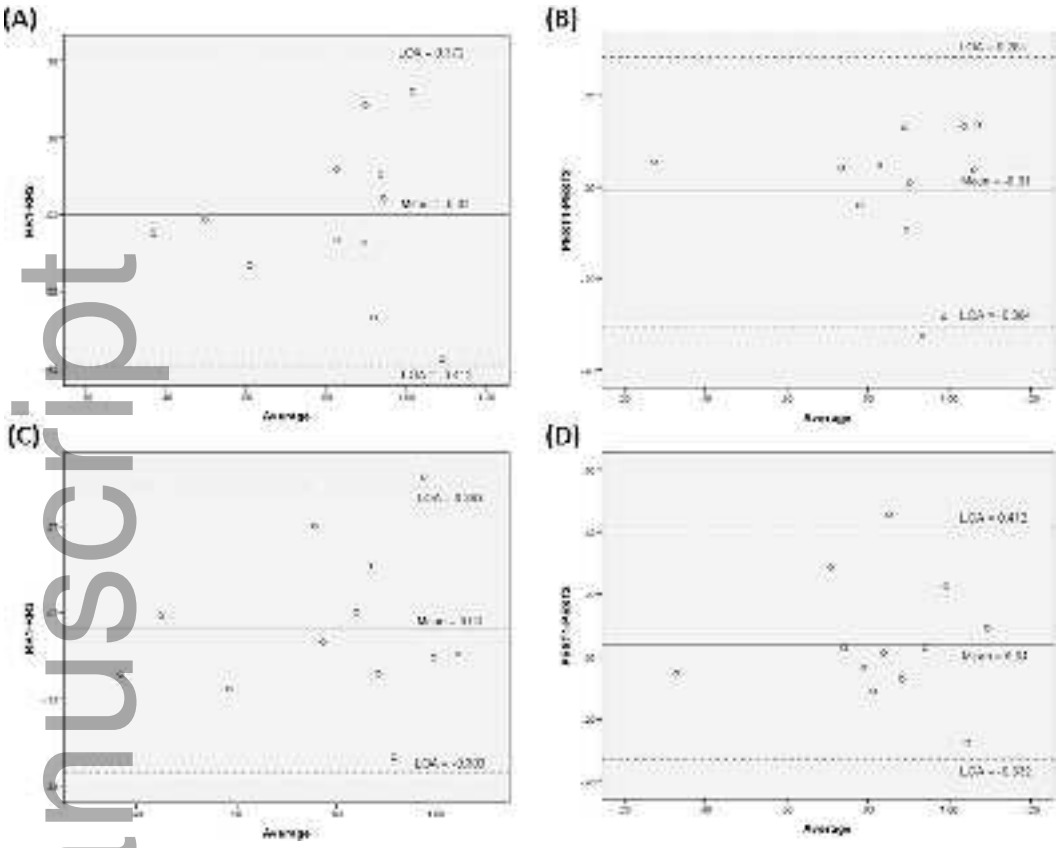

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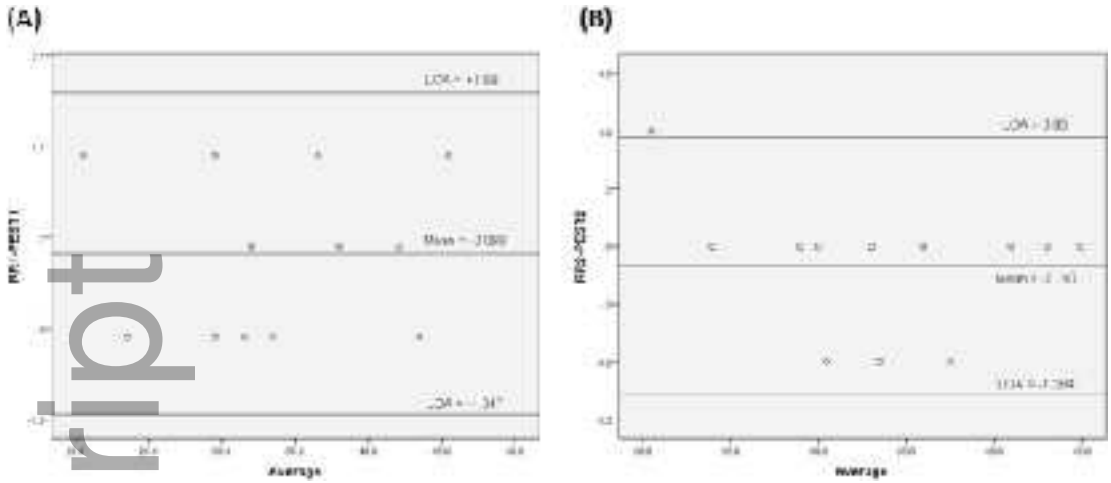

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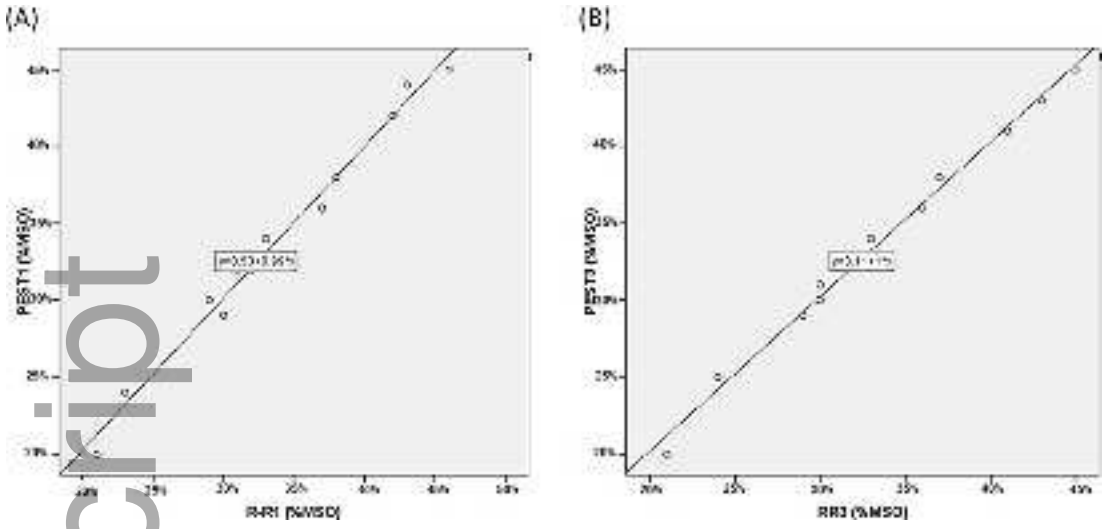

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