CoBeN

Novel Network-Based Approaches for Studying Cognitive Dysfunction in Behavioural Neurology

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D3.4 Network-based approaches to modulation of brain plasticity and micrographia in PD using non-invasive brain stimulation

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1 Introduction

Handwriting involves mapping visual/orthographic representations produced during the linguistic spelling process onto motor systems responsible for the programming and execution of handwriting movements (Rapcsak & Beeson 2015). Damage to subcortical motor areas in Parkinson's disease (PD) interferes with generating the sufficient kinematic parameters for writing movements resulting in defective control of writing speed, force and amplitude with relative preservation of overall letter shape (Kim et al. 2005, Letanneux et al. 2014).

Alterations in the spatio-temporal and kinematic control of handwriting movements are difficult to quantify by visual inspection alone. Therefore, a digitizing tablet has been used by researchers to better examine kinematic abnormalities affecting handwriting. It was shown that both in-air movement and pressure can help to assess subtle characteristics of handwriting and to discriminate between PD patients and healthy controls (HC) (Drotar et al. 2014, 2015). In fact, in-air movements distinguished PD from HC with higher accuracy than on-surface handwriting parameters. It may relate to impaired cognitive functions, particularly executive functions, attention or visuospatial functions. Drawing of intersecting pentagons and its impairment has been shown to predict cognitive decline in PD (Williams-Gray et al. 2013). However, assessment of drawing pentagons using digitized tablet and both on-surface and in-air movements has not been used so far.

Pathophysiological mechanisms of PD dysgraphia remain unclear. Study of Wu et al. (2016) found that consistent micrographia (an overall reduction of letter size) is associated with reduced activity in the basal ganglia motor circuit; while progressive micrographia (decrement of letter size during writing process) is related to disconnections between he rostral cingulate motor area, the anterior supplementary motor area and the cerebellum. However, according to study by Nackaerts et al. (2018), PD dysgraphia could be also associated with impairment of visuomotor integration. This research team found that PD patients had a reduced effective connectivity between right middle temporal visual area and superior parietal lobe compared to HC during handwriting. Similarly, only few studies focused on neural correlates of pentagon drawing in PD. Previous research by Filoteo et al. (2014) has found that the score of pentagon copying test significantly correlates with decreased cortical volumes in the left rostral middle frontal cortex, the right supplementary motor area, pars triangularis and the left cuneus in PD patients. Another study by Garcia-Diaz et al. (2014) focused on the whole brain cortical thickness and the authors have found that PD patients with abnormal pentagon drawings had significant thickness reductions in the left superior temporal gyrus and precuneus, as well as in the right precentral and postcentral gyri, superior parietal region and posterior cingulate cortex. A recent longitudinal study (Garcia-Diaz et al. 2015) also revealed that the change in visuospatial functions of PD-MCI correlated with the change of cortical thinning of temporo-parietal regions.

There has been only a single attempt (Randhawa et al. 2013) to explore whether repetitive transcranial stimulation (rTMS) can have a beneficial effect on writing performance in PD and

this study only targeted the SMA. We applied for the first time rTMS over other specific cortical regions implicated in handwriting and pentagon drawing.

2 Methods

2.1 DATA ACQUISITION

The patients were asked to perform a drawing/handwriting protocol on an A4 paper, that was laid down and fixed to a digitising tablet Wacom Intuos Pro L (PHT-80). For this purpose, they used a Wacom Inking pen that enabled them to have immediate visual feedback and feeling like they write with a conventional inking pen. Online drawings were sampled with frequency f_s = 150 Hz. Drawing/handwriting protocol was done before and after each stimulation session.

We used the Czech version of the protocol that was developed in the frame of deliverable D3.1 "Pilot data for kinematic assessment and analysis released", see Fig. 1. The protocol contains following tasks: TSK1 – cursive graphemes "l"; TSK2 – connecting two dots horizontally; TSK3 – signature with eyes opened; TSK4 – signature with closed eyes; TSK5 – a sentence containing 4 Czech words (in English: "A tram will no longer go today."); TSK6 – a sentence containing 7 Czech words (in English: "Mother and father have gone twice for a vacation."); TSK7 – Archimedean spiral; TSK8 – overlapped pentagons. In the case of TSK1, and TSK5–TSK8, the patients were asked to replicate the template

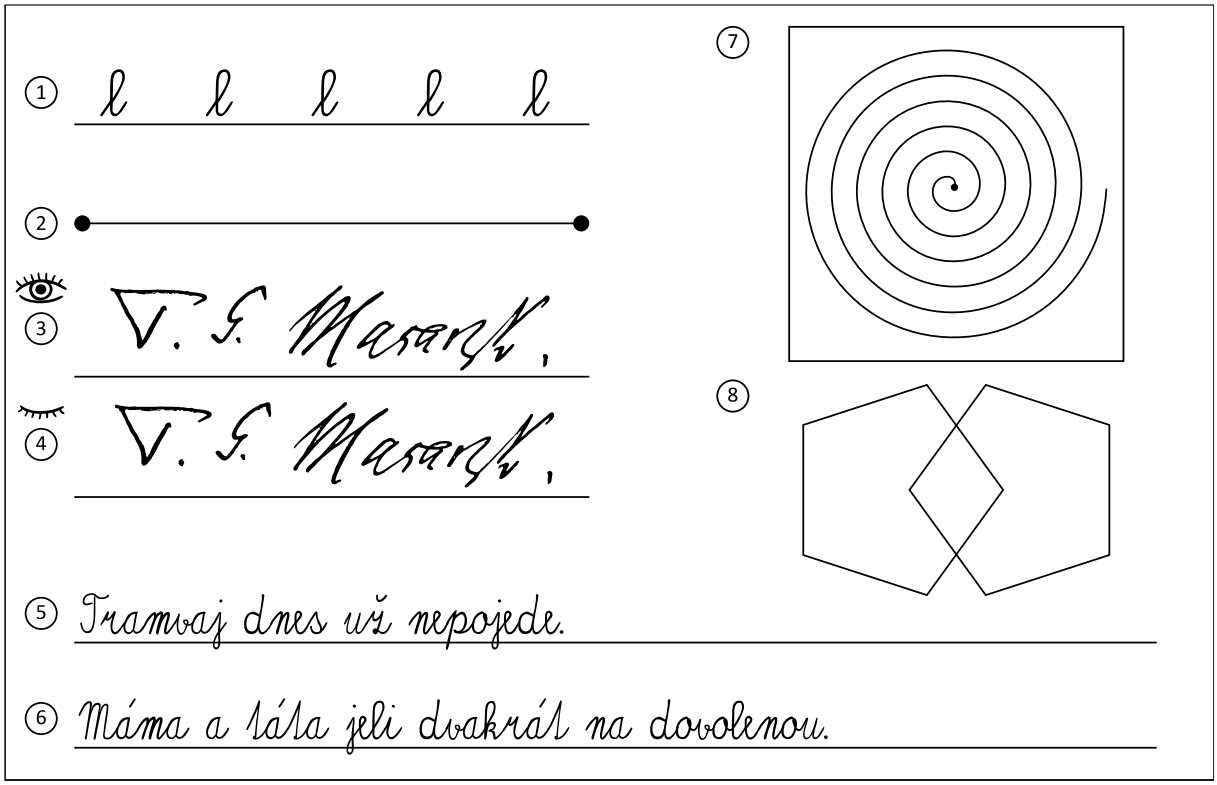

Figure 1: CoBeN handwriting protocol (the Czech version).

2.2 HANDWRITING/DRAWING ANALYSIS

The digitizer captures this information: x and y position ($x[n]$ and $y[n]$); timestamp ($t[n]$); a binary variable ($b[n]$), being 0 for in-air movement (i.e. movement of pen tip up to 1.5 cm above the tablet's surface) and 1 for on-surface movement (i.e. movement of pen tip on the paper), respectively; pressure exert on the tablet's surface during writing ($p[n]$); pen tilt ($a[n]$); and azimuth ($az[n]$).

During parameterisation of the drawings, we focused on the most commonly used online handwriting features, that could be split into five categories:

1. spatial – width (WIDTH), height (HEIGHT), and length (LEN) of the whole product, as well as its particular strokes, i.e. stroke width (SWIDTH), height (SHEIGHT), and length (SLEN)
2. temporal – duration of drawing (DUR)
3. kinematic – velocity (VEL), acceleration (ACC), and jerk (JERK)
4. dynamic – pressure (PRESS), tilt (TILT), and azimuth (AZIM)
5. other – Shannon entropy (SHE), number of interruptions (pen elevations; NINT) and relative number of interruptions (RNINT)

Shannon entropy, spatial, temporal and kinematic features were extracted from both on-surface and in-air movements. Moreover, kinematic features were also analysed in horizontal and vertical projection. Features that are represented by time series, e.g. the velocity profile, were consequently transformed to a scalar value using mean, median, slope, 95th percentile and relative standard deviation (rstd).

2.3 REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION

All subjects underwent six rTMS (DuoMAG™ XT-100, Deymed Diagnostic, Czech Republic) sessions for two weeks at Central European Institute (CEITEC), Masaryk University. Each stimulation session lasted about 40 minutes. Stimulation was applied consecutively over two active stimulation sites (the right superior parietal lobule (SPL) and the left middle frontal gyrus (MFG)) and over a control stimulation site (vertex; V). Frameless was used to navigate a figure-eight coil over our targets of interest. Both high-frequency stimulation (10 Hz, 90% of the resting motor threshold (RMT), 2250 pulses per session) and low-frequency stimulation (1 Hz, 100% RMT, 1800 pulses per) were utilized over all targets. We used a cross-over study design and stimulation conditions were randomised across subjects and sessions. Each stimulation session was separated by at least one day without any stimulation.

2.4 MRI SEQUENCES AND PROCESSING

Subjects were scanned with a 3T Siemens Prisma MR scanner (Siemens, Erlangen, Germany). High-resolution anatomical T1-weighted images were acquired at baseline assessment for the Brainsight neuronavigation system (TR = 2300 ms, TE = 2.33 ms, FA = 8°, FOV = 224 mm, slice thickness 1 mm, 240 sagittal slices, matrix size 224×224). Multi-echo EPI resting-state sequences (60 transversal slices, slice thickness = 2.5 mm, TR = 800 ms, TE = {15, 33, 52} ms, FA = 26°, FOV = 200 mm, matrix size 68×80, 735 volumes), were acquired.

Preprocessing and data analyses were performed in SPM12 running under Matlab 2014a. The preprocessing of the functional data consisted of realignment and unwarping, normalization into standard anatomical space (MNI), and spatial smoothing with 5mm FWHM. The level of motion was assessed visually during scanning sessions by trained technicians. In addition, the resting-state extent of motion data was controlled in terms of framewise displacement. The subjects with at least 15% of scans with FD>0.75 mm were excluded. Moreover, the six-motion parameter time series (obtained from the realign procedure in SPM), the framewise displacement time series, and the signals from white matter and cerebrospinal fluid were regressed out of the data in subsequent analysis.

3 Results

In our exploratory pilot study focused on the short-term effect of transcranial magnetic stimulation, the main goal was to identify a site and protocol that would have an optimal effect on micrography (or dysgraphia in general) in PN. We enrolled 20 PD patients for a micrography

study, ten of them completed all stimulation sessions. The average age was 66.35 years (SD 8.79).

The results of the analysis of behavioral data showed that the greatest improvement in the written parameters was achieved with 1 Hz stimulation above the right SPL. After this stimulation, there was a significant reduction in fluctuations of the writing speed of the Archimedean spiral ($p = 0.011$) (See Figure 2). This improvement was also significant compared to the effect of stimulation over the control stimulation site (vertex), ($p = 0.038$). Furthermore, after 1 Hz stimulation above the right SPL, there was a significant reduction in the time the pen tip was above the paper (time in air) when drawing overlapping pentagons ($p = 0.019$) (See Figure 3). Based on this result, we assume that there was probably an improvement in visual and spatial abilities – patients needed less time to think about strokes. This improvement was again significant compared to the effect of stimulation over the control site ($p = 0.028$). Furthermore, even after 1 Hz SPL stimulation, there was a significant reduction in the number of pen elevations when writing sentences ($p = 0.031$), so patients were able to write longer sections of sentences without having to interrupt the stroke. However, this improvement was not significant in comparison to the stimulation control site.

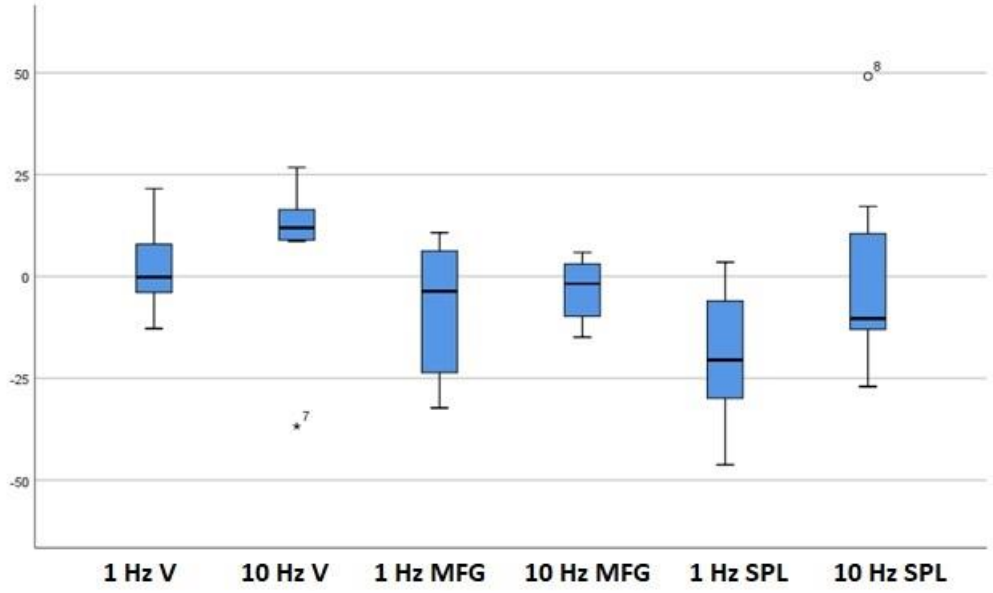

Figure 2: Percentual changes in Relative standard deviation of velocity (on surface) after stimulation (*Archimedean spiral*)

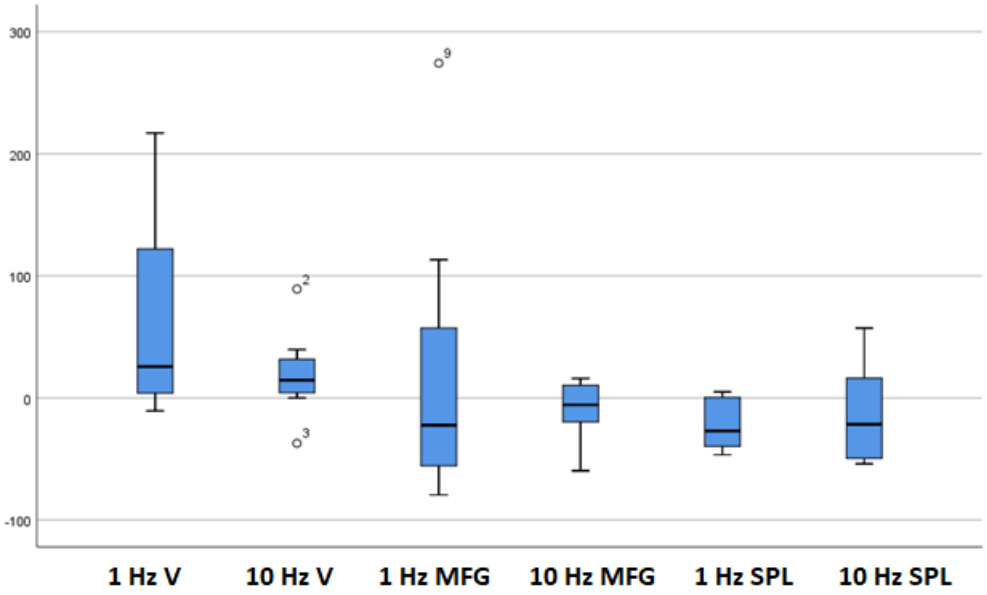

Figure 3: Percentual changes in Duration of writing (in air) after stimulation (*Overlapped pentagons*)

With regard to local and global neural network properties, we found several significant correlations between graph metrics and changes of handwriting/drawing parameters after 1 Hz rTMS over the SPL. Changes in duration of drawing of pentagons correlated with global path length ($R = 0.690$, $p = 0.058$) and with local path length metric in right SPL node ($R = 0.881$, $p = 0.004$). Changes in median of Shannon entropy (vertical in-air) in drawing of pentagons significantly correlated with path length metric in left SPL node ($R = 0.714$, $p = 0.047$) and insignificantly with path length metric in in right SPL ($R = 0.643$, $p = 0.086$).

4 Conclusions

Results of the exploratory study suggest a positive effect of 1 Hz rTMS over right SPL, more specifically this stimulation improved kinematic characteristics in terms of fluency and velocity of writing and drawing. These behavioral changes also correlated with global neural network properties and with local neural network properties of the stimulated brain area.

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