Ref. Ares(2019)2223897 - 28/03/2019

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

H2020-MSCA-RISE-2016-734718

D3.2 Report on clinical and MRI data acquisition and analysis

Work Package:	WP3
Task:	-
Deliverable due date:	31.3.2019
Responsible partner:	MU
Deliverable number:	D3.2
Deliverable type:	R/O
Dissemination level:	CO

1 Introduction

One of the aims of work package 3 (WP3) is to use multimodal MRI imaging and digitizing tablet to identify the neural correlates of impaired handwriting in various brain diseases, especially patients with Parkinson's disease (PD), and to conduct detailed analysis of kinematic abnormalities produced by both cortical and subcortical damage to brain regions engaged handwriting motor control.

2 Methods

Online handwriting from 15 Czech patients with Alzheimer's disease (AD) or mild cognitive impairment (MCI), 19 PD and 28 age-matched Czech healthy controls (HC) was recorded using a digitizing tablet Wacom Intuos 4M. These subjects also underwent MRI and neuropsychological examination.

Data obtained using digitizing tablet were analysed and several handwriting features were selected. These parameters originated from handwriting task no. 6 (copy of longer sentence) and consisted of relative standard deviation (rstd) of duration of stroke, rstd of horizontal velocity, length of writing and duration of writing. They were assessed separately for on-surface and in-air movements. Mann-Whitney U test was used to evaluate differences in chosen handwriting features between groups. Age and sex were included as covariates of no interest.

Functional MRI BOLD MultiEcho resting state sequence (735 scans, TR=0.8 s, TE=15, 33, 52 ms) was chosen for the analysis. Images with different echo times were realigned and then combined into weighted mean using temporal signal to noise ratio. Composite images were then coregistered to T1 volumes, normalised into standard anatomical space and smoothed. Data was checked for excessive movement and signal dropouts, resulting into exclusion of 1 HC, 1 AD and 4 PD. Images were further cleaned by regressing out six movement parameter time series, framewise displacement and signals from white matter and cerebrospinal fluid.

Regions of interest comprising writing network (WN) were identified. The exact position of cortical ROIs was chosen based on recent neuroimaging meta-analyses of handwriting (Planton et al., 2013; Purcell et al., 2011) and seeds (spheres with 6 mm radius) were created. For the last subcortical ROI seed the mask from the FSL striatal atlas (Tziortzi et al., 2014) was used. All ROIs were located in left hemisphere. The time-series of each seed of the studied networks was averaged and cross-correlated using Pearson's correlation coefficient to form a correlation matrix for each subject. Pearson's correlation coefficients were converted into z-values using Fisher's r-to-z transformation. Representative WN connectivity was calculated as mean of these z-values. WN connectivity was compared across groups using Mann Whitney U test and abovementioned covariates of no interest. In addition, Spearman's partial correlations of WN connectivity with selected handwriting features were calculated.

3 Results

Mann-Whitney U test revealed significant differences between groups in both WN connectivity and handwriting features. PD displayed significantly higher rstd of on-surface horizontal velocity, in-air length of writing and both on-surface and in-air duration of writing when compared to HC ($p=0.03$, $p=0.02$, $p<0.01$ and $p=0.02$, respectively). AD group exhibited

significantly higher rstd of in-air horizontal velocity and in-air length of writing (p=0.01 and p<0.01) when compared to HC.
Concerning WN connectivity, PD group showed significantly decreased connectivity in contrast to HC (p=0.04).
High negative correlation between rstd of in-air duration of stroke (R=-0.71, p=0.01) was observed in PD group.

4 Conclusion

Writing long sentences requires higher cognitive effort and escalates effect of dysgraphia in patients with PD. PD display lower velocity and longer duration of writing. However, in-air time is prolonged, too, due to disturbed motor planning. On the other hand, AD also manifest changes in several handwriting features, probably as a result of impaired planning. Higher rstd of in-air duration of stroke is associated with lower writing network connectivity which suggests involvement of writing network ROIs in writing control and implies these ROIs as possible targets for non-invasive brain stimulation protocols. In subsequent analyses, we will bulid on these pilot results, and thus determine whether kinematic analysis can distinguish handwriting impairments in various diseases, including stroke and PPA patients, and multimodal MRI will be used to identify their neural correlates.

5 References

Planton, S., Jucla, M., Roux, F. E., and Démonet, J. F. (2013). The “handwriting brain”: A meta-analysis of neuroimaging studies of motor versus orthographic processes. *Cortex*. doi:10.1016/j.cortex.2013.05.011.

Purcell, J. J., Turkeltaub, P. E., Eden, G. F., and Rapp, B. (2011). Examining the central and peripheral processes of written word production through meta-analysis. *Front. Psychol.* doi:10.3389/fpsyg.2011.00239.

Tziortzi, A. C., Haber, S. N., Searle, G. E., Tsoumpas, C., Long, C. J., Shotbolt, P., et al. (2014). Connectivity-based functional analysis of dopamine release in the striatum using diffusion-weighted MRI and positron emission tomography. *Cereb. Cortex*. doi:10.1093/cercor/bhs397.