Working memory performance is associated with functional connectivity between the right dlPFC and DMN in glioma patients

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P01.04.A. LESION-SYMPTOM MAPPING BASED ON STROKE OR GLIOMA: ETIOLOGY MATTERS!

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BACKGROUND: Lesion-symptom mapping is a key tool in understanding the relationship between brain structures and behavior. However, the behavioral consequences of lesions from different etiologies may vary as a result of how they affect brain tissue, and how they are distributed. The inclusion of different etiologies would increase the statistical power and improve generalizability of results, but has been critically debated. Findings from lesion studies are a resource for clinicians and used across different etiologies. This study directly compared lesion-symptom maps (LSM) between two populations (diffuse glioma versus ischemic stroke) in order to investigate if brain areas with adequate coverage in both groups, show topographical overlap in lesion-symptom associations. MATERIAL AND METHODS: Data from two studies were combined. Both the glioma (N = 196, WHO grade 2-4) and stroke (N = 147) population underwent neuropsychological testing and an MRI, pre-operatively for the tumor population and within three months after stroke. For the purpose of this study, we selected two widely used cognitive tasks, the Rey Auditory Verbal Learning Test and the verbal fluency test. We used a state-of-the-art machine learning-based, multivariate voxel-wise approach to produce LSM for these cognitive tasks for both populations separately. RESULTS: For both tumor and stroke, our etiology-specific LSM largely followed the expected neuroanatomical pattern based on previous literature. Nevertheless, for both tasks substantial differences in LSM-results were present between the populations in brain areas with adequate coverage in both groups, though we did find similar white matter tracts involved in memory and semantic fluency performance across etiologies. Post-hoc analyses of these locations confirmed an interaction between lesion presence and etiology for a majority of these regions; damage by a tumor, but not a stroke, was related to worse cognitive performance for these regions. CONCLUSION: This study provides the first direct comparison of LSM in a large cohort of patients. Differences in LSM were found between the glioma and stroke group, confirming that etiology matters when investigating the cognitive consequence of lesions. These differences could partly be explained by differences in lesion volume and topography. Nonetheless, the pattern shown by glioma patients on the group level is consistent with localizations found in earlier studies on both stroke and glioma patients using different techniques. While glioma series thus can be used to provide converging evidence about functional localization, we do suggest that findings from LSM studies in neuro-oncological populations should be considered as cause-specific. Findings from functional localization research from non-glioma populations should only be applied to a glioma population with caution.

P01.05.A. WORKING MEMORY PERFORMANCE IS ASSOCIATED WITH FUNCTIONAL CONNECTIVITY BETWEEN THE RIGHT DLPFC AND DMN IN GLIOMA PATIENTS

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BACKGROUND: Patients with primary brain tumors frequently suffer from cognitive impairments in multiple domains, leading to serious consequences for socio-professional functioning and quality of life. The functional-anatomical basis of these impairments is still poorly understood.

The study of correlated BOLD activity in the brain (i.e. functional connectivity) has greatly contributed to our understanding of how brain activity supports cognitive function. In particular, activity observed during the execution of specific tasks can be related to various distributed functional networks, stressing the importance of interactions between remote brain regions. Among these networks, the Default Mode Network (DMN) and the Fronto-Parietal Network (FPN) have consistently been associated with working memory performance.

Recently, using task-fMRI in glioma patients, poor performance in a working memory task was associated with less deactivation of the DMN during this task and to a lack of task-evoked changes in the DMN-FPN structure. In this study, we investigated whether these effects are reflected in the resting-state (RS) functional connectivity of the same patient group, i.e. when no task was performed during fMRI. We additionally zoomed in on the part of the FPN located in the dorsolateral Prefrontal Cortex (dlPFC), since this region is believed to be mainly responsible for DMN deactivation. MATERIAL AND METHODS: Resting-state functional MRI data were acquired pre-operatively from 45 brain tumor patients (20 low- and 25 high-grade glioma patients). Results of a pre-operative in-scanner N-back working memory fMRI task were used to assess working memory performance.

Patient brains were parcellated into ROIs using both the Gordon and Yeo atlas, which have the FPN and DMN network identities readily available. The dlPFC was defined based on masks retrieved from NeuroSynth.

To measure DMN-FPN functional connectivity the average Pearson correlation between the activation time series in the regions belonging to the FPN and the DMN was calculated. Functional connectivity between the DMN and the dlPFC was calculated in a similar way. RESULTS: The average correlation between the resting-state fMRI activity in the right dlPFC and in the DMN was negatively associated with working memory performance for both the Gordon atlas ($p < 0.003$) and Yeo atlas ($p < 0.007$). No association was found for the correlation between activity in the left dlPFC and the DMN, nor for the correlation between the activity in the whole FPN and the DMN. CONCLUSION: Our findings show that working memory performance of glioma patients is related to interactions between networks that can be measured with resting-state fMRI. Furthermore, the results provide further evidence that not only specific brain regions are important for cognitive performance, but that also the interactions between large-scale networks should be considered.

P01.06.B. INTERIM RESULTS FROM CAR-STUDY B: AN ONGOING RANDOMIZED TRIAL ON THE EFFECT OF SRS OR WBRT ON COGNITIVE PERFORMANCE IN PATIENTS WITH 11-20 BRAIN METASTASES

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BACKGROUND: Both stereotactic radiosurgery (SRS) and whole brain radiation therapy (WBRT) have proven to be effective treatments for multiple brain metastases (BM) with similar overall survival. Cognition and Radiation (CAR) Study B is a randomized trial on the effect of Gamma Knife radiosurgery (GKRS) or WBRT on cognitive performance in patients with 11-20 BM. The primary and secondary aim of this interim analysis were to check whether Bayesian stopping rules for cognitive failure were met, and to compare cognitive changes after treatment respectively, for the first 45 patients enrolled. MATERIAL AND METHODS: Patients with 11-20 newly diagnosed BM on a triple-dose contrast-enhanced MRI-scan, expected survival >3 months and Karnofsky Performance Status (KPS) ≥70, were stratified by age, histology, total BM volume, systemic treatment, KPS, and baseline Hopkins Verbal Learning total recall (HVLT-R TR) score, and randomized 1:1 (minimization) to GKRS or WBRT. Neuropsychological tests were administered before (T0) treatment (n=21 vs n=20), and at 3 (T3; n=16 vs n=14) and 6 (T6; n=9 vs n=9) months thereafter. A decline of ≥5 points in HVLT-R TR score was considered a cognitive failure. The trial would be halted if the posterior probability for a higher cognitive failure rate in one group versus the other was >0·975 at T3 or T6 according to the employed beta (2.09,2.91) prior (prior mean of 42%), based on the average failure rates at 4 months reported by Chang et al. (2009). Between-group differences in changes of test performances over 6 months were analyzed using mixed ANOVAs. Proportions of cognitive changes (T0-T6) at the individual level based on reliable change indices correcting for practice effects, were determined. RESULTS: HVLT-R TR failure rates in the GKRS versus WBRT group were 31% versus 29% at T3, and 0% versus 33% at T6. The observed failure rates after WBRT at T3 and T6 were lower than the average failure rates of Chang et al. (2009). Posterior probabilities were 0·451 at T3 and 0·918 at T6. Over 6 months, changes in performance on tests of immediate (p=·003) and delayed recall (p=·024), and information processing speed (p=·003) were significantly different between groups (large effect sizes), with significant declines after WBRT, but not after GKRS. Over 6 months, at the individual patient level, there were no declines in performances across all tests in the GKRS group (n=8) while performances declined in 4 out of 8 patients in the WBRT group. CONCLUSION: The stopping rules were not met since the posterior probabilities did not cross the threshold. Other preliminary findings in this small sample suggest that cognitive decline, both at group and individual level, is more pronounced after WBRT compared to GKRS. Accrual is continued (NCT02953717; ZonMw 842003006).

P01.07.A. NEUROCOGNITIVE OUTCOMES AFTER PROTON BEAM THERAPY FOR SKULL BASE TUMOURS

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BACKGROUND: Evidence suggests that Proton Beam Therapy (PBT) may lessen the risk of neurocognitive decline (NCD) by reducing the dose to the normal brain as compared to conventional photon radiotherapy (XRT). We report the incidence of moderate-severe (Grade ≥3) NCD in