Altered Resting-state Functional Connectivity in Central Post Stroke Pain

Xiuhui Chen[1,3], Eleni Panagoulas[1,2,3], Samyogita Hardikar[1], Jana Maidhof[3], Susanna Asseyer[3], Esra Al[1,2,5], Kersten Villringer[3], Karsten Muller[1] , Thomas Krause[3,4], Gerhard Jan Jungehülsing[3,4], and Arno Villringer[1,2,3]

[1]Department of Neurology, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

MAX PLANCK INSTITUTE FOR HUMAN COGNITIVE AND BRAIN SCIENCES

[2]Berlin School of Mind and Brain and MindBrainBody Institute at Humboldt-Universität zu Berlin, Germany [3]Charité – Universitätsmedizin Berlin [4]Jewish Hospital Berlin

[5] Columbia University New York

Introduction

Central post stroke pain (CPSP) is a common consequence of somatosensory stroke, typically occurring within 3 to 6 months after the stroke (Leijion et al., 1989). CPSP is often refractory to therapy and dramatically affect patients' quality of life (Klit et al., 2009). We conducted a prospective longitudinal study in which we recruited patients with somatosensory stroke in the acute phase and performed detailed clinical, behavioral, and MRI assessments. The aim of this subanalysis of our data was to identify potential changes in resting-state functional connectivity in patients who develop CPSP before the onset of pain and during the course of pain development. Specifically, we hypothesized that differences in resting-state connectivity between patients with CPSP and patients with nonpain somatosensory stroke (NPSS) are identified by (1) measuring seed-based connectivity of predefined brain areas ("seeds") that are part of the pain network, (2) assessing connectivity gradients in an exploratory whole-brain analysis (Huntenburg et al. 2018, Margulies et al., 2016) and (3) an analysis of dispersion within brain networks.

Methods

77 stroke patients were recruited at Charité – Universitätsmedizin Berlin and followed up over a 6-month period for the occurrence of pain. Resting-state fMRI were performed before the pain (day2-10 days post-stroke) and after the pain (>60 days post-stroke). In total 61 patients were included in the analysis, 18 CPSP and 43 non-pain patients. For the seed-based connectivity analysis, seeds were chosen from the pain network (including contralesional inferior frontal gyrus and ipsilesional superior parietal lobule). T-tests were used to compare pain and non-pain patients at baseline and in the chronic phase. Furthermore, a group by time interaction analysis was run to investigate changes in seed-based correlation over time. For the connectivity gradients, we constructed affinity matrices and decomposed them using principal component analysis. The first gradient was included in the regression analysis. Additionally, we calculated within network dispersion (sum squared Euclidean distance between network nodes and the network centroid), between network dispersion (the Euclidean distance of different network centroids), and connectivity within and between networks. We applied linear models to analyze the correlation of group and time with network dispersion. For each linear model, we calculated a null distribution of group and time differences using 1000 permutation tests.

1

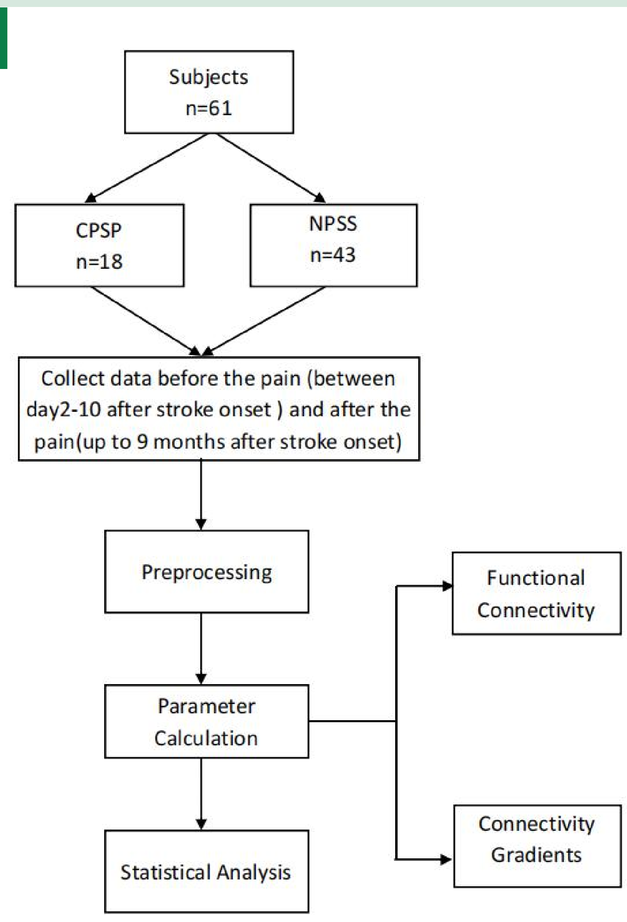

Figure 1. Flowchart of methods

Results

2

Seed	Cluster level				Peak coordinate			Cluster area			Cluster abbreviation	area	Increase/ decrease
	Cluster size	*p*-unc	*p*-FWE	*p*-FDR	M	N	I						
Cross-sectional analysis before the pain													
Contralesional Inferior Frontal Gyrus, pars triangularis	399	*<0.001*	*0.009*	*0.009*	+51	+12	+27	Contralesional Inferior Frontal Gyrus, pars opercularis			IFG oper r		Increase
Cross-sectional analysis after the pain													
Ipsilesional Superior Parietal Lobule	330	*0.002*	*0.033*	*0.026*	-32	-08	-03	Ipsilesional Putamen			Putamen l		Decrease
Longigudinal analysis between group (CPSP vs NPSS) and time (before the pain vs after the pain)													
Ipsilesional Superior Parietal Lobule	373	*<0.001*	*0.102*	*0.012*	-30	-06	-03	Ipsileisonal Putamen			Putamen l		Decrease

Table 1. In the cross-sectional analysis based on the acute MRI, CPSP patients showed stronger functional connectivity between the contralesional pars triangularis and pars opercularis in the inferior frontal gyrus. When the pain had occurred, CPSP patients showed lower functional connectivity between the ipsilesional superior parietal lobule and putamen as compared to NPSS patients. There was a significant group by time interaction showing that pain patients have lower functional connectivity between the ipsilesional superior parietal lobule and putamen over time.

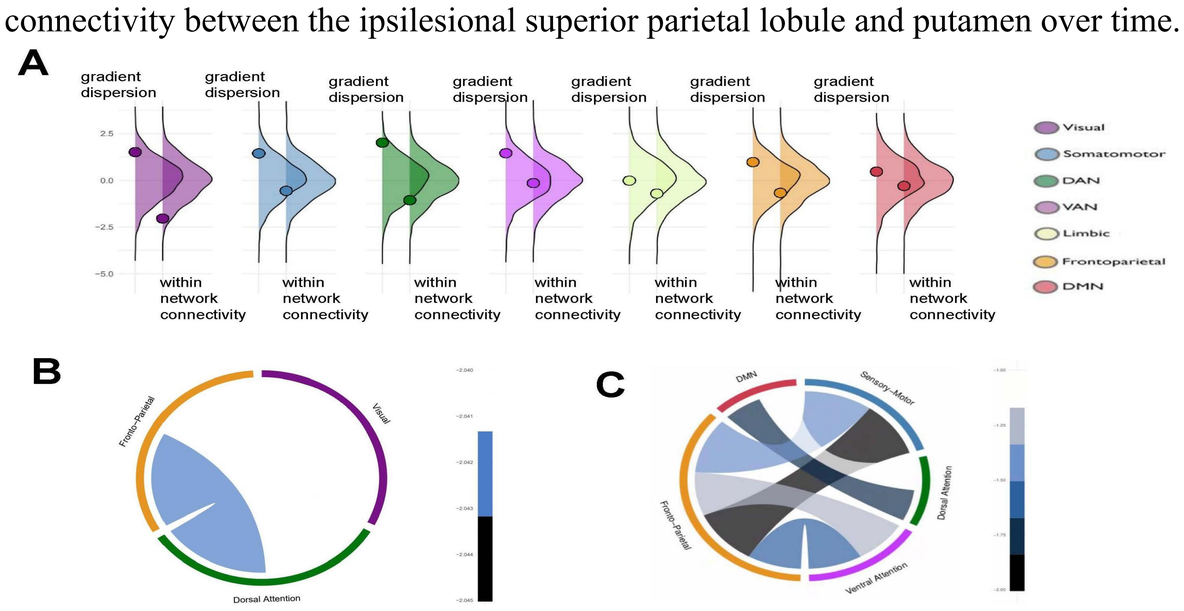

Figure 2. A) The dorsal attention network became more dispersed in the 3D gradient space for patients of the CPSP group before the pain;B) The NPSS group showed increased connectivity between the dorsal attention and frontal parietal network before the pain;C) Over time pain patients show increased connectivity in somatomotor and frontal parietal networks, as well as dorsal attention and default networks.

3

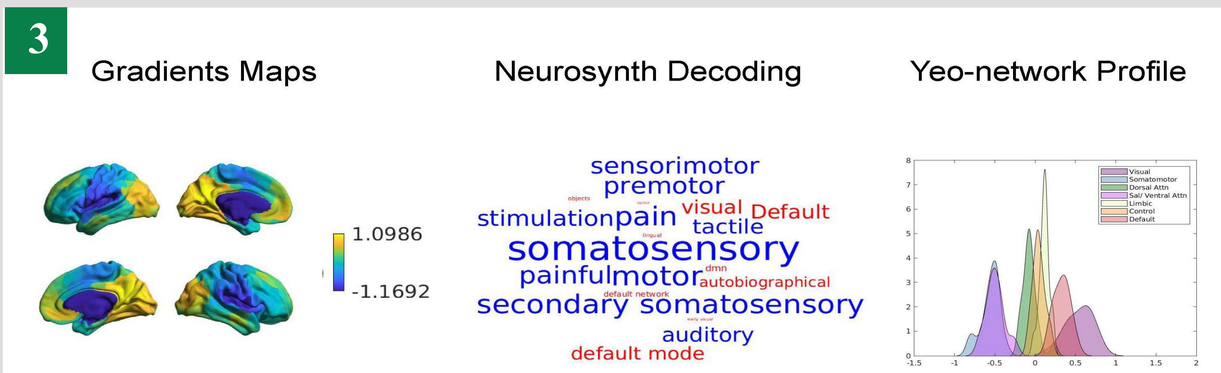

Figure 3. On the left, On the left is the maps of gradient 1. Regions with similar connectivity are shown in similar colours, with high (yellow) and low (blue) value regions indicating most dissimilar connectivity patterns. In the middle, word cloud represents the top 10 positively (red) and negatively correlated (blue) Neurosynth decoding topic terms for gradient 1 map. On the right, network shows the mean gradient density for all parcels within the seven Yeo-network on gradient 1.

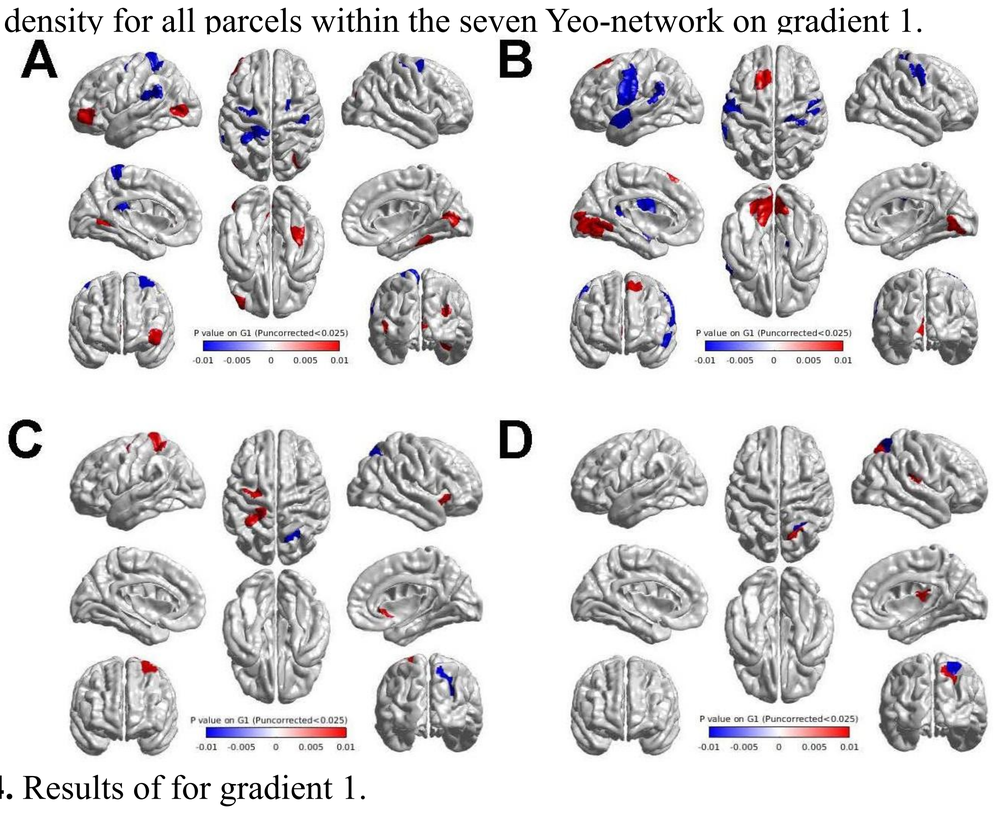

Figure 4. Results of for gradient 1.
Parcels within the first gradient that show significant ($P_{uncorrected}$<0.025) differences, blue indicating regions which are close to somatosensory and pain, and red indicating regions which are close to default.A) CPSP vs NPSS before the pain;B) CPSP vs NPSS after the pain;C) Interaction between group and time;D) post vs pre for CPSP patients.

Conclusion

This analysis shows for the first time that functional connectivity of multiple brain areas differs between CPSP patients and non-pain patients. The changes in connectivity before pain development could help predict who will develop pain after stroke.

Reference

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