Peer Review File

Article information: http://dx.doi.org/10.21037/atm-20-4865.

Reviewer Comments

Abstract

Comment 1. The objective was missed to be mentioned, instead it is presented as Methods.

Reply 1: Thank you for your professional comment. We adjusted the content of objective in the background part for better presentation

Changes in the text: We modified our text as advised.(see Page 3, line 4-7).

Comment 2. There are some odd characters that must be corrected "… patientsâ€™ locally distributed properties in the sensorimotor network (SMN) and ventral default mode network (vDMN) were reduced. It revealed that ï•§ (10,000 permutations, p = 0.048)".

Reply 2: We checked the text and corrected it throughout the paper.

Changes in the text: We corrected the presentation. (see Page 3, line 18)

Comment 3. In the results, the abbreviation of HCs is mentioned, but it was not included in the previous appearance of the term.

Reply 3: We added the extension of HCs when first mentioned.

Changes in the text: We added the extension of HCs when first mentioned. (see Page 3, line 14-15)

Comment 4. "It revealed that □ (10,000 permutations, p = 0.048) and synchronization (10,000 permutations, p = 0.022) within the SMN progressively decreased in patients with PFPS (Figure 3)". It does not seem appropriate to mention a figure in the abstract.

Reply 4: We checked the text and removed it.

Changes in the text: We modified it as your request. (see Page 3, line 20)

Comment 5. Conclusion: "Our results demonstrated a reduction in local network processing efficiency in patients with post-facial palsy synkinesis. Therefore, we speculate that decreased characteristics in the intra-vDMN and intra-SMN, rather than the whole-brain network, may contribute to distinct symptoms such as facial nerve impairment or more synkinetic movements". The speculation suggests that the findings justify the nerve impairment or synkinetic movement… nevertheless, the findings are related to the lack of sufficient network or resources to control these aberrant new movements that appeared with the nerve regeneration. Please confirm.

Reply 5: Thank you for your professional comment. We are fully aware of the limitation of neuroimaging study design, which has a blurred statement on causal relationship. Our ultimate goal is to find out the target for clinical treatment. Of course, the correlation is not exactly same as causality. But we believe that describing the alteration of facial synkinesis is the very first

step to the underlying mechanism. We hope the readers and reviewers could agree this work is a little advancement and does contributes to our understanding of facial synkinesis.
Changes in the text: We have modified the statement and pointed out the contribution of our work in a more proper way. (see Page 4, line 7-8)

Introduction

Comment 1. Page 8, line 108, The authors mention that "We hypothesize that functional sub-networks, rather than the whole-brain network, contribute to abnormal movement, collectively inducing neural plasticity of pathologic involuntary activity". Nevertheless, the abnormal movement resulting from a facial nerve injury does not come from the re-arrangement of the brain. Instead, the re-arrangement of the brain must be a consequence of the aberrant growth of new facial nerve axons. The hypothesis might be rewritten. If the authors do not change their view of the regeneration pattern of the synkinesis, it would jeopardize the interest of the reader.

Reply 1: Thank you for your professional comment. We totally agree with your opinion. Most facial nerve injuries are lower motor neuron injuries that do not involve the cortex. Any cortical changes that might be seen in these patients are likely caused by the more peripheral injury rather than be the origin of the problem. That said, they certainly could contribute to the problem. Hence the biggest question is who precedes who: the chicken or the egg. Further verification should be conducted with interventional studies or electrophysiological experiment. However, we discussed here is a correlation study rather than a causal study.
Previous researches showed that functional deficits caused by nerve injuries can be compensated by reinnervation of denervated targets by regenerating axons or remodeling of nervous system circuitry related to the lost functions.(1) Currently, functional reorganization associated with the acquisition, consolidation and retention of motor skills has been widely studied in neuroimaging. Plastic changes involving structural reorganization that occurs after motor skill learning.(2) However, as the prognosis of peripheral nerve injury, patients recovered with an adaptation of the brain when learned well, or else a maladaptation of the brain, even it is useless if the nerves are reconnected.(3,4) The negative consequences of nerve mismatch are inevitable. We devoted to recognizing effective neural plasticity in brain to reverse this negative consequence to the greatest extent.
We believe that describing possible correlation with synkinesis is the first step in understanding causality so that we can identify a hidden target for intervention. Our contribution is to provide the potential target and narrow the scope of subsequent exploration.
Changes in the text: We have reorganized the hypothesis to make it more reasonable. (see Page 6, line 3)

Methods

Comment 1. Participants. Patients characteristics and demographics, as well as recruitment details must be presented.

Reply 1: Thank you for your professional comment. We have provided more specific content about subjects' recruitment.
Changes in the text: We rewrite the recruitment part and attached a table. (see Page 6, line 11-21 and Page 7, line 1-2).

Comment 2. Healthy controls abbreviation must appear in the text.
Reply 2: Thank you for your professional comment.
Changes in the text: We added it in the text (see Page 6, line 12).

Comment 3. Page 8, line 120. "The medical history (with unilateral synkinesis history for more than 9 months but no nerve transposition, psychiatric disorders, or contraindications to MRI) of all participants was taken. In addition, a neurological examination (normal vision and the capability to follow instructions) and an interview (the Sunny-Brook facial grading system for patients) were conducted." Please explain how they were recruited, mean, median, min and max time of PFPS onset. Had they participated in any rehabilitation method? Rewrite the inclusion (selection criteria), separating from variables that were collected from the medical records. Etiology may impact the regeneration pattern of the facial nerve as well as the onset time on the plastic changes of the brain. These data would not change the answering of the objective, but would allow the reader to understand and make assumptions from the results.
Reply 3: Thank you for your professional comment. We totally agree with you. We have considered the influence of factors on the brain's performance, such as the onset time and sub-category of etiology. We have made some balancing efforts to control the homogeneity while ensuring the sample size of the group and make our research convincible.
In fact, we considered these issues in advance. The patients have tried many conservative treatments but there is still no significant improvement, including acupuncture, massage, neurotrophic drugs/nerve growth factor, physical therapy, electrical stimulation, etc. And they did not have the history of surgery or Botox injection. Besides, sample size included in our research is a subgroup with high homogeneity in our series of studies. We have provided demographic details according to your requirements.
Changes in the text: As your advice, we modified the recruitment part. (see Page 6, line 11-21 and Page 7, line 1-2).

Procedure
Comment 1. The authors might detail the time that each patient had to dedicate for the whole assessment. Were all the procedures performed in the same session?
Reply 1: All fMRI measurements and clinical assessments at one time of following-up were performed on the same day. It costs about 45 minutes of fMRI procedure and 30 minutes of clinical scale evaluation.
Changes in the text: We modified the recruitment part (see Page 7, line 2-3).

Comment 2. This reviewer has no experience with the detailed fMRI procedure, thus I will not comment on its description. Nevertheless, in the Data analysis, the authors may help the unexperienced reader to understand the studied variables. As for instance, the detailed description of ALL the studied variables must be included.
• Area under the curve (AUC)
• Cp
• Lp

• □
• □
• **Eglobal**
• **Elocal**
• **Assortative**
• **Hierarchy**
• **Synchronization**

Reply 2: Thank you for your professional comment. We added the detailed description of the studied variables following your advice.

Changes in the text: We added some description of variables involved in our research as advised. (see Page 10, line 2-8)

Results

Comment 1. Page 14, line 238. Since the authors are in the cognitive and neuroscience area, they know that too high demands may lead to quitting the task. The first paragraph of the results may be more friendly to the less familiarized with the technique reader. "Translating" the data and formula into clinical and functional representation would be helpful and more attractive for more readers. Even the sentence "which indicates a certain property of small-worldness" is not concrete for the clinical practitioner.

Response: We have adjusted the statement of sentences concerning fMRI technique.

The sentence means the organizational characteristic of several related brain regions about how they were gathered and how they were ranked during communication.

Changes in the text: We reorganized the sentence and give the descriptions of studied variables. (see Page 13, line 8)

Comment 2. For the clinical professional, the sentence "the statistical comparison of the AUC showed no significant difference in Cp, Lp, □, □, Eglobal, Elocal, assortativity, hierarchy, or synchronization between the groups (Figure 2)" is meaningless, except when the authors mention "In general, there was no significant difference between the patient group and the HCs on the whole-brain scale"…

Reply 1: Thank you for your careful work.

Changes in the text: We modified the statistical results of whole-scale brain network (see Page 13, line 7-9).

Discussion

Comment 1. Page 16, in 272. "Therefore, facial synkinesis is a minor complication of facial paralysis that does not induce extensive plasticity of the whole brain. Instead, it only causes limited topological changes in a few nodal properties and functional subnetworks. A complication does not need to induce a whole brain plasticity to be considered a major complication…" In fact, facial synkinesis may be indeed considered a major complication, and the fact that the authors did not find any topological changes in the studied properties, does not mean that the brain control is not damaged or altered.

Response: We realized that the statement could lead to misunderstanding. We have made some modification to the sentence and make them consistent with the context.

Changes in the text: We modified the sentence to make reasonable. (see Page 14, line 18)

Comment 2. Line 283, I suggest that the sentence must be ´translated´, "In this study, it was found that the subjects' functional complex sub-networks had small-world attributes, and the γ of the SMN, the γ, Elocal, and the hierarchy of the vDMN decreased, while Eglobal did not significantly change." since these are results terms collected from the assessment, but the functional meaning must be used in the Discussion session.
Response: We modified the blurred statement.
Changes in the text: We modified the statistical results of whole-scale brain network (see Page 16, line 14-16).

Comment 3. Page 17, line 301 "In addition, we discovered several measurements, including network efficiency and synchronization, that show neither significant nor trending differences in any subnetwork. Therefore, we believe that they may not be involved in the neural plasticity of facial synkinesis. Such interpretations are not difficult as facial paralysis only triggers changes in topological properties to a limited extent due to being a relatively mild symptom"… sentences are vague and again describe synkinesis as a mild symptom with huge consequences in the patient´s quality of life and facial emotions control. The changes in brain network, gathering the sensorimotor, cerebellar and cognitive control is compromised after a PFPS.
Response: We must apologize for the blurred expression of mild symptoms. Actually, we want present this concept that synkinesis is one severe but limited in extent.
Changes in the text: We modified the sentence (see Page 17, line 8-9).

Comment 4. Page 18, line 235 "Consequently, these intrinsic networks and dedicated connectomes may be engaged during facial synkinesis. The primary aim of this study was to define the scale affected by facial synkinesis" may appear earlier in the Discussion session.
Reply 1: Thank you for your professional comment.
Changes in the text: We adjusted the paragraph order in the discussion to make it reasonable. (see Page 15, line 10-21 and Page 15, line 17-19).

Conclusion
Comment 1. Page 19, line 344 "this study provides new insights into the pathophysiological mechanisms of PFPS" may be clarified that pathophysiological mechanisms that involved the brain reorganization after PFPS.
Reply 1: Thank you for your professional comment.
Changes in the text: We adjusted the paragraph order in the discussion to make it reasonable. (see Page 18, line 7-8).

References
Comment 1. Reference 30, "Genovese CR, Lazar NA, Nichols T. Thresholding of Statistical Maps in Functional Neuroimaging Using the False Discovery Rate1. :9" seems to be incomplete.

Response: Genovese CR, Lazar NA, Nichols T. Thresholding of Statistical Maps in Functional Neuroimaging Using the False Discovery Rate. Neuroimage. 2002 Apr; 15(4):870-8. (see Page 24, line 2-3).

Comment 2. Why reference 35 "Hall A. THE ORIGIN AND PURPOSES OF BLINKING*. Br J Ophthalmol. 1945 Sep;29(9):445–67." Has an asterisk *?
Response: Hall A. THE ORIGIN AND PURPOSES OF BLINKING. Br J Ophthalmol. 1945 Sep;29(9):445–67. (see Page 24, line 17).

References

1. **Navarro X. Chapter 27 Neural Plasticity After Nerve Injury and Regeneration. In: International Review of Neurobiology [Internet]. Elsevier; 2009 [cited 2020 Sep 18]. p. 483–505. Available from: https://linkinghub.elsevier.com/retrieve/pii/S007477420987027X**

2. **Dayan E, Cohen LG. Neuroplasticity subserving motor skill learning. Neuron. 2011 Nov 3;72(3):443–54.**

3. **Sagheddu C, Aroni S, De Felice M, Lecca S, Luchicchi A, Melis M, et al. Enhanced serotonin and mesolimbic dopamine transmissions in a rat model of neuropathic pain. Neuropharmacology. 2015 Oct;97:383–93.**

4. **Mao CP, Zhang QL, Bao FX, Liao X, Yang XL, Zhang M. Decreased activation of cingulo-frontal-parietal cognitive/attention network during an attention-demanding task in patients with chronic low back pain. Neuroradiology. 2014 Oct;56(10):903–12.**