Spectrum of neuropsychiatric symptoms in chronic post-stroke aphasia

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Comments to the reviewers

Reviewer 1: 05916903

Criteria Checklist

1 Title. Does the title reflect the main subject/hypothesis of the manuscript?

YES. Thank you.

2 Abstract. Does the abstract summarize and reflect the work described in the manuscript?

PARTIALLY.

The abstract needs to include the methods used to assess the literature, as this section only contains details regarding the proof-of-concept study's methodology.

We have expanded the Methods and Results section of the **abstract (Pages 3 - 4)** to provide further details regarding study 1 (Narrative literature review). Please see more comments below covering this section.

3 Keywords. Do the key words reflect the focus of the manuscript?

YES.

4 Background. Does the manuscript adequately describe the background, present status and significance of the study?

YES, but it can be improved by adding some relevant information (please see comments below). We have given answer to your comments below.

5 Methods. Does the manuscript describe methods (*e.g.*, experiments, data analysis, surveys, and clinical trials, etc.) in adequate detail?

PARTIALLY.

The introduction section includes a vast amount of literature, as one of the aims was to analyze the current state of the art; thus, it would be a good idea to provide some details of how the literature review was done.

As you have kindly stated, this was not a systematic but a narrative literature review, paralleling other recently published works by one of our co-authors (Robinson & Jorge, 2016) and other scientists (Medeiros et al., 2020). We have included a search strategy methods section within Study 1 (Literature review) covering the inclusion criteria and screening/revision process of the bibliography included in this work (**Pages 7-8**).

- **Reference 31. Robinson RG**, Jorge RE. Post-stroke depression: A review. *Am. J. Psychiatry* 2016; **173**: 221–231
- **Reference 32. Medeiros GC**, Roy D, Kontos N, Beach SR. Post-stroke depression: A 2020 updated review. *Gen. Hosp. Psychiatry* 2020; **66**: 70–80

The inclusion of the selection criteria kindly recommended by you is essential because several published reviews covering post-stroke neuropsychiatric disorders do not include a methods/search strategy section. This issue probably resulted from the limited methodological quality of included articles which do not allow for a systematic review or meta-analysis. Some of these studies are listed below.

- **Reference 17. Nemani K**, Gurin L. Neuropsychiatric complications after stroke. *Semin. Neurol*. 2021; **41**: 85–100
- **Reference 19. Hackett ML**, Köhler S, O'Brien JT, Mead GE. Neuropsychiatric outcomes of stroke. *Lancet Neurol.* 2014; **13**: 525–534
- **Reference 20. Ferro JM**, Caeiro L, Figueira ML. Neuropsychiatric sequelae of stroke. *Nat. Rev. Neurol.* 2016; **12**: 269–280
- **Reference 21. Zhang S**, Xu M, Liu ZJ, Feng J, Ma Y. Neuropsychiatric issues after stroke: Clinical significance and therapeutic implications. *World J. Psychiatry* 2020; **10**: 125–138
- **Reference 22. Bourgeois JA**, Chang CH, Wineinger MA, Servis ME. Poststroke neuropsychiatric illness: An integrated approach to diagnosis and management. *Curr. Treat. Options Neurol*. 2004; **6**: 403–420
- **Reference 27. Laures-Gore JS**, Dotson VM, Belagaje S. Depression in poststroke aphasia. *Am. J. Speech-Language Pathol*. 2020; 29: 1798–1810

- **Reference 87. Khan AA**, Chen L, Zhang G, Guo X, Wu G, Wang H, You Y. Management of post-stroke neuropsychiatric disorders. *Transl. Neurosci. Clin*. 2016; **2**: 244–251

6 Results. Are the research objectives achieved by the experiments used in this study? What are the contributions that the study has made for research progress in this field?
YES.

7 Discussion. Does the manuscript interpret the findings adequately and appropriately, highlighting the key points concisely, clearly and logically? Are the findings and their applicability/relevance to the literature stated in a clear and definite manner? Is the discussion accurate and does it discuss the paper's scientific significance and/or relevance to clinical practise sufficiently?
YES.

8 Illustrations and tables. Are the figures, diagrams and tables sufficient, good quality and appropriately illustrative of the paper contents? Do figures require labeling with arrows, asterisks etc., better legends?
YES. Minor details to be corrected (see comments). We give answer to our comments below.

9 Biostatistics. Does the manuscript meet the requirements of biostatistics?
YES.

10 Units. Does the manuscript meet the requirements of the use of SI units?
YES.

11 References. Does the manuscript cite appropriately the latest, important and authoritative references in the introduction and discussion sections? Does the author self-cite, omit, incorrectly cite and/or over-cite references?

YES, although some minor corrections need to be made (see comments). Answers to your comments are found further below.

12 Quality of manuscript organization and presentation. Is the manuscript well, concisely and coherently organized and presented? Is the style, language and grammar accurate and appropriate?

PARTIALLY.

It was a bit confusing that the introduction section was at the same time a "study" in itself, analyzing state of the art. I would recommend adding a clearer structure in the introduction section, maybe explaining the aim of this section more precisely. Language and grammar were appropriate.

Thank you for pointing out this critical issue. We have now divided the manuscript into a general Introduction (**Page 5**) followed by an "Overview of Post-Stroke Aphasia (**Pages 5 -7**) and two studies [Study 1 (**Pages 7 -16**) and Study 2 (**Pages 17 - 24**). In the first part of our manuscript (Study 1), we reviewed the extant data on NPS in patients with chronic post-stroke aphasia. Our narrative literature review showed that the co-occurrence of several disorders (depression, anxiety an others) is prevalent in stroke patients with aphasia, whereas the scientific literature scarcely covers the issue of neuropsychiatric comorbidity. In support of this assertion, in our Study 2, we found that all but one aphasic patient had more than one NPS (~ 5 NPS). Therefore, this comorbidity is clinically relevant and alerts about the need to use multidomain testing tools like the Neuropsychiatric Inventory (NPI) or several single-domains scales to uncover the spectrum of NPS in stroke patients with aphasia.

13 Research methods and reporting. Authors should have prepared their manuscripts according to manuscript type and the appropriate categories, as follows: (1) CARE Checklist (2013) - Case report; (2) CONSORT 2010 Statement - Clinical Trials study, Prospective study, Randomized Controlled Trial, Randomized Clinical trial; (3) PRISMA 2009 Checklist - Evidence-Based Medicine, Systematic review, Meta-Analysis; (4) STROBE Statement - Case-Control study, Observational study, Retrospective Cohort

study; and (5) The ARRIVE Guidelines - Basic study. Did the author prepare the manuscript according to the appropriate research methods and reporting?
NOT CLEARLY STATED. This is an important point to include in the manuscript.
This manuscript draft includes two differentiated research approaches. Study 1 is primarily a narrative review that did not employ the Preferred Reporting Items for Systematic Reviews and Meta-Analysis [PRISMA] as a systematic article search. Thus, covering systematically all data of prevalence, risk factors, assessment strategies, pathophysiological mechanisms, and treatment interventions of the total neuropsychiatric symptoms published for PWA would go beyond the scope of one single article. However, Study 2 presents the original data of a baseline evaluation of a registered clinical trial (EudraCT:2017-002858-36; ClinicalTrials.gov identifier: NCT04134416), prepared according to the **CONSORT 2010 Statement** for clinical trial studies. Likewise, we have prepared the manuscript according to the **STROBE Statement-Observational study**. The STROBE checklist file will be uploaded with the information corresponding to this point.

14 Ethics statements. For all manuscripts involving human studies and/or animal experiments, author(s) must submit the related formal ethics documents that were reviewed and approved by their local ethical review committee. Did the manuscript meet the requirements of ethics?
YES.

Specific comments to authors

Dear authors,

Thank you for the opportunity of reviewing this interesting manuscript.

I realize the importance of clarifying and providing an NPS profile in those living with post-stroke aphasia. I am happy to accept this manuscript after some minor revisions.

I share with you some comments to improve the strength and clarity of this work. Please also read the checklist comments.

Abstract

1. Aim section: no need to write again "persons with aphasia (PWA)", as it is previously written in the background section. Checked (**Page 3**).
2. Methods: I would recommend mentioning how you reviewed the literature for the first section (current state of the art analyzes). Thank you very much for pointing out this critical aspect of our work. We have included a Methods and a brief Results section (**Pages 7 - 8**) for Study 1 (narrative literature review) in the revised version. We have also reflected this modification in the Methods section of the Abstract (**Page 3**).
3. Core tips: is this section required by the journal? Should this be part of the introduction section? As required by submission guidelines of the World Journal of Psychiatry, *Core tips* shall be presented below the abstract and above the introduction. Thus, we believe we must leave them in the same position (**Page 4**).
4. Word count: what is the word count of this work? Is it under the word limits of the journal? The abstract contains 350 words. We have modified the length of each section to conform to the limits required by the Editorial. Without references (but including the figure captions and tables), the manuscript contains 7544 words. Please note that the Baishideng Editorial invited us to submit a manuscript with no word limit.

Introduction

1. I am not sure if the comparison between the prevalence of PWA and the other neurodegenerative disorders mentioned is absolutely relevant, as this looks quite arbitrary. I would rather recommend including some prevalence data. The comparison of PWA with other disorders (e.g., Parkinson's disease, multiple sclerosis) has been excluded from the revised version following your recommendation. Moreover, as you kindly stated, it is essential to provide specific prevalence data of post-stroke aphasia. Therefore, we have now introduced a new sentence in the Introduction section (first paragraph) showing the frequency of occurrence on aphasia in the acute and chronic covering this topic (**Page 5**).

2. Please provide a reference for the sentence ending "…*the event and its functional impact in daily life (reference?)*". We have included the following references 17 (Nemani et al. 2021) and 18 (Bullier et al., 2021) (**Page 8**).

- **Reference 17. Nemani K**, Gurin L. Neuropsychiatric complications after stroke. *Semin. Neurol*. 2021; 41: 85–100
- **Reference 18. Bullier B**, Cassoudesalle H, Villain M, Cogné M, Mollo C, De Gabory I, Dehail P, Joseph PA, Sibon I, Glize B. New factors that affect quality of life in patients with aphasia. *Ann. Phys. Rehabil. Med*. 2020; 63: 33–37

3. I believe it is essential to provide a brief paragraph explaining what a stroke is and provide more information about the different types of aphasia. Also, you are focusing on "chronic" aphasia but never explained the parameters to define chronic aphasia vs acute aphasia. Although it might be evident, I would recommend providing a brief rationale for choosing chronic aphasia. Many thanks for alerting us about the need to include a brief paragraph on stroke and aphasia. Therefore, we have included an overview dealing with this topic (**Pages 5 - 6**) including the classification of stroke in acute/subacute, chronic, and very chronic periods (Page 5).
4. Would you mind providing in some part of the introduction how you gathered the relevant literature for the first section of this manuscript? Was it a literature review? How many authors seek and analyzed the studies? Did you rate/check the quality of the studies? Even though it is not a systematic review, I think it would improve the strength of your work to show which steps you took and where you found your relevant studies. Following your helpful suggestion, we have included a Methods section (search strategy) for Study 1 (**Pages 7-8**), highlighting the fundamental points of the literature review. In addition, we have given higher importance to meta-analysis, systematic reviews, and randomized control studies over other articles, sometimes pointing out how sparse high-quality literature is for specific NPS in PSA.
5. I would strongly recommend explaining the different types of aphasia, their main characteristics and neuropathological correlates in the introduction section before exploring NPS. Maybe it would help to briefly explain the importance of the hemisphere affected by the stroke and how this could lead to different aphasias. As

already stated, we have included a brief "Overview of Post-Stroke Aphasias" addressing all these crucial issues raised by you (**Page 5-6**).

6. I would strongly recommend providing an explicit subheading for the first section of your manuscript. The current structure is confusing, as everything is under the introduction section. We have now subdivided the manuscript into a general **Introduction** and a **Study 1** (Narrative literature review, with its additional methods section, as requested) and **Study 2** (case-controlled study of a baseline evaluation of a registered clinical trial). We believe that it is now easier to follow the structure and aims of this work.

Depression

1. p. 5: in the second paragraph, you mentioned a comparison about acute and chronic aphasia; it would be clearer for the reader to know in advance the differences between them (briefly). On **page 9** (page 5 in the original manuscript) of the revised manuscript, we provided data from Hermann et al. (1993) study, who reported no differences in depression in acute and chronic aphasia. However, Kauhanen et al. (1999) found that aphasia increases the risk for developing depression in the chronic period (6 months post-stroke onset). To our knowledge, there are no further studies comparing depression in acute and chronic stroke.
2. p. 8: tDCS and rTMS are only mentioned once in the manuscript; there is no need to add the acronyms. We appreciate that you have singled out this aspect, and we have omitted the acronyms accordingly.

Anxiety

1. The first paragraph would benefit from having a brief explanation of types of aphasia and correlates in the introduction. We have included an overview dealing with aphasia and stroke (**Pages 5 - 6**).
2. "*Adult anxiety comprises a class of conditions that includes generalized anxiety disorder, panic disorder, and phobias[38,88]. The DSM-5 classifies these conditions as anxiety disorders due to another medical condition…*" In this previous sentence is not clear in which context the DSM classifies anxiety as due to another medical condition. I would

recommend writing something like " *…in the context of PWA, the DSM-5 classifies these conditions as anxiety disorders due to another medical condition…"* We appreciate your suggestion, and we have introduced your sentence accordingly in the manuscript and different NPS sections (adapted to each NPS). (**Page 11**)

3. The last sentence about the effect of b-blocker could be more elaborated; please briefly explain the relationship of this drug and naming. We have introduced a paragraph indicating the potential role of the anxiolytic effects of propranolol in improving anomia in aphasia (last paragraph of the anxiety section; **Page 13**).

Apathy

1. Please provide reference to the following sentences:

- "Prevalence of apathy in PSA is currently unknown". This is our team's conclusion based on our lack of found articles covering prevalence data of apathy in PWA. We have expanded this sentence into "Prevalence of apathy in PWA is currently unknown as a previous meta-analysis covering post-stroke apathy could not provide any specific data for the aphasic population" (**Page 13**).
  - **Reference 110. Caeiro L**, Ferro JM, Costa J. Apathy secondary to stroke: A systematic review and meta-analysis. *Cerebrovasc. Dis.* 2013; **35:** 23–39
- "However, no studies have specifically evaluated the neuroimaging correlates of apathy in PWA". We have included this sentence (**Page 14**) because, to our knowledge, no studies are covering the neuroimaging correlates of apathy in PSA.
- Regarding the Canadian Stroke best practice recommendations, are these specific for apathy? Please clarify. Yes, these specifications were made explicitly for post-stroke apathy (with or without depression). "For people who have experienced a stroke with marked apathy, with or without clinical depression, it is reasonable to offer nonpharmacological intervention such as exercise or music therapy [Evidence level C]." In this context, we have indicated that no special recommendations were given for PWA[119]. (**Page 14**).

  We have included the word "*specifically*" in the sentence to improve comprehension. (**Page 14**).

- **Reference 121. Lanctôt KL**, Lindsay MP, Smith EE, Sahlas DJ, Foley N, Gubitz G, Austin M, Ball K, Bhogal S, Blake T, Herrmann N, Hogan D, Khan A, Longman S, King A, Leonard C, Shoniker T, Taylor T, Teed M, de Jong A, Mountain A, Casaubonn LK, Dowlatshahi D, Swartz RH. Canadian stroke best practice recommendations: Mood, cognition and fatigue following stroke, 6th edition update 2019. *Int. J. Stroke* 2019; 15: 668–688

- Do we know when is more likely to develop apathy in post-stroke patients? Does apathy occur in the early stages? Is there any information in the literature about this? An exploratory longitudinal study exploring apathy in non-aphasic stroke patients found that "apathy was present in 17 [out of 76] patients in the acute phase and in 18 (23.7%) patients at 1 year after stroke. At 1 year after stroke, 41% of the acute apathetic patients remained apathetic"

  Caeiro L, Ferro JM, Pinho E Melo T, Canhão P, Figueira ML. Post-stroke apathy: an exploratory longitudinal study. *Cerebrovascular diseases*, 2013; 35: 507–513

  However, PWA were not mentioned in this article so that we cannot adopt the same conclusions for our work.

Behavioral disorders

1. Please provide a reference for the first sentence. The following references have been included in the revised version. (**Page 14**)
   - **Reference 122. Angelelli P**, Paolucci S, Bivona U, Piccardi L, Ciurli P, Cantagallo A, Antonucci G, Fasotti L, Di Santanionio A, Grasso MG, Pizzamiglio L. Development of neuropsychiatric symptoms in poststroke patients: A cross-sectional study. *Acta Psychiatr. Scand.* 2004; **110**: 55–63
   - **Reference 123. Osa García A**, Brambati SM, Brisebois A, Désilets-Barnabé M, Houzé B, Bedetti C, Rochon E, Leonard C, Desautels A, Marcotte K. Predicting early post-stroke aphasia outcome from initial aphasia severity. *Front. Neurol.* 2020; **11**: 120
2. This is a personal opinion: "affected people" has an overall negative connotation. Sometimes we try to use words with a more neutral symbolic meaning, such as "people living with PWA". We have changed "affected people" by PWA

3. Comments and information about paranoia might go in another section? Is paranoia a behavioural disorder? We have abandoned the initial idea of subgrouping NPS into various clusters (initially Mood, Behavioral disorders, Euphoria, and Psychosis) and present now each neuropsychiatric symptom/syndrome on its own. After consideration, we have moved the following paragraph from the "agitation/aggression section to the psychosis section: "The symptoms were found to be more common with posterior left hemisphere lesion, particularly in patients with Wernicke´s aphasia, who are more paranoid and aggressive than patients with anterior lesions, who instead may become more frustrated and depressed (**Page 16**).
4. Are anger and aggression the same thing? Would it be worthwhile providing a brief conceptual clarification? We have now provided a brief conceptual clarification indicating that anger is the emotional component of a hostile reaction and aggression is the behavioral expression of this reaction (**Page 14**). For an extensive theoretical approach of anger, hostility, and aggression we refer to:
   - **Reference 124. Ramírez JM**, Andreu JM. Aggression, and some related psychological constructs (anger, hostility, and impulsivity); some comments from a research project. *Neurosci Biobehav Rev*. 2006; **30**: 276–291

Euphoria

1. Please provide references for the following sentences:

- The neuropsychiatric constructs of mania and hypomania have been included under the cluster of Euphoria. Elevated mood, euphoria and mania are seldomly reported in PWA.
  - **Refrence 132. Santos CO**, Caeiro L, Ferro JM, Figueira ML. Mania and stroke: A systematic review. *Cerebrovasc. Dis*. 2011; **32**: 11–21 (**Page 15**).
- In a study conducted by Signers et al. (reference here), one-fifth of participants with chronic fluent aphasia and posterior left hemisphere lesions were elated, happy, and unaware of their language impairment. This evidence justifies the including it in the abovementioned sentence (see 1)

- **Reference 131. Signer S**, Cummings JL, Benson DF. Delusions and mood disorders in patients with chronic aphasia. *J. Neuropsychiatry Clin. Neurosci*. 1989; **1**: 40–45 (**Page 15**).

2. The same comment about the DSM 5 classification from the previous sections (context). We include your previous mentioned sentence in this section of the article (**Page 15**): *"In the context of PWA, the DSM-5 classifies these conditions as bipolar and related disorders due to another medical condition"*
   - **Reference 35. American Psychiatric Association**. Diagnostic and statistical manual of mental disorders. 5th ed. Washington: American Psychiatric Publishing, 2013: 1–492
3. Maybe explain or make earlier reference to the concept of elation, as it is not mentioned in your mania/hypomania definition. We have included the Cambridge Dictionary definition of elation together with its reference (https://dictionary.cambridge.org/dictionary/english/elation) (**Page 15**).
   - **Reference 133. Cambridge University Press**. Elated: a state of extreme happiness or excitement. Cambridge International Dictionary of English. 23 June 2021. Available from: https://dictionary.cambridge.org/dictionary/english/elation
4. *"For example, the relationship of anosognosia and aphasia..."* This seems out of context. Why is this point about anosognosia in the Euphoria paragraph? Would you please provide arguments/rationale for this? Thanks for calling our attention to this point. There was a mistake in this sentence; we wanted to link anosognosia with hypomania/mania in the context of aphasia. The revised version stresses that the relation between anosognosia for aphasia and hypomania/mania is a pending issue that needs further research. (**Page 16**).
5. The last paragraph sounds more like a discussion or recommendation for future studies section; do you have references for this? This is now included in the end of the manuscript (General conclusions and directions for further research) (**Page 25**).

Psychosis

1. The same comment about the DSM 5 classification from the previous sections (context). We include your previous mentioned sentence in this section of the article (**Page 15**).
2. Please correct grammar: "The development of delusions after PWA is a not a rare phenomenon" (delete the "a"). Many thanks. This error has been corrected.
3. Please provide reference to the following sentences:

- Another study (reference) found that 28 PWA out of 61 chronic participants developed delusions, being mostly of persecutory nature. We have included a reference for the sentence. (**Page 16**).
  - **Reference 131. Signer S**, Cummings JL, Benson DF. Delusions and mood disorders in patients with chronic aphasia. *J. Neuropsychiatry Clin. Neurosci*. 1989; **1**: 40–45
- Up to now, there is no coherent pathophysiological model to explain psychosis in PWA. We explain that pathophysiological mechanisms underlying psychosis in PWA are unknown. There are no references on that.
- As repeatedly observed in studies of NPS after stroke, PWA are not represented in epidemiology studies. We have changed the sentence into "Up to now, the pathophysiological mechanisms underlying psychosis in PWA are unknown, in part, because PWA are typically excluded from stroke studies on NPS". (**Page 16**)
  - **Reference 26. Townend E**, Brady M, McLaughlan K. Exclusion and inclusion criteria for people with aphasia in studies of depression after stroke: A systematic review and future recommendations. *Neuroepidemiology* 2007; **29**: 1–17
  - **Reference 143. Stangeland H**, Orgeta V, Bell V. Poststroke psychosis: A systematic review. *J. Neurol. Neurosurg. Psychiatry* 2018; **89**: 879–885

Proof of concept study

1. Even though you mention this later in the limitations section, It would be a good idea to briefly give some rationale for including domain-specific scales for only 3 NPS. We used these three rating scales because they evaluate the most common NPS in stroke patients and because the three scales have been validated to be proxy-administered to the main informants of PWA.

2. Please provide a reference: "The HADS is a 14-item instrument evaluating both anxiety and depression (seven items for each subscale)." We have included this reference. (**Page 19**)
   - **Reference 101. Zigmond AS**, Snaith RP. The Hospital Anxiety and Depression *Scale. Acta Psychiatr. Scand*. 1963; **67**: 361–370
3. I think the word "study" is missing in this sentence: "In the present, the HADS was directly administered to the PWA." We have included the missing word (*study*). (**Page 19**)
4. SAS: is this scale valid for strokes and PWA? Would you mind providing a reference for this? Which domains of apathy are measured by the SAS?x The Starsktein apathy scale (SAS) is employed in stroke patients (Starkstein et al., 1993) and has been proxy-administered to the main career of the PWA. We have based our decision on the work of Kennedy et al. (2015) who also proxy assessed PWA with a validated apathy scale: "we defined apathy based on clinician reports using the Apathy Inventory–Clinician (AI-C) version.10 This scale is based completely on observed behavior, allowing us to include patients with aphasia".
   - **Referennce 157. Starkstein SE**, Paul Fedoroff J, Price TR, Leiguarda R, Robinson RG. Apathy following cerebrovascular lesions. *Stroke* 1993; **24**: 1625–1630
   - **Reference 112. Kennedy JM**, Granato DA, Goldfine AM. Natural history of poststroke apathy during acute rehabilitation. *J. Neuropsychiatry Clin. Neurosci*. 2015; **27:** 333–338

   We have included the following sentence in the manuscript: This scale was developed to assess apathy in patients with neurological diseases included stroke (Starkstein et al., 1993). **(Page 19).**
5. Please provide a reference: "The questionnaire has an excellent internal consistency, with a Cronbach's alpha of 0.80 and a split-half reliability of r = 0.81." We have included the reference. (**Page 20**)
   - **Reference 159. Leeds L**, Meara RJ, Hobson JP. The utility of the Stroke Aphasia Depression Questionnaire (SADQ) in a stroke rehabilitation unit. *Clin. Rehabil.* 2004; 18: 228–231

6. Not clear which studies are you referring to in this sentence: "All studies were performed on a 3-T MRI scanner (Philips Intera, Amsterdam, The Netherlands)". We have committed an error. It should have said: "The MRI sequence was acquired on…" (**Page 20**).
7. The following results are based only on the NPI? "The majority of PWA (75%) had depressive symptoms, followed by agitation and irritability (70%), anxiety and appetite/eating disorders (65%). Half of all PWA also showed symptoms of apathy and sleep disturbances were also relatively frequent (40%)." Please specify. Yes, we assessed neuropsychiatric symptoms with the NPI. The following sentence was included in the manuscript: "Based on the results of the NPI, the majority of PWA (75%) had depressive symptoms…" (**Page 21**).
8. Would you please explain or give a rationale of why is it important to include data regarding handedness? In all research studies on aphasia is mandatory to include information on handedness and years of education on a demographic data. The hemispheric organization of language function correlates with handedness. Almost all right-handed individuals have their left hemisphere dominant for language, while brain lateralization of language in left-handed individuals is more variable (left hemisphere: 70%, bilateral: 20; right hemisphere: 10%). These differences often explain why the atypical profile of aphasia is more common in left-handed PWA. Moreover, there is some evidence that the lateralization of emotions might be different in left-handed individuals compared to right-handed subjects. Left-handedness may underlie part of the association with some psychiatric disorders (schizophrenia and bipolar disorder).
    - **Cuellar-Partida G,** et al. Genome-wide association study identifies 48 common genetic variants associated with handedness. *Nat Hum Behav*. 2021; **5**: 59-70
9. Table 1: maybe include in brackets or at abbreviation what does the Barthel index measures. We have included a note in table 1 detailing that the Barthel index measures participant´s independence in activities of daily living. (**Page 48**).
10. Discussion: regarding this sentence: "The SAS, on the other hand, showed a significant interaction effect with NPI subdomains of apathy and depression. In general, it seems that proxy-rated neuropsychiatric instruments are more sensitive to

evaluate PWA than directly evaluating affected individuals themselves. In fact, outcome differences between proxy-based and directly administered instruments have also been described in other studies evaluating PWA[158]. "…might be interesting to include some thoughts regarding the role of impaired awareness in this population. We believe that PWA awareness is not the main reason why proxy-rated neuropsychiatric instruments are more sensitive to evaluating PWA. The central issue of directly evaluating PWA is affected individuals may not self-report on such measures because of cognitive or communication problems. We have rewritten this sentence as follows: "it seems that proxy-rated neuropsychiatric instruments (e.g., SADQ-10) are more sensitive to evaluate PWA than directly considering aphasic individuals themselves (e.g., HADS) because of cognitive or communication problems". (**Page 23**).

- **Reference 163. Hilari K**, Owen S, Farrelly SJ. Proxy and self-report agreement on the Stroke and Aphasia Quality of Life Scale-39. J. Neurol. Neurosurg. Psychiatry 2007; **78**: 1072–1075

11. Maybe explain briefly what the salience network is? Thank you. We have included the following paragraph in our manuscript: "The Salience Network is composed of two major hubs, anterior insula and dorsal anterior cingulate cortex. It also included three interconnected subcortical hubs: amygdala, ventral striatum, and substantia nigra/ventral tegmental area. This network, among others, contributes to complex brain functions such as communication, social behavior, and self-awareness, by means of integrating of sensory, emotional, and cognitive information." (**Page 24**)

- **Reference 167. Menon V**. Large-scale brain networks and psychopathology: A unifying triple network model. Trends Cogn. Sci. 2011; **15**: 483–506

12. Finally, in the general conclusion section, you have the following sentence: "The first study shows the very constrained number of studies targeting the diagnosis and treatment of NPS in PWA whereas in the proof-of-concept study we found high comorbidity of NPS among a small sample of PWA." If you refer to this paper as 2 studies, the first one needs to have some more specific sections/subheadings, as currently, everything is under the "Introduction" section. Also, if the first section will be understood as a study, we need some information on how you revised the

literature. We thank you once more for highlighting this critical point. Again, we have divided the manuscript into a general Introduction plus two studies (including information on how we revised the literature).

Reviewer 2: 05306560

This is a frontier article focusing on the spectrum of neuropsychiatric symptoms (NPS) in chronic post-stroke aphasia. The authors made a comprehensive review about the neuropsychiatric symptoms in people with aphasia and post-stroke aphasia. They also conducted the neuropsychiatric study in 20 patients who had a preceding stroke with the sequela of chronic aphasia. The authors concluded that NPS are frequent in the chronic phase of post-stroke aphasia This is a well-written manuscript which may provide useful information to the readers. We much appreciate the comments made by reviewer 2.

There are several points to be concerned.

1. The manuscript was too lengthy. It's better to streamline the content to make it easier to read. We agree that this is a long article and have shortened the Introduction words. We have also provided subheadings for the manuscript [Introduction (**Page 5**) and two studies: Study 1 (**Pages 7 - 16**) and Study 2 (**Pages 17 - 24**)] to facilitate reading and comprehension. Please note that the other reviewer recommended the inclusion of a section on stroke and aphasia. Therefore, we have included a brief overview of this topic.

2. Too many abbreviations can easily confuse readers. By the way, does PWA stand for person or people with aphasia? A list of abbreviations found in the text has been included (**Pages 45 - 46**), and abbreviations that appear in the text less than three times have been removed. PWA stand for persons with aphasia.

3. Would the authors summarize the neuropsychiatric symptoms as a table list? Thank you for pointing out this subject. We believe that we have provided a detailed description of all NPS reported in PSA so that the inclusion of a Table summarizing these NPS would be redundant because it may duplicate data already presented in the text.

4. For small patient groups using non-parametrical analyses, data are better expressed as median instead of mean. We thank you for pointing out this methodological aspect.

We have changed all t-student analyses to non-parametric Mann U Whitney tests and ANOVA to Kruskal-Wallis test while providing our sample's median instead of mean data. (See: statistical analysis section, **Page 20**, and results section, **Pages 21-22**).