Relationship Between Interpersonal Depressive Symptoms and Reduced Amygdala Volume in People with Multiple Sclerosis

Considerations for Clinical Practice

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Background: The lifetime prevalence of depression in people with multiple sclerosis (MS) is approximately 50% compared with around 15% in the general population. There is a relationship between depression and quality of life in people with MS and evidence that depression may contribute to disease progression.

Methods: This cross-sectional pilot study assessed the association between depression and regional brain atrophy, including amygdala and hippocampal volume. Forty-nine participants with MS recruited through a hospital MS clinic were administered the Center for Epidemiological Studies Depression Scale Revised (CESD-R) to investigate whether higher endorsements on the items depressive affect and interpersonal symptoms were associated with volumetric magnetic resonance imaging measurements of hippocampal and amygdala atrophy.

Results: Regression analysis revealed an association between depression-related interpersonal symptoms and right amygdala volume. No association was found between depression and hippocampal volume.

Conclusions: These results provide preliminary support for a unilateral, biologically based relationship between the right amygdala and characteristic interpersonal depressive symptoms expressed by people with MS and add to the growing body of literature implicating regional brain atrophy in MS-associated depression. Given that the interpersonal subcomponent of the CESD-R measures social functioning, and the neural networks in the amygdala are known to be implicated in processing social stimuli, this research suggests that targeted diagnosis and treatments for depression in people with MS may be particularly beneficial. Further confirmatory research of this relationship is required.

Multiple sclerosis (MS) is an immune-mediated neurodegenerative disease that attacks the central nervous system, causing multifocal lesions, neuronal demyelination, and brain atrophy. Common symptoms include optic neuritis, vertigo, sensory loss, urinary dysfunction, spasticity, cognitive deficits, fatigue, and pseudobulbar affect. Depression is also common in people with MS, with the lifetime prevalence estimated to be 50% compared with around 15% in the general population. Given the frequency of depression in people with MS compared with other populations with chronic and disabling illnesses, including spinal cord injury and various cancer types, it is likely that its development is an interplay between reactive and neurobiological factors.

In the general population, major depressive disorder (MDD) is commonly experienced episodically (in single or recurrent episodes) and usually lasts weeks to months before resolving either fully or partially. Conversely,
Depression in people with MS tends to have a longer duration and is comparatively stable over time compared with the otherwise medically healthy population. For example, one study reported that two-thirds of people with MS experiencing clinically significant depression at baseline were still experiencing depression at 10-year follow-up, and a large study (N = 258) found that depression scores remained relatively static 4 years after diagnosis. A longitudinal study of 132 people with relapsing-remitting MS found that higher self-reported depressive symptoms were related to frequency of relapse and that 6-month post relapse depressive symptoms remained in the moderate-to-severe range, despite remission from MS.

Furthermore, depression in people with MS may present as more labile than in patients with MDD, with symptoms of irritability, anger, and anxiety being more prominent in people with MS compared with the apathy, anhedonia, and psychomotor retardation symptoms seen more commonly in otherwise medically healthy people with depression. It is possible that these characteristics of depression, in particular irritability and anger, may be linked to impaired social function and relationship disruption, known to be a common consequence of MS.

Detecting depression in people with MS can be problematic due to symptom overlap. Symptoms such as fatigue, altered sleep patterns, changes in appetite, and impaired memory and concentration all underpin a diagnosis of depression, but they may also indicate neurologic brain changes caused by MS. As a result, depression is frequently unrecognized and often untreated in people with MS despite its major contribution to disability. Depression left untreated in people with MS significantly decreases quality of life, having potentially deleterious consequences, the most serious being suicide, with the risk being approximately twice that in people with MS compared with the general population.

The relationship between structural brain changes and depressive symptoms in MS has been extensively researched. Depressive symptoms in people with MS have correlated with brain atrophy and lesions in areas including the inferior prefrontal, superior frontal, superior parietal, and temporal lobes and whole brain atrophy, as well as with abnormalities in the normal-appearing gray and white matter in the left superior frontal and left anterior temporal regions using diffusion tensor imaging. However, associations have not been consistent. For example, a person with MS may have high lesion load/brain atrophy and very few depressive symptoms or may experience severe depression but show relatively low lesion load/brain atrophy. Some research has shown damage lateralized to the right hemisphere to be implicated in depression. Research assessing lesion load reported a right-sided temporal lobe relationship with depressive symptoms, and Nigro et al identified a communication disconnect between the right hippocampus and the amygdala and prefrontal regions using diffusion tensor imaging. It has been hypothesized that the higher rate of depression in MS may be a consequence of damage resulting in a communication disconnect with limbic system structures.

The hippocampus has been consistently found to be altered in MS-associated depression. Indeed, hippocampal and amygdala morphology have been implicated in depression in the general population, making them plausible candidates for a neurobiological substrate of depression in MS.

Psychometric scales that use total depressive symptom scores averaged across multiple domains make it difficult to identify the biological substrates of mood disturbances in people with MS. In an attempt to better identify potential neural correlates of depression in people with MS, Gold et al investigated three subcomponents derived from a factor analysis using the Center for Epidemiological Studies Depression Scale (CESD): depressive affect (loss of interest/low mood), vegetative (somatic/fatigue), and psychosocial (interpersonal/emotional). Gold and colleagues divided a sample of 109 female participants with MS into two groups: low depression (CESD score, 0-20) and high depression (CESD score, ≥21). After controlling for age, disease-modifying medication use, disease duration, and disability, they found that the high depression group showed smaller right hippocampal volume compared with the low depression group. When they analyzed the subcomponents of depression (depressive affect, vegetative, and psychosocial) with hippocampal size, they found a significant (albeit small) correlation ($r = -0.22$) between

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right hippocampal volume and depressive affect but no correlation between the vegetative and psychosocial subcomponents and hippocampal atrophy. This suggests that right hippocampal atrophy is uniquely related to the depressive affective symptoms (loss of interest/low mood) in people with MS.

Although 57.7% of the high depression group was taking antidepressants, Gold et al. did not control for antidepressant medication use. Antidepressants, particularly selective serotonin reuptake inhibitors, have been linked to reduced hippocampal atrophy in people with depression. It is possible that the neuroprotective influence of the selective serotonin reuptake inhibitors may have confounded results, contributing to the small correlation found by Gold et al. The potential mediating effect of antidepressant drug use between depressive affect and hippocampal volume requires investigation in people with MS.

Furthermore, if high symptoms of depressive affect are associated with right hippocampal atrophy, this raises the question of whether other brain regions related to the emotional dysregulation symptoms seen in MS show an association with clusters of depressive symptoms. Discussed previously herein, depressive symptoms present differently in people with MS compared with those with MDD more generally, with irritability, anxiety, personality change, and interpersonal difficulties common in MS-associated depression. The amygdala plays a key role in emotion regulation, especially fear, anger, and anxiety, and is part of a neural network sometimes referred to as the “social brain” due to its essential role in social relationships. Damage to the amygdala has been shown to heavily influence social behavior and has been associated with difficulties in interpersonal and social domains, including in people with MS.

Given that the amygdala has been implicated in depression and is a key structure in the brain responsible for emotional regulation and social interaction, and amygdala damage in people with MS is associated with poorer performance on social cognition tasks compared with controls, association between depression-related interpersonal difficulties and amygdala morphology in MS-associated depression is plausible.

Despite the prevalence of emotional disturbance in people with MS, research into the relationship between emotional expression of depression and its neurobiology is lacking. Many studies have identified specific areas of the brain that seem to be broadly related to depression; however, only Gold et al. have looked at the influence of subcomponents of depression and their neural correlates. Their study did not assess the relationship between subcomponents of depression and the amygdala or, as previously mentioned, control for antidepressant use, a potential confound on hippocampal volume. Identifying potential neural substrates related to subcomponents of depression in people with MS will improve our understanding of the mechanisms of depression in people with MS. Given the high prevalence of depression in this population, and the effect on quality of life, further research in this area is critical.

The aim of the present study was to investigate the relationship between neural structures linked to depression (the hippocampus and amygdala) and subcomponents of depression in people with MS. This study replicates and expands on that by Gold et al. by controlling for antidepressant medication use and examining the relationship between subcomponents of depressive symptoms and amygdala volume given that irritability, anger, and anxiety are common symptoms in people with MS.

**Methods**

**Participants**

People with MS attending a hospital MS clinic in Melbourne, Australia, were invited to participate in the study if they met the following inclusion criteria: 1) a confirmed diagnosis of MS, 2) a routine T1-weighted three-dimensional sagittal magnetization-prepared rapid acquisition gradient echo (MPRAGE) protocol performed at the participating hospital’s magnetic resonance imaging (MRI) department, and 3) 18 years or older. Participants were excluded if they had a severe psychiatric illness other than depression, any comorbid neurologic conditions, or severe drug- or alcohol-related issues.

**Measures**

**Depression**

Depressive symptoms were assessed using the CESD Revised (CESD-R), a 20-item self-report questionnaire that uses a 4-point Likert scale ranging from 0 (rarely or none of the time) to 3 (most or all of the time). Possible scores ranged from 0 to 60, with higher scores indicating a greater presence of depressive symptoms. Participants respond to questions about how they felt or behaved during the past week. In addition to the overall depression rating (total CESD-R), the scale was subdivided into four depression subscales based on its originally intended structure and factor analysis. The four factors were depressive affect (eg, “I feel sad”), positive affect (reverse scored; eg, “I enjoy my life”), somatic (eg, “my sleep was restless”), and interpersonal (eg, “I felt that people disliked me”). These subscales have high construct validity and reliability (Cronbach α = 0.85-0.90).

**Image Acquisition and Processing**

Participants’ routinely performed structural MRIs were accessed retrospectively for this study. The MRIs were acquired using a Siemens 3-Tesla Verio system with a 32-channel head coil. The MPRAGE protocol included three-dimensional sagittal; repetition time, 2300 ms; echo time, 3.05 ms; inversion time, 900 ms; flip angle, 9°; parallel imaging.
acceleration factor, 2; voxel size, 0.9 × 0.9 × 0.9 mm; slice thickness, 0.9 mm; in-plane field of view, 230 × 230 mm; and acquisition time, 5 minutes 30 seconds. The MRIs were processed using the FreeSurfer image analysis suite (release v4.2.5) (http://surfer.nmr.mgh.harvard.edu/), a fully automated segmentation processing stream, which has shown equivalent validity to processing with manual intervention.33 Volumes of interest included the right and left hippocampus and amygdala, as well as third and lateral ventricle width, as surrogates of brain atrophy.34 Hippocampal and amygdala volume and density were measured using surface-based volume calculations and voxel counts of total gray and white matter subcortical regions because they are considered a more accurate measure compared with total voxel addition alone.35 Intracranial volume was used to control for interindividual variations in head size and premorbid brain size.36

Procedure
After providing informed consent, participants completed a structured online questionnaire, including demographic and disease-related information and the CESD-R, which took approximately 20 minutes to complete. Retrospective MRIs were obtained from the participating hospital. The time between MRI and depression data acquisition ranged from 1 to 16 (median, 5) months. Given that depression has been shown to be relatively unremitting in people with MS compared with controls, this temporal gap was considered acceptable.3 Human research ethics approval was obtained through the hospital ethics committee.

Analyses
Power analysis using G*Power identified that an alpha of 0.05, power of 0.80, and sample size of 49 would enable detection of a small-to-medium effect of 0.24 with three predictor variables in a multiple regression model.37 Preliminary analyses were conducted to ensure that all assumptions required of linear regression were met, with no violations to normality, homoscedasticity, linearity, and multicollinearity. Missing Expanded Disability Status Scale (EDSS) scores from two participants were estimated using the expectation maximization algorithm.38 Correlation analyses were performed to identify significant relationships between demographic and disease-specific variables and depressive symptom indices and outcome variables, consistent with the requirement of independent variables to be correlated with the dependent variables in regression analysis. Only demographic and disease-related variables that were significantly correlated at $P \leq 0.05$ with the outcome variable of interest were used in subsequent hierarchical multiple regression analysis to comply with power analysis requirements for the sample size.35

In addition to disease-related and demographic variables that significantly correlated with the outcome variable of interest, intracranial volume was entered at step 1 of each regression model to control for head size variation because this has been found to have a large effect on volumetric brain analysis results.39 A regression analysis controlling for time in months between MRI and completion of the CESD-R (time between scan) was undertaken. The analysis did not change the outcome and violated the maximum number of variables for the sample size. Therefore, time between scan was excluded from the regression models. Regression modeling with time between scan can be found in Table S1 (published in the online version of this article at ijmsc.org). The depression index of interest was entered into a regression model at step 2 to identify its unique change in $R^2$. All analyses were performed using SPSS Statistics for Windows, version 21.0 (IBM Corp).

Results
Participant demographic and disease-related information is provided in Table 1. In total, 49 people with relapsing-remitting MS (85.7%) or secondary progressive MS (14.3%) subtypes participated in the study. Females composed 75.5% of the sample, reflecting the skewed sex distribution in the MS population.

Depression Scores and Brain Volumes
The total CESD-R scores ranged from 4 to 49 (mean score, 17.18). More than half of the sample (n = 28; 57.1%) scored 21 or higher on the CESD-R, classifying them as having clinically significant depressive symptoms according to the suggested cutoff score for populations with a comorbid illness.40 Less than one-third of the participants (n = 15; 30.6%) scored ≤ 10.

Table 1. Demographic and disease-related data for the 49 study participants

| Characteristic                          | Value       |
|----------------------------------------|-------------|
| Sex, M/F                               | 12/37       |
| MS subtype, RR/SP                      | 42/7        |
| Age, y                                 | 47.16 ± 10.93 [22.00-73.00] |
| Time since diagnosis, y                | 9.61 ± 6.87 [0.30-31.20] |
| EDSS score (n = 47)                    | 2.99 ± 2.23 [0.7-5.0] |
| Education                              |             |
| Secondary                              | 20          |
| Technical and further education        | 15          |
| Undergraduate                          | 6           |
| Postgraduate                           | 8           |
| Employment status                      |             |
| Unemployed                             | 17          |
| Part-time                              | 18          |
| Full-time                              | 14          |
| Relationship status                    |             |
| Single/dating                          | 14          |
| Married/de facto                       | 31          |
| Divorced/separated                     | 4           |
| Disease-modifying therapy (n = 47)     |             |
| Fingolimod                             | 19          |
| Natalizumab                            | 12          |
| Teriflunomide                          | 5           |
| Dimethyl fumarate                      | 5           |
| Interferon beta-1a                     | 2           |
| Alemzutumab                            | 2           |
| Nil                                    | 2           |
| Antidepressant medication (yes)        | 10          |

Note: Values are given as number or mean ± SD [range]. Abbreviations: EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; RR, relapsing remitting; SP, secondary progressive.
between 16 and 20, indicating a risk of depression. Only six participants (12.2%) scored less than 16, indicating no-to-minimal depressive symptoms. Means, SDs, and ranges of depression and brain volume measures can be found in Table S2.

Correlations

Demographic and disease-related variables that significantly correlated with the outcome variable of interest included sex with right hippocampus ($r = 0.33$), sex with right amygdala ($r = 0.46$), and age and EDSS score with third ventricle width ($r = -0.35$ and $r = -0.44$, respectively). These variables were entered into step 1 of the regression model with intracranial volume to control for their effects. The depressive affect index significantly correlated with right hippocampal volume ($r = -0.30$), right amygdala volume ($r = -0.30$), and third ventricle width ($r = -0.31$); total CESD-R correlated with right amygdala volume ($r = -0.31$) and third ventricle width ($r = -0.28$), and the interpersonal indices correlated with right amygdala volume ($r = -0.30$). These variables were subsequently entered into step 2 of the regression model. In contrast, there were no significant correlations between the somatic and positive affect indices and any of the brain regions of interest, or with the depressive affect or interpersonal indices and the left or right lateral ventricles, the left hippocampus, or the left amygdala. The interpersonal index was not significantly correlated with the right hippocampus or the third ventricle. See Table S3 for correlation results.

Regression

Table 2 displays the regression analyses, with relevant demographic and disease-related variables entered at step 1 and depression variables entered at step 2: step 2a, depressive affect; step 2b, interpersonal; and step 2c, total CESD-R.

Disease-related and demographic variables entered into step 1 did not show a significant relationship with the outcome variables. As shown in step 2a, the negative affective subscale did not significantly predict right hippocampal volume. However, as identified in step 2b, higher scores on the interpersonal depression subscale significantly predicted reduced right-sided amygdala volume ($F_{3,45} = 4.36, P = .04$; $B = -0.33$, 95% CI = $-0.65$ to $-0.01$). This relationship uniquely accounted for 6% of the variance in amygdala volume. Higher total CESD-R scores did not significantly predict amygdala volume, although the result was trending toward significance ($F_{3,45} = 3.50, P = .07$; $B = -0.09$, 95% CI = $-0.18$ to 0.01). As seen in steps 2a and 2c, higher negative affective depression scores and total CESD-R scores did not significantly predict third ventricle width (both $P > .05$). Figure 1 displays a scatterplot of the relationship between interpersonal depression and right amygdala volume.

Discussion

The aim of this study was to investigate the relationship between neural structures related to depression (the hippocampus and the amygdala) and subcomponents of depression (negative and positive affect, interpersonal and somatic difficulties) in people with MS. A significant relationship was found between right amygdala volume and higher scores on the interpersonal difficulties depression subscale. This relationship was independent of brain atrophy given that we did not find a relationship between third ventricle volume and this subscale or, indeed, any of the depression subscales when disease-related and demographic factors were controlled. However, we did not find negative affect to be associated with reduced right hippocampal volume, as found by Gold et al.\textsuperscript{20} Similarly, positive affect and somatic difficulties were not related to any neural regions. No correlation was found between antidepressant use and brain volume, but the sample may have been too small ($n = 10$) to detect a signal.

The relationship between the depression-associated interpersonal difficulties subscale and reduced

**Table 2. Hierarchical multiple regression analysis predicting brain volume from depression scores in the 49 study participants**

| Predictor | Right hippocampus | Right amygdala | Third ventricle |
|-----------|-------------------|----------------|----------------|
|           | $\beta$ | $R^2$ | $\Delta R^2$ | $\beta$ | $R^2$ | $\Delta R^2$ | $\beta$ | $R^2$ | $\Delta R^2$ |
| Step 1: control variables | — | 0.23 | — | — | 0.35 | — | — | 0.31 |
| Step 2a: depressive\textsuperscript{a} | $-0.21$ | 0.27 | 0.04 | $-0.18$ | 0.39 | 0.03 | $-0.18$ | 0.34 | 0.03 |
| Step 2b: interpersonal\textsuperscript{b} | — | — | — | $-0.25$ | 0.41 | 0.06 | — | — | — |
| Step 2c: total CESD-R\textsuperscript{c} | — | — | — | $-0.22$ | 0.40 | 0.05 | $-0.15$ | 0.33 | 0.02 |

Note: Demographic and disease variables in analysis (control variables): sex, age, intracranial volume. Abbreviation: CESD-R, Center for Epidemiologic Studies Depression Scale Revised.

\textsuperscript{a}Step 2a-c refer to depressed affect and interpersonal CESD-R subcomponents and overall total CESD-R score achieved, entered at second step of three separate regression models.

\textsuperscript{b}$P < .05$.

\textsuperscript{c}$P < .10$. 

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MS, particularly neuronal and functional changes to the limbic system, may contribute to interpersonal difficulties. Both bilateral amygdala damage as measured by cortical lesion volume and amygdala atrophy have been shown to be the main predictors of impaired social cognition in people with MS. The amygdala plays a key role in theory of mind, that is, the ability to infer others’ mental states, including beliefs and desires, as well as predicting and interpreting behavior. People with MS who have reduced amygdala volume perform significantly poorer on theory of mind tasks compared with controls, suggesting that social difficulties in people with MS may be in part due to an inability to read social cues or infer other people’s mental states. The finding that interpersonal depressive symptoms share a relationship specific to amygdala volume, independent of brain atrophy, may suggest that people with MS who display impairments in social cognition are at risk for interpersonal depressive symptoms. Although this was beyond the scope of the present study, it is an area for future research.

The present study’s finding that significantly smaller right amygdala volume (but not left) was related to increased interpersonal depression scores is consistent with literature supporting unilateral amygdala functions. For example, a previous study that adopted direct intracerebral stimulation in people with epilepsy found that stimulation of the right amygdala was specific to the induction of negative emotions, including fear and sadness, whereas stimulation of the left amygdala induced both positive and negative responses. Right amygdala resting-state functional connectivity has been shown to be reduced in social anxiety disorder, suggesting that disruption to the right amygdala plays a key role in social stimuli processing.

Interestingly, previous research has established a relationship between impaired social cognition and amygdala damage in people with MS without depression. This suggests that brain morphology in people with social difficulties in people with MS may be in part due to an inability to read social cues or infer other people’s mental states. The finding that interpersonal depressive symptoms share a relationship specific to amygdala volume, independent of brain atrophy, may suggest that people with MS who display impairments in social cognition are at risk for interpersonal depressive symptoms. Although this was beyond the scope of the present study, it is an area for future research.

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with MS often goes unrecognized.

Implications
A key theoretical implication of this study is that the presentation of interpersonal depressive symptoms in people with MS (higher irritability, anxiety, and social withdrawal) may be linked to reduced right hemisphere amygdala size, which provides support for a neurobiological basis for the difficulties in maintaining interpersonal relationships commonly seen in MS. This is further supported by previous research that found reduced amygdala volume and amygdala cortical lesions to be the main predictors of social cognition impairment in people with MS.

Taken together, the results of the present study and that of Gold et al suggest that there may be a right hemisphere–lateralized relationship between specific brain structures and expression of depressive symptoms. That is, in the present study the relationship between right hemisphere amygdala and interpersonal depressive symptoms was seen. Although Gold et al did not assess the amygdala, they found a relationship between the right hippocampus and depressive affect symptoms. Therefore, the results of this study support the undertaking of further research to understand whether this relationship between amygdala volume and depression-related interpersonal difficulties would be upheld in a rigorous prospective study design, as well as the relationship between right hippocampus and depressive affect found by Gold et al.

From a clinical perspective, the finding of a relationship between interpersonal difficulties and reduced amygdala volume suggests that therapeutic interventions targeting interpersonal difficulties may be advantageous for people with MS who express interpersonal depressive symptoms. This recommendation is supported by the knowledge that impaired social cognition has been linked to damage or reduced amygdala volume and is common in both depression and MS. Impaired social cognition disrupts social functioning and can result in social exclusion, withdrawal, symptoms of irritability, perceived social rejection, and perceived lack of social support. Perceived lack of social support has been linked to lower satisfaction with life in people with MS. Greater clinician awareness about the manifestation of interpersonal depressive symptoms might assist in better detection and management of depression in this population, especially given that depression in people with MS often goes unrecognized. Better identification of depression in people with MS will enable more timely and directed interventions. Interventions that target an interpersonal depressive symptom profile (where present) have the potential to improve interpersonal relationships and social connection, decreasing the risk of a cyclical depression-withdrawal process.

Limitations and Future Directions
This pilot study used retrospectively collected MRI data with a time lapse between the participants’ MRI and administration of the depression measure (median, 5 months; range, 1-16 months). However, given that depression is relatively longer in duration in people with MS compared with people without MS, this temporal gap was considered acceptable for the purposes of a pilot study. Furthermore, MS is heterogenous by nature, with well-observed variability across disease progression, clinical presentation, and MRI measures. It would, therefore, be valuable for future studies to select specific subpopulations of people with MS (eg, people with MS who have significant social cognitive disruption and those without) to better depict the relationship between specific endorsement of interpersonal depressive symptoms and potential neural substrates.

Conclusion
Given that networks in the amygdala are known to be related to processing of social stimuli, the results of this study provide preliminary support for a biologically based relationship between the right amygdala and characteristic depressive symptoms (irritability, anxiety, and social withdrawal) expressed by people with MS. This research adds to our knowledge of the neurobiological basis of depression in MS and how atrophy in particular regional structures may be expressed as specific depression symptom profiles in people with MS and warrants further confirmatory investigation.

**PRACTICE POINTS**

- Interpersonal difficulties in people with MS may be a symptom of underlying depression and should be assessed.
- This study provides preliminary support for a unilateral, biologically based relationship between the right amygdala and characteristic interpersonal depressive symptoms expressed by people with MS.
- Interventions targeting interpersonal difficulties may be advantageous for people with MS who are experiencing depression.
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