Interleukin-1 receptor accessory protein expression could link to the insula-default mode network connection and clinical depression in fibromyalgia: a preliminary exploratory study

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Abstract

Objective

The expression of interleukin-1 receptor accessory protein (IL-1RAP) and connections between the anterior insula (AI) and the default mode network (DMN) regions might contribute to the heterogeneity of clinical depression in fibromyalgia (FM). This preliminary observational study provides early insight for a further large-scale study investigating the associations among IL-1RAP expression, AI-DMN connectivity, and clinical depression in FM.

Methods

We recruited seventeen FM patients and conducted clinical assessments, serum proteomic analysis, and magnetic resonance imaging (MRI) of the brain at baseline and 1-year follow-up. We analysed serum IL-1RAP expression from the proteomic analysis. With functional MRI data, we extracted the seed-based functional connectivity (FC) z-scores between the bilateral AI and DMN regions. We performed robust linear regressions among IL-1RAP, AI-DMN FCs, and the Beck Depression Index version II (BDI-II) scores. We performed ridge regressions to examine the impact of IL1RAP and AI-DMN FC interactions on BDI-II scores at baseline and follow-up.

Results

IL-1RAP expression significantly predicted the FC between the bilateral AI and posterior cingulate cortex (PCC). The right AI-PCC FCs negatively affect BDI-II scores. In addition, the negative effects of interactions between the IL-1RAP and the right AI-PCC FCs were significant at baseline but not at one-year follow-up.

Conclusion

IL-1RAP could modulate depression through the AI and PCC connections in FM patients. The findings support further large-scale study to improve the understanding of symptomatic heterogeneity in FM.

Key word

fibromyalgia, IL-1RAP, pain, depression.

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Introduction

Fibromyalgia (FM) is a common chronic syndrome characterised by widespread pain and psychological distress (1). Depression presentation is heterogeneous among FM patients, and the exact mechanisms underlying the association between those two disorders remain uncertain (2). However, neuroinflammation (3) and genetic abnormalities (2) were considered to play roles in the underlying mechanisms.

Interleukin-1 receptor accessory protein (IL-1RAP) plays a vital role in neuroinflammation, serving as the molecular mediator between the immune system and the brain (4). IL-1RAP expression was considered a potential feature for FM identification (5). Changes in IL-1RAP expression were also associated with prenatal maternal depression levels (6). Moreover, when IL-1RAP is knocked down, the stress-induced abnormally activated hypothalamic-pituitary-adrenal pathway could occur (7). Those findings imply that the IL1RAP expression might be associated with causes of depression in FM. Further understanding of the IL-1RAP role might provide new insight into FM pathomechanisms and support future studies addressing targeted therapies in FM.

Evidence from magnetic resonance imaging (MRI) studies suggests that both brain structures and functions were altered in FM, especially the large-scale networks, such as the salience network (SAL) and the default mode network (DMN) (8). Among the SAL nodes, the insula has been considered a central region causing the heterogeneous presentations in FM, including depression symptoms (9). In addition, the functional connectivity (FC) between SAL and DMN, particularly between the anterior insula (AI) and posterior cingulate cortex (PCC), was associated with pain catastrophising in FM (10). Aberrant effective connectivity between the insula and DMN was a characteristic of depression (11, 12). Changes in the insula could predict the treatment responses of depressive patients (9). Hence, differences in functional communication between the AI of SAL and the DMN regions might also reflect depression levels in FM patients.

Given IL-1RAP roles in the immune and brain connections and the specific changes in the AI-DMN FCs in patients with FM and depression, we hypothesised that the IL-1RAP expression could impact the depression presentation modulated by insula functions in patients with FM. We conducted this preliminary exploratory study to investigate the association among IL-1RAP expression, the AI-DMN FCs, and depression level in FM.

Methods

Patients

FM patients were enrolled at Taipei Medical University (TMU) Hospital. Those patients met the inclusion requirement, reaching the ACR 2016 criteria for FM at diagnosis (13). The exclusion criteria included: 1. having any other neurological disorders, psychiatric disorders, systematic inflammation, or cancers; 2. being pregnant; and 3. having contraindications to MRI techniques.

The Joint Institutional Review Board-TMU approved the procedure of this study (N202102048). Patients gave informed consent before participating in this study. During the study period, the participants received the treatment as usual, prescribed by experienced physicians in TMU Hospital.

Clinical assessment

We used a visual analog scale (VAS) to measure pain intensity and a handheld pressure gauge to measure pressure pain threshold (PPT). We assessed patient psychological distress and sleep quality using the Beck Depression Inventory Version II (BDI-II), the Beck Anxiety Inventory (BAI), and the Pittsburgh Sleep Quality Index (PSQI). The overall impact of patients with FM was investigated using the Fibromyalgia Impact Questionnaire (FIQ). The scale details and measurements were described previously (5).

Serum collection and IL-1RAP expression by proteomic analysis

We collected blood samples of 40 millilitres from patients in the morning following overnight fasting. The serum supernatants were prepared, col-

lected, and kept at -80°C before use. A total of 750 μg of serum proteins was aliquoted for the depletion of the top 14 high-abundance proteins using a MARS Hu-14 column (Agilent Technologies, Waldbronn, Germany) with several optimisations. After depletion, 50 μg of depleted serum proteins were subjected to gel-assisted digestion with trypsin individually to collect peptides for subsequent 10-plex tandem mass tag (TMT) labelling (Thermo Fisher Scientific, San Jose, USA). TMT-labelled samples were combined for Hp-RP StageTip fractionation to generate six reversed-phase fractions, followed by duplicate analysis using an Orbitrap Fusion™ Lumos™ Tribrid™ Mass Spectrometer equipped with an Ultimate system 3000 nanoLC system and a NanoSpray interface (Thermo Fisher Scientific, Bremen, Germany). Protein identification and quantification were performed using MaxQuant (14). The mass spectrometry proteomics data were deposited in the jPOST repository with the dataset identifier PXD013905. We focused on IL-1RAP expression in the present study.

MRI acquisition, preprocessing and analysis

We acquired patients' MRIs using a 3T MRI system (MAGNETOM Prisma; Siemens). The participants were instructed to remain awake and keep their eyes closed. A 3D magnetisation-prepared rapid gradient-echo sequence obtained T1-weighted images: repetition time/echo time =2 s/2.3 ms, flip angle =8°, pixel matrix =256 x 256, voxel-size =1 mm^3, and 192 slices. A sequence collected the T2*-weighted images: repetition time/ echo time = 2.72s/24 ms, flip angle = 84°, pixel matrix = 64 x 64, voxel size = 3 mm^3, 50 slices, and interleaved order. MRI images were pre-processed using the CONN toolbox (15). Seed-to-region of interest (ROI) analyses were performed. The correlation coefficients among ROIs were calculated and transformed into z-scores. Based on our hypothesis, we extracted z-scores (FCs) among ROIs of the AI nodes and the DMN nodes, including the bilateral posterior cingulate cortices (PCC), the bilateral parietal regions (LP), and the medial prefrontal cortex (MPFC). The ROIs were defined by the network atlas in the CONN toolbox (15).

Data analysis

We expressed the data as the mean and standard deviation for continuous variables or as the ratio for the gender variable. We used pairwise deletion to handle missing values. During our data exploration, we discovered a significant outlier (more than three times the interquartile range) in the IL-1RAP variable but not in any other variables. Consequently, we excluded this outlier case from our statistical analyses.

We analysed the baseline data to establish the prior theory about the associations among IL1RAP, AI-DMN FCs, and depression level (BDI-II scores) in FM. Simple, robust linear regressions were performed to investigate whether IL1RAP expression impacts AI-DMN, whether AI-DMN FCs impact BDI-II scores, and whether IL1RAP expression impacts BDI-II scores. Bonferroni correction for multiple tests was applied. According to a previous recommendation (16), the sample size is required to be ten times larger than the number of predictors to fit the reliable regression models; our sample size might be adequate to perform simple, robust linear regression analyses. When the interaction between IL-1RAP and FC on BDI-II happens, simple regressions between them and BDI-II may not exhibit statistical significance. Therefore, we performed univariate regressions on the baseline but not the follow-up dataset to obtain the prior theory about the association among those variables.

We explored the impact of the interaction between IL-1RAP and AI-DMN FCs on clinical depression (BDI-II scores) using baseline data, then investigated whether this impact still occurred in the follow-up data. The 3D correlation charts were plotted to visualise the associations among IL-1RAP, AI-DMN FCs, and BDI-II at baseline and one-year follow-up. Given the small sample size that was not able to perform the multivariate ordinary least squares regressions, we evaluated the interaction between IL-1RAP and AI-DMN FCs on depression presentation in FM at baseline and one-year follow-up by the Ridge regression. We chose this method because it performs well with a small sample size and a large number of variables, as evidenced by its low mean squared error. We applied the leave-one-out cross-validation to find the best lambda value and performed the permutation tests to assess the significance of coefficients in those ridge regressions. We performed data analysis and visualisation using the R language (v. 4.1.2; R Foundation for Statistical Computing, Vienna, Austria) and Jeffrey's Amazing Statistics Program (v. 0.17.2.1; The JASP Team).

Table I. Patient characteristics.

	Overall (N=17)
Age	49.4 (10.2)
Gender (female/male)	16/1
PSQI	12.4 (3.84)
BAI	21.5 (12.9)
BDI	18.5 (12.6)
VAS	5.70 (2.17)
WPI	10.0 (3.76)
FIQ	54.3 (12.9)
SSS	7.35 (2.89)
PPT	1.82 (0.779)

Data are expressed as mean and standard deviation, except for gender (number female to male). PSQI: Pittsburgh Sleep Quality Index; BAI: Becker's anxiety inventory; BDI: Becker's depression inventory; VAS: Visual Analog Scale; WPI: Widespread Pain Index; PPT (kg/cm^2): pain pressure thresholds measured in kg/cm^2; SSS: Symptom Severity Scale; FIQ: Fibromyalgia Impact Questionnaire.

Results

Participant characteristics

We analysed data from 17 participants after removing an outlier. Only 15 patients provided the follow-up clinical data because the other two patients did not complete the follow-up clinical assessment. The baseline BDI scores varied from 2 to 40, indicating a range of depression levels in FM patients, from minor depression to severe depression (Table I). Other symptoms varied among patients (Table I).

Associations between IL-1RAP and AI-DMN FCs

We performed robust regression analyses with IL-1RAP expression as a predictor and each of the FC factors as an

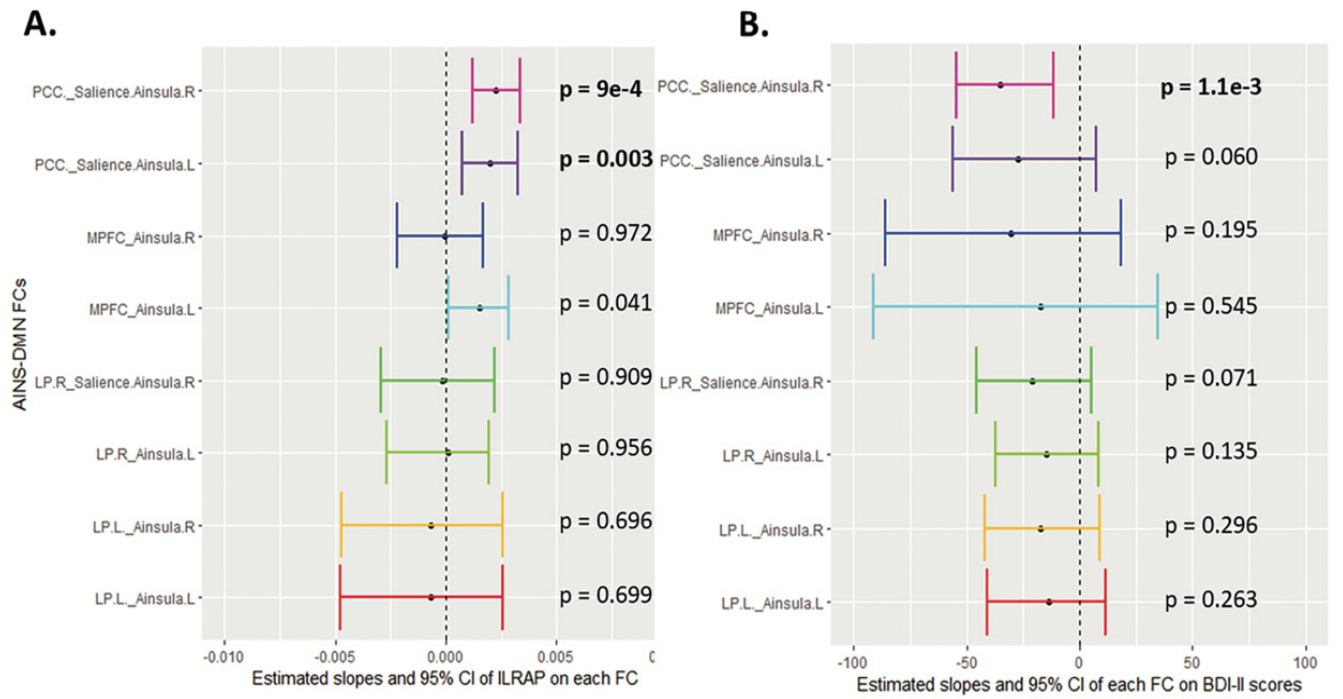

Fig. 1. The associations among Interleukin-1 receptor accessory protein (IL-1RAP), functional connectivity between the anterior insula and default mode network regions (AI-DMN FC), and depression were measured by the Beck Depression Index version II (BDI-II).
A: Forest plots showed the estimated slopes and 95% confidence intervals of IL-1RAP expression on each AI-DMN FC. Because multiple tests were conducted, only FCs between the bilateral AI and posterior cingulate cortex (PCC) were considered significant to be predicted by IL-1RAP expression after Bonferroni correction.
B: Forest plots showed the estimated slopes and 95% confidence intervals of each AI-DMN FC on BDI-II scores. Because multiple tests were conducted, and only the right AI-PCC FC were significant predictors of BDI scores after Bonferroni correction.
MPFC: medial prefrontal cortex; LP: lateral parietal regions; PCC: posterior cingulate cortex.

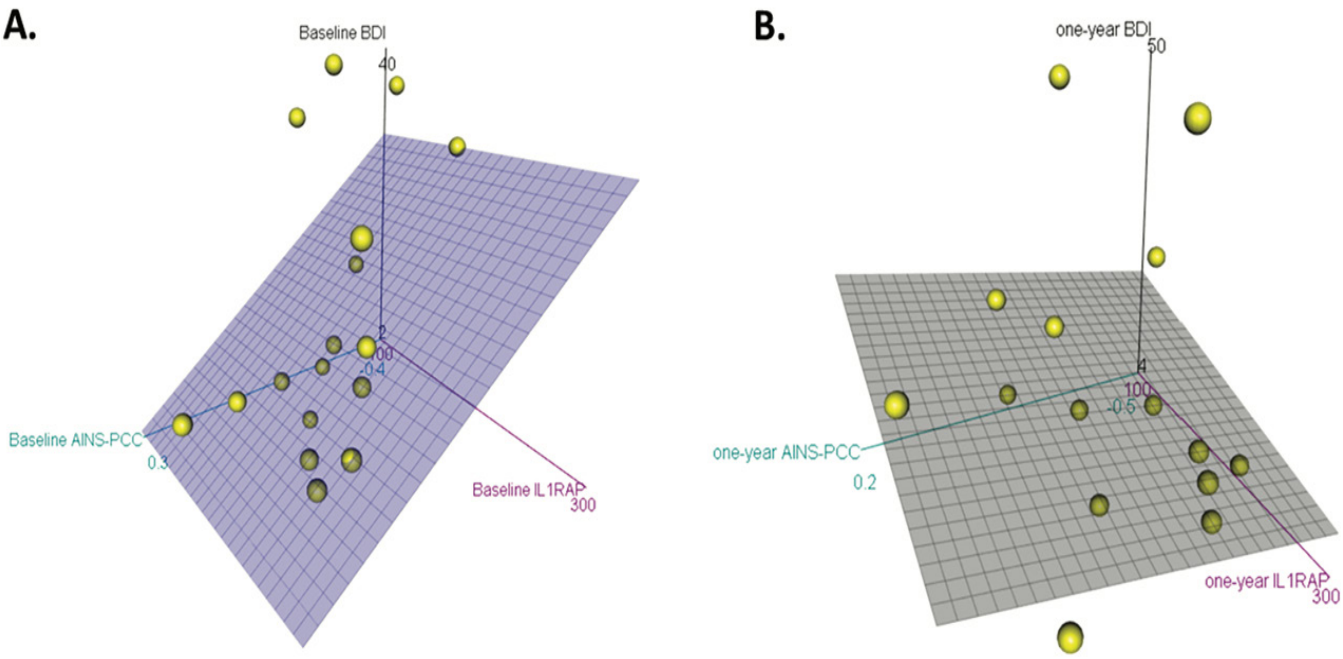

Fig. 2. The impacts of interactions between Interleukin-1 receptor accessory protein (IL-1RAP), functional connectivity between the anterior insula, and default mode network regions (AI-DMN FC) on clinical depression measured by the Beck Depression Index version II (BDI-II).
A: The 3D plot visualises the associations among IL-1RAP, the right AI-PCC FC, and BDI-II scores in FM patients at baseline. IL-1RAP expression tends to be negatively associated with BDI-II scores.
B) The 3D plot visualises the associations among IL1RAP, the right AI-PCC FC, and BDI-II scores in FM patients at one-year follow-up. Associations between IL-1RAP and BDI-II scores are also tended to be negative. Note that the follow-up data of two patients are missed, therefore the plot has constructed based on the data from 15 participants.

outcome to investigate the association between IL-1RAP expression and the changes in the AI-DMN FCs. Because we conducted eight regression tests on this hypothesis, the adjusted significant level was 0.05/8 = 0.00625. IL-1RAP expression was shown to be a significant predictor of FC from both the right AI (p=9 x 10-4; 95% CI = 1.1 x 10^{-3} to 3.4 x 10^{-3}) and the left AI to PCC (p=3 x 10-3; 95% CI = 7.8 x 10^{-4} to 3.2 x 10^{-3}), but not the other FCs (Fig. 1A, B).

Associations between AI-DMN FCs and clinical depression

To investigate the association between the changes in the AI-DMN FCs and clinical depression, we conducted robust regression analyses with each AI-DMN FC as a predictor and BDI-II score as an outcome. The adjusted significant threshold was also 0.05/8 = 0.00625. Only FC between the right AI and PCC significantly predicted BDI-II scores (p=0.001; 95% CI= -53.676 to -16.598) (Fig. 1C-D).

Impacts of IL-1RAP on depression in FM

The predictive ability of IL-1RAP expression on BDI-II scores was not significant at baseline (p=0.413; 95% CI =-0.252 to 0.109).

Impacts of IL-1RAP and AI-DMN FCs interaction on depression in FM

Given the abovementioned associations, we hypothesised that the right AI-PCC FC might interact with IL-1RAP expression to impact BDI-II scores. We plotted the 3D plots to show the impacts of IL-1RAP and right AI-DMN FCs interactions on BDI scores at baseline and one-year follow-up (Fig. 2 A-B). The ridge regression with permutation tests showed that the interaction between IL-1RAP and the right AI-DMN FCs significantly impacted BDI-II scores at baseline (p=0.011). However, at one-year follow-up, the impacts of the IL-1RAP and right AI-DMN FCs interaction on BDI-II scores did not reach statistical significance (p=0.628).

Discussion

Our study explored the associations among serum IL-1RAP expression, the DMN-AI FCs, and depression in FM. We found that IL-1RAP expression could change FCs between the AI and PCC, which might further affect depression in patients with FM. The findings suggest that neuroinflammation modulating brain functions (including insula functions) might be a potential explanation for the heterogeneous clinical presentation in FM. Our study might support a large-scale survey examining this hypothesis and future studies addressing the therapeutic effects of anti-inflammatory approaches in patients with FM.

Our study demonstrated that serum IL-1RAP expression was positively associated with bilateral AI-PCC FC in FM patients at baseline. Given that serum IL-1RAP exhibits anti-inflammatory effects in contrast to its membranous form (17), our findings suggest that inflammation could decrease FCs between the bilateral AI and PCC. Supportively, a previous study showed that inflammation reduced FCs from the insula in bipolar disorder (18). Another study showed that the activated systemic inflammation was related to reduced activity in limbic regions, including the AI (19). In addition, PCC was shown to be negatively associated with peripheral inflammation in depression patients (20). Changes in the AI and PCC connectivity were also reported in FM (10). Although the comprehensive role of the insula and DMN in inflammation has not been established, the findings imply that the insula and DMN, especially the PCC, might be inflammation targets, a typical mechanism in depression and FM.

This study found that higher FCs between the right AI and PCC were associated with a lower depression level in FM. Consistently, previous studies observed a negative association between FCs from the insula and depression levels (21). Another study demonstrated that reduced FCs from PCC are associated with depression levels (20). Evidence also shows that the insula and DMN regions are involved in emotional and cognitive processing, and dysregulation of those might be hallmarks of depression pathomechanisms (22). Our findings repeatedly emphasised this association in FM patients with comorbid depression.

In addition, the current study demonstrated that serum IL-1RAP expression interacting with the right AI-PCC FC significantly impacted depression levels at baseline but not at one-year follow-up. Our results might suggest the responsibility of AI-PCC connections in modulating the impacts of inflammation on clinical depression in FM. The AI and PCC are key nodes of the SAL and the DMN (10), and altered coupling between these regions might influence how interoceptive and immune-related signals are integrated into self-referential processing (23-25). The long-term effects of inflammation in FM have been shown to induce neural plasticity adaptation in the brain (26), especially in pain- and emotion-related networks (*e.g.* insula and cingulate regions), which might, in turn, change the effects of peripheral inflammation on depression presentation. This mechanism could partly explain why the interaction between IL-1RAP expression and AI-PCC FC was evident at baseline but not at one-year follow-up, as ongoing neuroplastic adaptation and treatment effects may weaken or remodel this specific coupling over time. In addition, reductions in depressive symptom severity and inflammatory activity over follow-up, combined with our small sample size, might also have reduced the power to detect an interaction at one year. In support of our findings, the evidence demonstrated that increased inflammation might link to depression (27), which could be heterogeneous among patients because of modulation by the insula - the brain region that could not only represent immune and inflammatory states but could also influence peripheral immune responses (9, 28). Taken together, these findings supported that interactions between peripheral inflammation and insula-based network responses, particularly AI-PCC connectivity, might explain the heterogeneous depressive presentation in FM. However, as a preliminary study with a small sample size, the hypothesis must be verified by further large-scale studies.

This pilot study has several limitations.

First, as a preliminary study, the sample size is small, which significantly limited the generalisability of the findings. We were unable to investigate the potential mediation or moderation effects. The current findings were inconclusive and exploratory, which needed to be validated in further large-scale studies. Second, we did not analyse inflammatory markers in cerebrospinal fluid or use neuroinflammation-specific imaging. In this study, IL-1RAP expression was measured in serum, which is considered a marker of systemic IL-1-related inflammatory activity rather than of direct neuroinflammation. Therefore, our findings should be interpreted as reflecting systemic inflammation that might only indirectly relate to neuroinflammatory processes in the central nervous system. Future studies should combine serum IL-1RAP with cerebrospinal fluid measurements or neuroinflammatory PET/MRI markers to clarify the relationship between peripheral IL-1RAP and brain inflammation. Finally, we could not exclude other confounding factors that could also affect depression in FM patients. We did not collect detailed data on time since FM diagnosis or on therapies individually. It should be noted that the onset of fibromyalgia symptoms is often subtle, there is frequently a discrepancy between the actual onset of the disease and the time of clinical diagnosis. Although we did ask patients about the timing of their initial symptoms, this information does not necessarily correspond to the time at which the diagnosis was formally established. Because disease duration and treatment might influence both inflammatory activity and brain network plasticity, these unmeasured factors could have affected IL-1RAP levels, AI-PCC connectivity, and depressive symptoms. However, all participants were diagnosed and were recruited from the same clinical setting with a standard treatment guideline, which may reduce (but not eliminate) extreme differences in disease course and management among patients.

In conclusion, our preliminary exploratory study suggested that IL-1RAP, a connector between immune and brain functions, and the insula-DMN connection in the brain might be associated with depression presentations. This pilot study supported a further large-scale study on this question and targeted therapies in FM.

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