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Negative interpretation of ambiguous bodily information by patients with relapsing-remitting multiple sclerosis

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ABSTRACT

Relapsing-remitting MS (RRMS) is characterised by the patients' experience of periods of exacerbation in symptoms. The fear associated with the relapse influence the quality of life in patients and their relationship with bodily experiences. Previous studies suggested that health anxiety (HA) contributes to fear of relapse but have not investigated cognitive mechanisms involved in developing and maintaining the fear of relapse in patients and we were interested to test this relationship. We used the online interpretation paradigm to investigate biased interpretation of ambiguous bodily information and its relationship to HA among patients and healthy controls (65 subjects in each group). Patients had higher levels of HA than controls. Patients also interpreted ambiguous bodily information more negatively than controls. There was a significant positive correlation between HA and negative interpretation of information in the whole sample. Among patients, HA mediated the relationship between interpretation bias and fear of relapse. Findings of this study suggest that negative interpretation bias can contribute to higher HA which in turn contributed to more fear of relapse among patients with RRMS. These findings have important implications for improving the quality of life in patients suffering from MS.

1. Background

Multiple sclerosis (MS) is a chronic neurological disease that affects the central nervous system (CNS) with a variety of neurological symptoms over multiple domains, including sensory-motor and cognitive abilities (Compston and Coles, 2008; Cook, 2001; Goodin, 2014). Data reported by the National MS Society (2020) shows that the most common initial diagnosis for MS is relapsing and remitting multiple sclerosis (RRMS) which accounts for 85–90% of newly diagnosed MS cases. Relapses are the unpredictable episodes of CNS inflammation on myelin and nerve fibres that are associated with the mentioned complications (Goodin, 2014).

MS has been suggested to be associated with major changes in the cognitive functioning of patients. Brochet (Brochet and Ruet, 2019) proposed that cognitive impairment is higher in RRMS patients compared to those diagnosed with clinically isolated syndrome. MS affects various domains of cognitive functions, including executive

functioning, attention, and memory (Chiaravalloti and DeLuca, 2008). Regarding the psychological aspect, it has been shown that even before diagnosis patients have reported negative emotional reactions like anxiety, anger, shock, fear, uncertainty and also loss of confidence (Topcu et al., 2020). Alterations in cognitive functioning is known to be associated with changes in mood and is regarded as a prognostic factor in the early stages of the disease (Oset et al., 2020).

A major burden of the disease on patients has been linked to anxiety related to the health status (Hayter et al., 2016). Previous studies have shown that approximately 25% of patients with MS experience clinical levels of health anxiety (HA; (Kehler and Hadjistavropoulos, 2009)). Cognitive models of HA propose that misinterpretation of disease-related information can contribute to elevated psychological distress in patients (Salkovskis, 1996). The model also suggests that learning experiences lead to dysfunctional beliefs about one's own health and can create secondary complications that impact a patient's quality of life (Salkovskis, 1996). To cope with the consequences of

Abbreviations: MS, multiple sclerosis; RRMS, relapsing remitting multiple sclerosis; CNS, central nervous system; HA, health anxiety; FoR, fear of relapse; IB, interpretation bias.

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misinterpretations, the patient adopts a variety of safety behaviours which temporarily reduce HA, but in the long term exacerbate the patient's HA (Warwick and Salkovskis, 1990).

Uncertainty about the course of the disease has been considered as a source of stress for MS patients (Alschuler and Beier, 2015). Previous studies have suggested that intolerance of uncertainty can contribute to the development of fear of relapse, which in turn has been proposed to be a prognostic factor of quality of life in patients with RRMS (Khatibi et al., 2021). Other studies suggested that intolerance of uncertainty in nonclinical populations is associated with bias processing of information (Dugas et al., 2005). They proposed that negative interpretation bias can contribute to fear associated with intolerance of uncertainty in ambiguous situations (Dugas et al., 2005).

No study has so far investigated biased interpretation of ambiguous bodily information among patients suffering from MS. In the current study we hypothesized that patients with RRMS tend to have negative interpretations in ambiguous situations as compared to healthy controls. We also predicted that interpretation bias in patients can increase fear of relapse through increased HA.

2. Methods

2.1. Aim, design, setting of the study

In this we aimed to compare biased interpretation of ambiguous bodily information among RRMS patients with matched control participants. We were also interested to investigate the mediating role of HA in the relationship between negative interpretation bias and fear of relapse. The design is a case-control, and the setting was a temporary experimental psychology testing set-up installed at the charity building of the place of recruitment of the patients.

2.2. Participants

This cross-sectional study was conducted with 65 patients with RRMS (36 females) and 65 control participants (36 females). Patients were randomly recruited from individuals in contact with a MS charity organization (Gol-Booteh Omid, in Tehran). Control subjects were recruited from social gathering centres by putting advertisements on public places. All participants were native in Persian language. Patients received official RRMS diagnosis from a neurologist between 1 and 7 years (3.71 ± 1.9 years). All patients were receiving their DMD medication (not specified for data protection reasons) for at least the last 9 months of their life. All participants were able to work with computers and had normal or corrected to normal vision and literacy knowledge to perform the task. Exclusion criteria included history of head and neck trauma, another patient in the family with diagnosis of a chronic disease, another comorbid neurological condition, experience of a relapse within the last month. We followed the guidelines outlined in the Declaration of Helsinki and all participants received information, both written and verbal, stating that completing the questionnaire was voluntary, anonymous, and that study results would be published. The study was approved by the ethics committee of the department of psychology, at Shahid Beheshti University.

2.3. Interpretation task

This task was implemented to examine whether participants demonstrate a biased pattern of interpretation when facing ambiguous situations. Participants completed a computerized interpretation assessment called the word-sentence correlation paradigm. A paradigm was a short scenario. First, a fixed dot appeared on the computer screen for 500 milliseconds. Then three sentences appeared on screen one after the other (500 ms to read each sentence; as an example: I was riding a bike/there was a hole in the street/tried to control the bike). Then a fourth sentence which contained a blank word appeared on the screen

(e.g., I fell and broke my ...). Next, two words that could be interpreted as threatening (e.g., hand) or neutral (e.g., bike) appeared in the middle of the screen for 500 milliseconds. The participant had to indicate which word was the first that came to their mind or was closer to the word that came to their mind by pressing the corresponding key on the response box. The next trial started immediately after the participant's response. Through the task The participants completed 50 trials. There were two familiarisation trials prior to the main block. For each participant, the rate of threatening and neutral selected sentences was calculated.

2.4. Fear of relapse scale

The fear of relapse (FoR) scale is a 26-item scale measuring fear related to the relapses in patients suffering from MS on a five-point Likert scale (0 = Never, 1 = Rarely, 2 = Sometimes, 3 = Often, 4 = Always). The questionnaires produce one total score and three scores from three following factors: fear of disability following a relapse, fear of the psychological and physiological consequences of a relapse, limitations resulting from fear, and only one item was loaded on two factors. The original version of the questionnaire was in Farsi language and is proven to be a valid and reliable measure (Cronbach alpha=0.92. Test-retest correlation=0.74) (Khatibi et al., 2020).

2.5. Health anxiety inventory (HAI-18)

The Short Health Anxiety Inventory (HAI; (Salkovskis et al., 2002)) is an 18-item self-report measure, which assesses anxiety relevant to physical health. Each item consists of four statements relevant to one aspect of health worries. Total score can vary between 0 and 54. The Farsi version of the questionnaire has been used in several previous studies and proven to be a valid and reliable measure (Cronbach's alpha = 0.75, (Rabiei et al., 2013)).

2.6. Procedure

Participants were invited to come to the office for the study. At the beginning of the session, they read the information sheet and signed the consent form. The experiment was conducted in an isolated room with each subject putting on noise cancelling headphones to perform the task. Only the participant and the experimenter were present in the room during the completion of the questionnaires and the task. The interpretation task was completed next with the experimenter out of the participants sight (in the room) during the task to not disturb them. All questionnaires were then presented on the same computer and were completed online. At the end of the experiment, the participant was debriefed, and the session was terminated.

2.7. Statistical analysis

For all analyses, we set statistical significance at <0.05 . The HAI total score and fear of relapse total score was calculated according to the instructions. Negative interpretation bias (IB) score was calculated by counting the number of threat-related resolutions chosen by the participant. Descriptive statistics were reported using statistical packages in R Studio including the basic information of the sample, the mean and standard deviation. Correlation analysis and heat map were achieved using the "Corrplot" package in R Studio. We analysed the correlation between the three variables IB, HAI, FoR. To test the mediating role of HA in the relation between a negative interpretation bias as the independent variable and fear of relapse as the dependent variable. The total effect of an independent variable on a dependent variable was shown by weight c and was composed of the direct effect of the independent variable on the dependent variable (weight c') and the indirect effect of the independent variable on the dependent variable (weight ab). Moreover, the effect of the independent variable on the defined mediator (HA) was presented by weight a . Finally, the effect of the

mediator on the dependent variable while excluding the effect of the independent variable was shown by weight *b*. The SPSS “PROCESS” macro was used for this analysis (Hayes, 2018). It should be noted that as described previously (Mohammadi et al., 2020), we calculated the significance level of direct effect (*c'*) and indirect effect (*ab*) of the independent variable on the dependent variable independently of the significance level of the total effect (*c*).

3. Result

3.1. Descriptive characteristics

Analysis of the demographics of the subjects (table 1) demonstrate that there was no difference between the patients and the control group regarding age, gender ratio or educational level of participants ($p > 0.3$).

As can be seen in table 2, performing a *t*-test on the independent samples showed that patients suffering from MS had significantly higher HA and negative interpretation bias scores than those in the control group ($p < 0.001$). These results suggest that RRMS patients demonstrate more negative interpretation of ambiguous bodily information. They also suggest that patients have higher levels of HA as compared to matched disease-free individuals.

Analysis of correlation data showed that there was a significant positive relationship between the negative interpretation bias and HA ($r(130) = 0.75$, $p < 0.001$) suggesting that increased HA is associated with more negative interpretation of ambiguous scenarios. Among patients, negative IB was positively correlated with fear of relapse ($r(65) = 0.67$; $p < 0.001$) suggesting that more negative interpretation is associated with increased fear about possible relapses in the future. Also, among patients, fear of relapse and HA had a significant positive correlation ($r(65) = 0.67$; $p < 0.001$) suggesting that the more the patients have fears about future relapses, the higher their anxiety is.

Finally, mediating analysis was used to test the mediating role of HA in the relationship between negative interpretation bias and fear of relapse.

3.2. Mediation analysis

3.2.1. Negative interpretation bias as the predictor and fear of relapse as an outcome

Our analysis demonstrated that the total effect of negative interpretation bias on patient fear of relapse (weight *c*) was significant, $r(65) = 0.675$, $p < 0.001$, $r^2 = 0.45$. Negative interpretation bias had also a significant direct effect on patient fear of relapse (weight *c'*), $r(65) = 0.378$, $p < 0.00$, $r^2 = 0.45$. Moreover, assessing the mediation role of patient HA between negative interpretation bias and patient fear of relapse revealed a significant indirect effect (weight *a*b*), $r(65) = 0.297$, $p < 0.001$, $r^2 = 0.09$. Fig. 1 summarises the mediation model.

Table 1

Demographic information (age, gender and education) among the subjects.

Variable	Group		t/ χ^2	df	p-value
	Patients	Control			
Age (mean \pm SD)	37.5 \pm 7.28	36.38 \pm 8.13	1.012	128	0.314
Sex (number in each group)					
male	29	29	0.00	1	1.00
female	36	36			
Education (number in each category)					
secondary school	21	24	1.007	3	0.80
bachelor	18	16			
master	22	23			
Ph.D.	4	2			

Table 2

Comparison of negative interpretation bias, health anxiety and fear of relapse between the MS patients and control groups (Mean \pm SD).

	Patient	Control	t	p-value
Negative interpretation bias	12.32 \pm 2.44	4.55 \pm 2.30	18.697	<0.001
Health anxiety	32.08 \pm 12.84	13.05 \pm 7.80	10.213	<0.001
Fear of relapse	60.92 \pm 25.36	–		

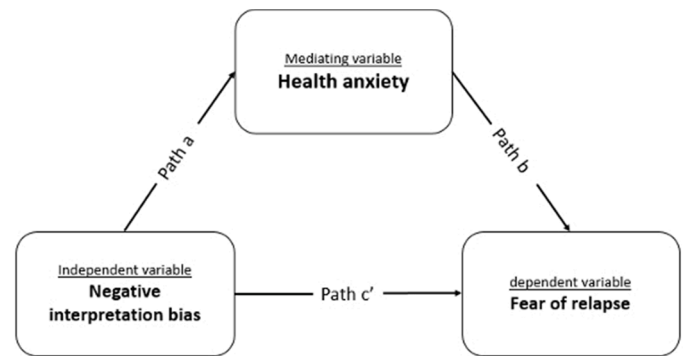


Fig. 1. Health Anxiety Mediates the relation between negative interpretation bias and fear of relapse.

4. Discussion

In this study we investigated biased interpretation of ambiguous health-related information among patients suffering from RRMS. Furthermore, we tested the relationship between interpretation bias and fear of relapse and examined whether HA in patients contributes to the relationship between interpretation bias and fear of relapse. Our results demonstrate that patients suffering from RRMS interpret ambiguous health-related information more negatively as compared to matched control non-patients. Negative interpretation bias in RRMS patients was positively correlated with fear of relapse among them showing that more negative interpretation is associated with higher levels of fear of relapse. Ultimately, we provided evidence supporting the claim that among patients, HA plays a mediating role in the relationship between negative interpretation bias and fear of relapse.

Cognitive bias in patients suffering from chronic disorders contributes to the development and maintenance of psychological problems (MacLeod and Mathews, 2012). Previous studies demonstrated that patients suffering from chronic pain show more negative interpretation of ambiguous pain-related information than other pain-free individuals (Khatibi et al., 2015). In line with the suggestion of the existing theories, our results supported our hypothesis on the negative interpretation bias for ambiguous bodily information among patients suffering from RRMS. Besides, observed negative interpretation among RRMS patients was positively correlated with patients' self-reported fear of relapse. The more individuals negatively interpreted ambiguous health-related information the higher their level of fear of relapse was. This finding is also in line with findings of studies in other clinical populations suggesting that biased processing of information is related to fears linked to the condition of the patient.

Relapses are the main characteristic of RRMS for diagnosis and play an important role in the prognosis of patients as well. They disrupt patients' daily lives and are a main source of anxiety and worry in patients (Brown et al., 2006; McCabe, 2005). The complications associated with the experience of a relapse and its consequences may lead to the development of fear of relapse among RRMS patients (Khatibi et al., 2020). Among other patient populations that live with a condition that

may have a chance of relapse or recurrence, fear has been shown to be a crucial factor in living with their condition and their quality of life (Hart et al., 2008; Herschbach et al., 2005). Previous studies also suggest that fear of recurrence (for example among breast cancer survivors) is linked to biased processing of disease-specific information among patients (Custers et al., 2015). Fear of relapse among RRMS patients has been suggested to be an important contributing factor to their quality of life (Khatibi et al., 2021). Other findings of the study by Khatibi and colleagues (Khatibi et al., 2021) suggest that HA is a contributing factor to the fear of relapse among RRMS patients. In line with the findings of the previous study, here we showed that the level of self-reported HA among patients suffering from RRMS is significantly higher than matched control disease-free participants. Indeed, it has been reported that patients with high anxiety levels, such as those with anxiety disorders, experience lower quality of life (Quilty et al., 2003). Based on these findings, some researchers suggest that a decrease in HA and associated fear can improve quality of life among patients (Hayter et al., 2016).

The mediating role of HA in the relationship between interpretation bias and fear of relapse might suggest an intervention for decrement of fear. This model suggests that more negative interpretation of ambiguous information contributes to elevated levels of HA among patients. Indeed, and in line with the findings of previous studies, increased HA is associated with heightened fear of relapse among patients suffering from RRMS. Earlier studies targeting patients suffering chronic disease suggest that management of fear is a crucial factor in the improvement of patients' quality of life (Crombez et al., 1999). Targeting fear directly is not possible in all clinical populations and may result in unavoidable complications. Management of fear can be achieved through modification of HA in patients suffering from chronic disease. An earlier study in our group suggests that a brief, multisession, computerised interpretation training is successful in reduction of HA in non-clinical population (Elhamiasl, 2019). Accordingly, based on the findings of the current study one can propose changes in HA among RRMS patients through modification of their interpretation bias. It is expected that changes in the HA can result in reduced fear of relapse in patients and improved quality of life. The existing result cannot make any conclusion and further studies are required to examine this effect and potential intervention.

Notwithstanding its novelty and importance this study has limitations that should be considered when interpreting the findings. The clinical sample and the control group were recruited separately because of the limitations in the access to unbiased participants through the charity organization. Besides, the scenarios included in the study were general health-related and not specific to complications that RRMS patients experience in their life. Future studies may benefit from development of disease-specific scenarios. Besides, although we measured HA in the current study, general anxiety as a comorbid condition may impact patients' life. Future studies may include measures related to anxiety to explore its relationship with fear of relapse and quality of life.

5. Conclusion

Here, we suggested that negative interpretation bias in RRMS patients contributes to increased HA, which acts as a mediator to indirectly lead to an increased fear of relapse. Moreover, we also demonstrated that negative interpretation bias also directly results in higher levels of fear of relapse in these patients. Future studies are needed to assess if modification of this interpretation bias can reduce HA and the ensuing fear of relapse. Furthermore, previous studies have suggested HA can be managed using methods such as cognitive behavior therapy (Cooper et al., 2017). Future work may explore if these strategies are effective in reducing fear of relapse in RRMS patients and improving their quality of life.

Conflict of interest and funding

Authors would like to declare there is no conflict of interests and the none of author have received external funding or support for this study.

Ethics approval and consent to participate

We followed the guidelines outlined in the Declaration of Helsinki and all participants received information, both written and verbal, stating that completing the questionnaire was voluntary, anonymous, and that study results would be published. The study was approved by the ethics committee of the department of psychology, at Shahid Beheshti University.

Consent for publication

No individual data is reported in the current manuscript.

Availability of data and materials

The data that supports the findings of this study can be obtained by contacting the corresponding author.

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CRediT authorship contribution statement

Parham Hosseini: Formal analysis, Writing – original draft, Visualization. **Erfan Ghalibaf:** Formal analysis, Writing – original draft, Visualization. **Ali Dehghani:** Writing – original draft, Writing – original draft, Visualization. **Ali Khatibi:** Conceptualization, Data curation, Funding acquisition, Supervision, Formal analysis, Visualization.

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