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Esophageal Hypervigilance is Prevalent across Gastroesophageal Reflux Disease Presentations

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Abstract

Background: There is a need to identify factors outside of abnormal reflux that contribute to gastroesophageal reflux disease (GERD). Esophageal hypervigilance is a psychological process impacting symptom experience in esophageal disease. However, little is known about the presence of hypervigilance in GERD phenotypes, especially in those with abnormal acid exposure or symptom index scores. The primary aim was to assess differences in self-reported esophageal hypervigilance across different GERD presentations. The secondary aim was to evaluate esophageal hypervigilance as a predictor of symptom severity.

Methods: We conducted retrospective data analyses on a cohort of adult patients with reflux symptoms that underwent 96-hour wireless pH monitoring from 9/2015 to 9/2017. Patients were stratified into groups based on the number of days they exhibited positive acid exposure time (AET; 0 days, 1-2 days, 3+ days), and symptom index scores (SI; 0 days, 1-day, 2+ days). Esophageal hypervigilance and anxiety, and symptom frequency and severity were assessed between groups.

Key Results: A total of 123 AET cases and 116 SI cases were included for analysis. Esophageal hypervigilance and anxiety scores did not significantly differ based on the number of days of positive AET ($p = .311$) or SI ($p = .118$). Symptom severity and perceived symptom frequency differed between groups. Hypervigilance significantly predicted symptom severity, when controlling for symptom-specific anxiety.

Conclusions: Esophageal hypervigilance is persistent across patients with reflux, irrespective of acid burden and symptom-reflux correlation, and significantly predicts symptom severity.

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Contributions: LG, LK, & JP were involved in the conceptualization and design of the experiment. MT, RY, & JP were involved in data collection. LG, MT, TT, & LK were involved in data interpretation and analysis. LG, TT, RY, LK, & JP were involved in drafting the manuscript. All authors provided final approval of the manuscript.

Hypervigilance should be considered as an independent factor contributing to esophageal symptom perception.

Keywords

gastroesophageal reflux; anxiety; psychological stress; behavioral medicine

Introduction

A prevailing issue in gastroesophageal reflux disease (GERD) management is the incomplete understanding of factors that mitigate or exacerbate the esophageal symptom experience. The vast heterogeneity of the GERD symptom profile results in stratification of patients across a phenotypic spectrum, making assessment and treatment difficult.^{1,2} Further, there is a disconnect between a patient's reported symptom experience (i.e. their perception of the frequency and intensity of symptoms) and the presence of abnormal acid exposure. Research in the refractory reflux population demonstrates the majority of reported symptoms are not related to reflux events or acid exposure.² In addition, more than one third of patients with normal reflux profiles on testing report abnormal reflux symptom burden.³ These outcomes suggest processes outside of reflux events and abnormal acid exposure are likely influencing a patient's symptom experience, underscoring the need for increased investigation and understanding of these factors.

Esophageal hypervigilance, or the increased awareness and amplification of esophageal symptoms and sensations,⁴ is one consideration. Highly hypervigilant patients focus their attention towards esophageal sensations, eventually developing fear of symptoms or situations they perceive may cause symptoms.⁵ This learned-fear response results in a vicious cycle of autonomic nervous system arousal, behavioral avoidance, and further reinforcement of unhelpful cognitions and beliefs about GERD symptoms and their ability to effectively manage them.^{4,5} Despite only recent conceptualization in esophageal patient populations, hypervigilance is a psychological construct studied in various mental health⁶ and medical populations.^{7,8}

Esophageal hypervigilance is implicated as a crucial process contributing to the onset and maintenance of esophageal symptoms⁹⁻¹¹ To date, the majority of hypervigilance research in reflux populations is limited to functional heartburn, due to the role of brain-gut axis dysregulation in the pathophysiology.¹²⁻¹⁴ However, a significant number of patients on proton-pump inhibitors (PPIs), the first-line treatment for GERD, experience refractory reflux,^{3,15-17} with one study finding that up to 45% of patients reported symptoms despite acid suppression therapy.¹⁷ As the refractory nature of GERD continues to pose a challenge to patients and clinicians, there is a growing interest to understand the role of esophageal hypervigilance and other psychological processes in patients across the GERD phenotypic spectrum, even in those with abnormal pathology (e.g. increased acid reflux).

The current study sought to investigate esophageal hypervigilance in a cohort of patients with GERD who underwent ambulatory pH monitoring. The primary aim was to assess for differences in self-reported esophageal hypervigilance between groups of GERD patients with varying presentations, determined by acid reflux testing results. As noted, research

in esophageal diseases has traditionally omitted the role of psychological processes in symptom perception, likely due to the belief is that the abnormal pathology accounts for the symptoms. However, given the poor symptom-reflux association² and high population of refractory symptoms,¹⁷ psychological processes, like hypervigilance may also be a factor of importance in esophageal disease patients with abnormal pathology. We hypothesized that hypervigilance would remain consistent across these groups, suggesting its role as a potential universal mechanism in GERD symptom experience. The secondary aim was to evaluate esophageal hypervigilance as a predictor of symptom severity.

Materials and Methods

The Northwestern University Institutional Review Board approved this retrospective cross-sectional study and granted a waiver of consent. Data was acquired from the Northwestern Esophageal Center Natural History Registry, a database of patients with various esophageal diseases that presented to a university-based outpatient gastroenterology clinic for ambulatory pH monitoring. Adult patients with reflux symptoms who underwent wireless pH monitoring off of acid suppression from September 2015 to September 2017 were included in the study. Patients presenting for post-lung transplant follow up or with a diagnosis of scleroderma or a motility disorder (e.g. achalasia) were excluded. The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Demographic and Clinical Data

Demographic and clinical data was collected at the time of the clinic appointment and included age, gender, and reported symptoms (e.g. heartburn, regurgitation). In addition, patients completed a questionnaire packet prior to undergoing esophageal pH monitoring to assess for self-reported clinical outcomes, including symptom severity, esophageal hypervigilance, and symptom-specific anxiety.

Symptom severity was assessed using the GerdQ,¹⁸ a six-item validated questionnaire evaluating reflux symptoms over a 7-day period. Four items considered positive predictors, are scored 0-3, while the remaining two items, considered negative predictors, are reverse scored (3-0). Scores range from 0-18, with higher scores indicating more severe symptoms. A score of eight is designated the cutoff for diagnosing GERD, while a score of six is considered normal.

Esophageal hypervigilance and symptom-specific anxiety was assessed using the Esophageal Hypervigilance and Anxiety Scale (EHAS).¹⁹ The EHAS is a 15-item validated questionnaire evaluating psychological symptom experience over the preceding month. The EHAS consists of two subscales, one measuring esophageal hypervigilance and the other evaluating symptom-specific anxiety. Scores from each subscale can be analyzed separately or pooled for a total score, which ranges from 0-60. Higher scores indicate greater esophageal hypervigilance and/or anxiety.

Ambulatory pH Monitoring

All patients underwent ambulatory esophageal pH monitoring off of acid suppression for up to 96-hours using a wireless pH capsule (Bravo™ pH System; Medtronic, Minneapolis, MN). The pH monitoring data was evaluated for completeness to ensure accuracy, and incomplete data was excluded. Several data variables were captured during the monitoring process, including the number of perceived reflux episodes (symptom frequency), the percentage of time esophageal pH < 4.0 (acid exposure time, [AET]), and the correlation between reported symptoms and pathological acid exposure (symptom index, [SI]).

Reflux Stratification

Data was organized into four distinct days, one for each of the four consecutive 24 hours of monitoring time. In accordance with standardized cutoffs, a day with an AET greater than 6% was considered positive AET and a day with a symptom index score greater than 50% indicated positive SI.²⁰ Next, patients were stratified into groups depending on the number of days of positive AET and SI. Patients were first divided into three groups based on the number of days they exhibited positive AET (0 days, 1-2 days, 3+ days). For SI outcomes, patients were initially grouped using the same breakdown as the AET group (0 days, 1-2 days, 3+ days). However, due to lack of patients in the 3+ days SI group, patients were stratified into groups based on 0 days, 1 day, 2+ days of positive SI. Thus, the data was stratified twice, once for each of the two physiological variables (AET and SI). Stratification was modeled after a recent paper that assessed longitudinal outcomes of acid exposure by grouping patients based off of the number of days they exhibited positive AET.²¹ It should be noted that esophageal pH monitoring alone is not sufficient to categorize patients into the established clinical GERD phenotypes (e.g. erosive esophagitis, nonerosive reflux disease, reflux hypersensitivity, functional heartburn) and other considerations, such as endoscopic findings and PPI responsiveness are required.¹

Statistical Analysis

Statistical analyses were performed using IBM SPSS v25 for Windows operating systems (Chicago, IL). First, all eligible AET cases were selected for analysis. Descriptive statistics evaluated mean, median, standard deviation, range, frequency, and percentage. Independent samples t-tests, one-way Analysis of Variance (ANOVA) with Tukey post-hoc, and Pearson's Chi Square tests assessed for differences in clinical and demographic variables between the groups (0 days AET, 1-2 days AET, and 3+ days AET). For non-normally distributed data, non-parametric Mann-Whitney U test and Kruskal-Wallis H Test with Dunn's post-hoc were applied where appropriate. The same statistical methodology was repeated for all eligible SI cases.

For our primary analyses, a one-way ANOVA with Tukey post-hoc test analyzed differences in EHAS scores across the three AET and SI groups. Subset analyses were performed to assess differences in the hypervigilance and anxiety subscales of the EHAS across the same groups. Pearson's correlations evaluated relationships between all relevant continuous variables. Hierarchical linear regression assessed hypervigilance and anxiety as a predictor of symptom severity. For this model, any relevant demographic variable that significantly correlated with symptom severity ($P < .05$) was included in the model.

Results

One hundred and seventy-two patients presented for pH monitoring between September 2015 and September 2017. Sixteen cases were excluded due to non-reflux related symptoms. Of the remaining 156 eligible cases, an additional 33 AET cases and 40 SI cases were excluded due to incomplete pH monitoring data. Thus, a total of 123 AET cases and 116 SI cases were included for analysis.

Demographic and Clinical Characteristics

Demographic and clinical characteristics are displayed in Table 1. Overall, patients were middle-aged (mean = 50.0 +/- 15.4) and majority (64%) female. For acid exposure, 49 (40%) had 0 days positive AET, 44 (36%) had 1-2 days positive AET, and 30 (24%) had 3+ days positive AET. With regards to symptom index, 72 (62%) exhibited 0 days positive SI, 23 (20%) exhibited 1-day positive SI, and 21 (18%) exhibited 2+ days positive SI. No significant differences were observed for age or gender between the three AET or SI groups.

Esophageal hypervigilance and anxiety scores were comparable to the EHAS initial validation sample.¹⁹ The mean GerdQ was above the standardized cutoff of eight, for both AET and SI groups, and the median self-reported symptom frequency was 7 (AET group) and 6.5 (SI group) symptoms per day, indicating both groups were relatively symptomatic.

Clinical Comparisons between GERD Presentations

Our main aim was to evaluate esophageal hypervigilance across GERD profiles. As predicted, total EHAS scores did not significantly differ based on the number of days of positive AET ($p = .311$) or SI ($p = .118$). These findings remained consistent when hypervigilance and anxiety subscales were examined individually (Table 2).

Symptom severity significantly differed between the number of days of positive AET (8.7 vs. 9.4 vs. 10.4; $p = .038$) and number of days of positive SI (8.8 vs. 9.8 vs. 10.9; $p < .01$). Tukey post-hoc analyses revealed the group exhibiting 3+ days of positive AET reported higher GerdQ scores compared to those with 0 days positive AET ($p = .029$). Similarly, patients with 2+ days of positive SI reported higher GerdQ scores compared to those with 0 days of positive SI ($p < .01$). Median self-reported symptom frequency also differed between AET (5.0 vs. 8.0 vs. 6.0; $p = .035$) and SI (4.0 vs. 7.0 vs. 12.0; $p < .01$) groups. Dunn's post-hoc analyses demonstrated that patients with 1-2 days of positive AET reported more symptoms ($p = .029$) than the patients with 0 days of positive AET. For SI groups, the 1 day ($p = .046$) and 2+ days ($p < .001$) of positive SI groups reported significantly more symptoms compared to individuals with 0 days of positive SI (Table 2).

Predictors of Symptom Severity in GERD

Total EHAS scores were significantly correlated with increased symptom severity for both AET ($r = .225$, $p < .05$) and SI ($r = .232$, $p < .05$) groups. When broken down by hypervigilance and symptom-anxiety subscales, these relationships remained significant. Age was also significantly associated with GerdQ scores, with younger patients reporting more severe GERD symptoms (AET: $r = -.272$; SI: $r = -.262$, all $p < .01$).

A series of hierarchical linear regression evaluated predictive factors contributing to symptom severity separately for the AET and SI groups (Table 3). For the first regression, age was entered into the model at Step 1 and EHAS Total Score entered at step 2 with GerdQ score set as the criterion variable. For both AET and SI groups, age and total EHAS scores significantly predicted symptom severity. Additional regression analyses entering age at Step 1 and the EHAS subscales, hypervigilance and symptom anxiety, at Step 2 evaluated how each contributed to symptom severity outcomes. While the hypervigilance and anxiety subscales were similarly correlated with symptom severity, regression analyses established age and hypervigilance as significant predictors of symptom severity scores for both AET and SI groups, while symptom anxiety was removed from the regression model as a non-significant predictor.

Discussion

The current study sought to evaluate esophageal hypervigilance in patients with reflux symptoms who underwent wireless esophageal pH monitoring. In line with our hypothesis, esophageal hypervigilance did not differ between patients depending on the number of days of positive AET or SI, even while other variables such as symptom severity and perceived symptom frequency did. In addition, hypervigilance significantly predicted symptom severity while symptom-specific anxiety was non-significant. Implications of these findings include advancement of our theoretical understanding of esophageal hypervigilance and esophageal symptom perception more broadly. The first finding, self-reported esophageal hypervigilance is consistent across reflux groups, demonstrates that esophageal hypervigilance is pervasive patients with reflux symptoms, independent of physiological outcomes such as acid exposure. The second finding, hypervigilance is significantly and independently associated with symptom severity, highlights the significance of why hypervigilance is an important process to study in the context of esophageal symptom perception.

Findings suggest that hypervigilance is present across patients with reflux, irrespective of acid burden or correlation between perceived symptoms and reflux events. This has implications for our current understanding of the factors involved in the onset, maintenance, and exacerbation of esophageal symptom perception more broadly. The pathophysiology of GERD is multifactorial and includes processes such as reflux exposure, mucosal permeability, and visceral hypersensitivity related to tissue inflammation, as well as underlying central sensitization.²² Psychological comorbidity, while considered, has traditionally been attributed to individuals with functional heartburn and reflux hypersensitivity as a way to conceptualize symptom perception for individuals who lack pathological reflux. Therefore, there may be an inclination to assume hypervigilance, considered a psychological process, would be more prominent in patients reporting symptoms in the absence of physiological abnormality (e.g. pathological reflux) compared to patients who exhibit physiological abnormalities that can “explain” such symptoms. Our findings challenge this current understanding by demonstrating hypervigilance is prevalent across GERD disease presentations, even in individuals with abnormal reflux. These findings enhance our theoretical understanding of esophageal hypervigilance and the factors that impact esophageal symptom perception, and shifts the narrative from esophageal

hypervigilance being a psychological process only important in patients with disorders of gut-brain interaction (e.g. reflux hypersensitivity and functional heartburn), to acknowledging hypervigilance as a potential process influencing esophageal symptom perception in general. In other words, increased attention to the esophagus and esophageal sensations may be a process that influences esophageal symptom perception more broadly, not just in those with reflux hypersensitivity or functional heartburn.

Previous research in esophageal-specific hypervigilance supports our findings. Prior to the development of the EHAS, a number of studies administered an adapted version of the Pain Vigilance and Awareness Questionnaire²³ to assess vigilance to heartburn symptoms in patients with persistent reflux. One study evaluated physiological and psychosocial variables in a sample of PPI non-responsive reflux participants that were stratified into four distinct GERD phenotypes. Results demonstrated hypervigilance scores did not significantly differ between the four groups.¹¹ A 2017 study assessed a myriad of factors associated with symptom perception in PPI non-responders that were categorized into three groups (Normal, Abnormal, Reflux Hypersensitivity) based on 24-hour pH-impedance monitoring results. While physiological outcomes, such as total acid exposure time, number of reflux episodes, and the number of reflux-associated symptoms differed between the three groups, psychological outcomes, such as dysphagia-related distress, quality of life, and hypervigilance to heartburn, remained consistent.³

In addition to hypervigilance, symptom-specific anxiety remained stable across patient groups. Psychological processes, including general and symptom-specific anxiety, are implicated as important factors in symptom perception in patients with GERD.^{24–26} Interestingly, one study in the Netherlands found the functional heartburn population reported significantly higher anxiety levels compared to the GERD patients, while anxiety levels between the GERD and reflux hypersensitivity patients did not differ.²⁷ One reason for potential differences in our findings could be the authors used the Hospital Anxiety and Depression Scale, a measure of general anxiety symptoms, as opposed to our study, which evaluated symptom-specific anxiety. While there is understandable overlap between the two, symptom-specific anxiety is a unique construct that encompasses worry, fear, and concern directly related to the symptoms themselves. Patients who do not meet criteria for generalized anxiety can still endorse symptom-specific anxiety and it is important this construct is addressed when working with patients with GERD. The study did not assess for aspects of general psychiatric functioning, such as measures of clinical anxiety and depression (e.g. HADS), known psychiatric disorders, and psychopharmacological use, and we therefore could not exclude or control for these potential confounding variables. Based on research, such as the aforementioned study, evaluating psychiatric diagnoses in functional heartburn compared to GERD,²⁷ is hypothesized that patients with normal pH may have higher levels of clinical anxiety and depression compared to those with more days of positive AET and/or SI. It is unclear if this would impact the rates of hypervigilance, as no research to date has assessed impact of clinical depression or anxiety on hypervigilance. However, it is hypothesized that processes involved in anxiety (e.g. worry, catastrophizing) may exacerbate hypervigilant behavior. Future research should control for these variables and explore the relationship between psychiatric diagnoses, such as anxiety and depression, on hypervigilance and attention to symptoms.

Esophageal hypervigilance and symptom anxiety were positively correlated with increased symptom severity as quantified by the GerdQ. Patients that are hypervigilant are focused on bodily sensations, which in turn, may increase the perceived frequency and severity of symptoms.²⁸ In addition, hypervigilance results in an activation of the body's sympathetic nervous system, which initiates a systemic stress response.⁶ Stress can influence symptom perception, tissue permeability and esophageal motility,^{26,29,30} and may modulate perceptual responses to esophageal acid, regardless of esophageal mucosal inflammation.³¹ In terms of anxiety, both general and symptom-specific anxiety are associated with increased symptom severity in patients with GERD.^{27,32} Patients experiencing anxiety may worry and catastrophize about symptoms, resulting in a tendency to report increased intensity or frequency of symptoms. It should be noted that the GerdQ reflects symptom frequency and does not assess other aspects of symptom severity, such as symptom intensity. Thus, a high GerdQ score may indicate the person is experiencing frequent symptoms but does not necessarily reflect the intensity or the interference of such symptoms. This results in limitations to our conclusions regarding hypervigilance and symptom severity. In addition, this may be one explanation for why GerdQ scores were different across groups, but hypervigilance scores were not. The SI score, like the GerdQ is reflective of self-reported symptom frequency, and it therefore makes sense that self-reported symptom frequency was different between the days of positive SI score. Hypervigilance appears to be independent of symptom-frequency scores. It is unclear if these results would change if symptom severity included a measure of intensity. Intensity ratings reflect symptom perception and can be influenced by psychological processes like fear and symptom-specific anxiety.^{33,34} Thus, there is some evidence to suggest if symptom severity was evaluated in the context of symptom intensity, results for symptom severity may also remain consistent across groups. Future research should consider evaluating symptom severity using measures that encapsulate the full experience of symptom severity.

Younger patients reported more severe reflux symptoms, which was also consistent with similar studies.^{3,35} One explanation for these findings could be that younger patients are more newly diagnosed with GERD. Individuals recently diagnosed may not have adjusted to the disease or found an adequate treatment regimen, resulting in more severe and frequent symptoms. However, due to the retrospective nature of the study, age of symptom onset cannot be determined, but should be considered in future research.

Finally, given the similar associations between hypervigilance and anxiety subscales with symptom reporting, we conducted regression analyses to evaluate which constructs had the greatest impact on symptom severity scores. Age and hypervigilance significantly predicted symptom severity while symptom-specific anxiety was non-significant. Prior research identifies heartburn-related hypervigilance as an independent driver of symptom reporting in PPI non-responsive reflux patients, responsible for up to 50% of the variance in GerdQ scores.¹¹ Our study is unique in that it demonstrated that between the two EHAS subscales, hypervigilance is the main driver of symptom severity scores and while anxiety was important, it was not as detrimental to outcomes.

While our study exhibits several strengths, including stratification of patients based on objective physiological measures, there are several limitations that should be discussed.

First, the retrospective study design prohibited us from controlling for several demographic and clinical variables that may be important, such as race, socio-economic status, age of symptom onset, weight, length of diagnosis, and comorbid mental health conditions. In addition, our sample size is small and patients were not equally distributed across the AET and SI groups. This is particularly apparent in the SI group, which had a very small number of patients exhibit three or four days of positive SI. Future, prospective research should aim to address these limitations by including a large sample of patients with a variety of demographic and clinical variables.

In conclusion, esophageal hypervigilance is persistent across patients with reflux, irrespective of acid burden and SI score, and significantly predicts symptom severity, even when controlling for symptom-specific anxiety. These results demonstrate the role of hypervigilance as an independent factor contributing to the onset and maintenance of esophageal symptom perception. Future research should aim to address the role of psychological processes in reflux symptom experience across all phenotypes and presentations of reflux, even in those with abnormal acid reflux profiles.

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Table 1.

Demographic and Clinical Characteristics for AET and SI Samples

Variable	AET Group (N = 123)	SI Group (N = 116)
Age (mean \pm SD)	50.0 \pm 15.4	50.1 \pm 15.4
Female	79 (64%)	74 (64%)
Total Symptoms [†]	7.0 (0-117)	6.5 (0-117)
GerdQ (mean \pm SD)	9.4 \pm 2.9	9.4 \pm 2.9
EHAS Total	31.3 \pm 13.6	31.1 \pm 13.8
Hypervigilance	12.14 \pm 5.68	12.10 \pm 5.68
Anxiety	19.19 \pm 8.78	19.00 \pm 8.86

[†]Self-reported symptom frequency presented as Median (range)

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Table 2.

Comparisons in Demographic, Clinical, and Psychological Variables between AET and SI groups

	AET Sample				SI Sample			
	0 Days (N = 49)	1-2 Days (N = 44)	3+ Days (N = 30)	P-Value	0 Days (N = 72)	1 Day (N = 23)	2+ Days (N = 21)	P-Value
Age	47.53	52.73	50.00	.267	49.92	52.96	47.33	.482
GerdQ	8.71	9.43	10.40 [‡]	.038	8.76	9.78	10.90 [‡]	<.01
Total Symptoms [‡]	5.00	8.00 [‡]	6.00	.035	4.00	7.00 [‡]	12.00 [‡]	<.01
EHAS Total	29.35	33.68	31.33	.311	29.08	35.30	33.38	.118
Hypervigilance	11.67	12.66	12.13	.709	11.51	12.87	13.24	.365
Anxiety	17.67	21.02	18.97	.183	17.57	22.43	20.14	.057

[‡]Self-reported symptom frequency presented as median scores and analyzed using Kruskal Wallace Test

[‡]P < .05 compared to 0 Day positive AET/SI group

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Table 3.

Hierarchical Linear Regression for Predictors of Symptom Severity in AET and SI Samples

	R²adj	β	SE	P
AET Sample				
Model 1	.067			.002
Age		-.272	.016	
Model 2	.092			.038
Age		-.244	.016	.006
EHAS Hypervigilance		.183	.044	.038
EHAS Anxiety		.070		.604
SI Sample				
	R²adj	β	SE	P
Model 1	.061			.004
Age		-.262	.017	
Model 2	.093			0.27
Age		-.238	.017	.009
EHAS Hypervigilance		.201	.046	.027
EHAS Anxiety		.065		.652

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