Gluten-induced Neurocognitive Impairment
Results of a Nationwide Study

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Goals: This study aimed to understand the neurocognitive symptoms associated with gluten exposure in individuals with self-reported celiac disease (CD) and nonceliac gluten sensitivity (NCGS).

Background: While gluten-induced neurocognitive impairment (GINI; eg, "celiac fog" or "brain fog") is commonly described by individuals with CD and NCGS, there are little data regarding the prevalence and symptoms associated with these experiences.

Study: A 9-question online survey was accessed by 1396 individuals (1143 with CD; 253 with NCGS). Forced choice and free-response questions were asked of participants to obtain a description of neurocognitive symptoms experienced after gluten ingestion. Free-response answers were coded using a coding structure developed based on the Health-Related Quality of Life Instrument.

Results: The majority of survey participants (89% of CD and 95% of NCGS) reported having GINI symptoms. When describing symptoms, the most common word descriptors for both groups were difficulty concentrating, forgetfulness, and grogginess. Timing of symptoms, including onset and symptom peak, were similar across the 2 groups. Coding of free responses found the most common references were to cognitive, physical, psychological, and overall quality of life impacts.

Conclusions: This survey suggests that GINI is common and may be severe in both individuals with CD and NCGS. Cognitive impairment and decline in physical functioning may be similar to that occurring in other illnesses, such as lupus. Clinical follow-up with both individuals with CD and NCGS should include assessment of GINI symptoms. Further research is warranted, including the development of a patient-reported outcome measure including neurocognitive effects of gluten exposure.

Key Words: celiac disease, gluten-induced neurocognitive impairment, brain fog

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Celiac disease (CD) is a systemic autoimmune disease induced by the ingestion of proline-rich and glutamine-rich gluten proteins in wheat, rye, and barley in genetically susceptible individuals. While the hallmark of CD is small intestinal mucosal injury, this disorder is characterized by a diverse clinical spectrum that ranges from asymptomatic to severely symptomatic illness.[1–5] Although multiple novel therapies are under investigation, a strict life-long gluten-free diet (GFD) is the only treatment currently available.

Life-long adherence to the GFD can be extremely challenging. Although GFD adherence rates in individuals with CD are generally quite high, inadvertent gluten exposure is common and can occur for a variety of complex reasons.[6] Individuals with CD can accidentally ingest gluten due to cross-contamination or poor GFD knowledge. Logistical factors such as reliance on packaged and convenience foods, poor access to gluten-free foods due to increased cost and geographical restrictions or psychological barriers can impede adherence and results in complex symptom presentations.

Classically, CD was understood to predominantly result in gastrointestinal symptoms including diarrhea, bloating, and gas. However, it is now recognized that CD affects multiple other body systems and is associated with a wide range of extraintestinal manifestations including central and peripheral nervous system conditions such as seizures, ataxia, peripheral neuropathy, as well as various neurological disorders such as chronic headaches, restless

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legs syndrome, developmental delays, and attention deficit hyperactivity disorder.[7–11] Less frequently described in the literature, but commonly expressed in clinical practice, is a constellation of neurocognitive symptoms known as gluten-induced neurocognitive impairment (GINI; often referred to by the patient community as "brain fog"), which includes transient mental confusion, as well as cognitive impairments to memory, attention, executive function, and processing speed.[12,13]

Despite being reported by patients in both clinical and community patient support settings, GINI has received minimal attention in the CD literature to date. Few studies have specifically looked at acute neurocognitive dysfunction in CD in a setting of acute exposure to gluten. This represents a significant gap in our understanding of a potentially common manifestation of CD, which may be highly impactful on individuals with CD and their families. To provide a better understanding of acute gluten-induced neurological symptoms, we conducted an online survey of individuals with CD and nonceliac gluten sensitivity (NCGS) regarding the specific clinical symptoms they experience associated with gluten exposure that are referred to when using the umbrella term "brain fog." An additional goal was to uncover the patterns of neurocognitive symptoms in terms of frequency and duration within and between persons with CD and NCGS.

MATERIALS AND METHODS

Participants and Recruitment

Individuals with self-reported CD and NCGS were recruited to participate in the study through an announcement of a survey entitled "Gluten Exposure and Brain Fog" that was sent by e-mail to the then 22,000 contact database of a US-based CD patient advocacy organization with an international presence, Beyond Celiac (formerly National Foundation for Celiac Awareness). This database was comprised of mainly white (93%), females (85%) with self-reported CD or dermatitis herpetiformis (82%) contacts. In addition, the study announcement was posted to the social media platforms (Facebook and Twitter) of Beyond Celiac.

Measures

Participants completed a questionnaire designed to assess neurocognitive symptoms after gluten exposure. The self-report questionnaire asked for statement of CD/NCGS diagnosis and method of diagnosis. Participants were asked if they experienced neurocognitive symptoms after ingesting gluten and if so the type of symptom experienced, including attesting to the presence or absence of 5 symptoms commonly described in the CD/NCGS community (difficulty concentrating, mental confusion, forgetfulness, detached, grogginess). The timing of the symptom onset, the peak of symptoms, and length of time until symptom resolution was also assessed. In addition, participants could share descriptions of their neurocognitive symptoms with open-ended responses.

Development of Qualitative Coding Schema and Coding Process

A coding schema was developed to describe, analyze, and better understand neurocognitive symptoms in individuals with CD/NCGS and to analyze the qualitative, open-ended survey responses provided by respondents. The Health-Related Quality of Life Instrument (HRQoL), as well as preliminary neuropsychological assessment (CogState) data collected by these investigators in a double-blind placebo control study of gluten exposure and neurocognitive symptoms in individuals with CD/NCGS, were used as the basis for the initial development of the coding structure.[14] The initial draft of the coding schema was reviewed by experts in gastroenterology, nutrition, psychology, neuropsychology, and neurology, and feedback was incorporated into the final structure used for qualitative analysis. Table 6 details the coding labels, including cognitive, motor, physical, psychological, impact to quality of life (QoL), burden of disease and symptom presentation, ameliorators, and exacerbators domains.

A deductive content analysis was performed independently by 2 coders, and on each open-ended response obtained. Both coders assessed each response and notated specific strings of text within the full response with a thematic code, referred to as nodes, which were derived from the coding schematic. Parent nodes consisted of broad categories of subjective effects that respondents described, and therefore each coder labeled specific strings of text to reflect the content of the response. Coders could further notate responses with a child node, or codes signifying a specific subtheme of the broader category/parent node. For example, a coder could identify a cognitive deficit inherent in the content of a response, notating it with parent node *1.0—cognitive impact*. If the response suggested a more precise annotation, the coder could use a child node such as *1.05—executive function*, or *1.06—psychomotor function*.

A reconciliation process was completed to resolve disagreements in the coding between the 2 coders. It consisted of a collaborative review with both coders in which coding disagreements were examined to reach agreement. Each text reference was exported to an Excel spreadsheet, and disagreements were highlighted based on the text and codes applied to the text. Each of these disagreements were deliberated between both coders to determine why the disagreement occurred and whether the disagreement could be reconciled. Disagreements occurred for a number of reasons, the majority being differences in the specific text coded. For example, on some occasions, 1 coder highlighted a full passage and coded it to a specific node, while the other coder split the passage into segments and directed the same code the first coder used to each segment. Several other disagreements were resolved by removing a code for a specific text reference. For example, 1 responder wrote "hard to make decisions." Coder A coded the entire reference as *cognitive impact* while coder B coded the entire reference with both *cognitive impact* and *psychological impact*. After deliberation, the coders agreed that the *psychological impact* code was not representative of the response, therefore, agreement was achieved by removing the code.

RESULTS

Descriptive statistics were calculated to describe and summarize the demographic and neurocognitive characteristics of the participants in Microsoft Excel. Survey responses were qualitatively analyzed using NVivo 11 (QRS International), a qualitative data analysis computer software package that is used to organize, analyze, and derive themes from unstructured or qualitative data. The free text, open-ended question responses were reviewed and coded by 2 independent coders using the coding schema. Coders reconciled all discrepancies in codes assigned, coming to agreement when possible.

TABLE 1. Percentage of Respondents Who Had CD or NCGS, and the Method by Which They Report Being Diagnosed

Method of Diagnosis	CD (n = 1143)
Diagnosed by serology and biopsy	52.4%
Diagnosed by serology alone	27.8%
Diagnosed by biopsy alone	19.8%
	NCGS (n = 253)
Diagnosed by physician	50.6%
Self-diagnosed	49.4%

CD indicates celiac disease; NCGS, nonceliac gluten sensitivity.

Demographic/Disease Specific Factors

A total of 1396 individuals with self-reported CD and NCGS accessed the survey. 73.2% of participants completed all items in the questionnaire (not including the open-ended responses). 1143 participants (81.9%) reported being diagnosed with CD (52.3% by both small intestine biopsy and serology, 19.7% from small intestine biopsy alone, and 27.7% by serology alone). 253 participants (18.1%) reported having NCGS (50.6% diagnosed by a physician and 49.4% were self-diagnosed) (Table 1).

Neurocognitive Symptoms

Neurocognitive symptoms after gluten exposure were reported by 90.1% of participants (89% of CD and 95% of NCGS). The most common descriptor reported was difficulty concentrating (72.4% of CD participants, 75.5% of NCGS participants), followed by forgetfulness (60.3% of CD participants, 65% of NCGS participants), and grogginess (58.2% of CD participants, 69.2% of NCGS participants). 45.3% of participants with CD and 57.4% with NCGS labeled their GINI as mental confusion. 47.3% of participants with CD labeled it as detached, along with 54% of the participants with NCGS. 25.3% of participants with CD and 30.4% of participants with NCGS elected to provide their description of neurocognitive symptoms in the open-ended "Other" question that were subsequently thematically analyzed. Figure 1 shows the percent of each group that selected each description.

Table 2 shows the reported timing of onset, peak, and duration of GINI. The onset of symptoms after gluten exposure was most often reported between 30 minutes to 1 hour after ingesting gluten in both CD and NCGS participants (20.6% CD, 23.0% NCGS). The majority of participants reported their symptom peak occurred in the first 24 hours after gluten ingestion. Participants most commonly reported GINI lasting 1 to 2 days (26.7% CD, 30.4% NCGS).

Thematic Analysis

Thematic analysis is conducted to derive themes from unstructured data, often inductively where content categories are extrapolated to derive conclusions about the overall data set. This study employed a deductive approach, whereby meaning is inferred with reference to a general principle, that being in this study, respondents' experiences of GINI manifested relative to QoL concepts (as in the HRQoL). Deductive analysis allowed us to confirm or disconfirm, from the text responses provided by respondents, whether the a priori template of HRQoL is a relevant configuration for characterizing GINI. Furthermore, by enumerating the thematic codes used across all responses, we can begin to identify the most prevalent patterns evident in respondents' descriptions of GINI.

The final coding schema consisted of 9 primary categories (parent nodes) and 52 corresponding subcategories (child nodes; total n = 61, Table 6). Of 61 total parent and child nodes, 20 child nodes were unused by the coders (32%). *Cognitive impact* and *physical impact* received the greatest number of coding references, while *psychological impact* and *QoL* impact received the third and fourth most coding references, respectively. Figure 2 depicts a hierarchy of node coding relative to the number of text references assigned to the node.

A cluster analysis was conducted, and results are shown in Tables 3 and 4. Table 3 presents the top 10 2-set parent

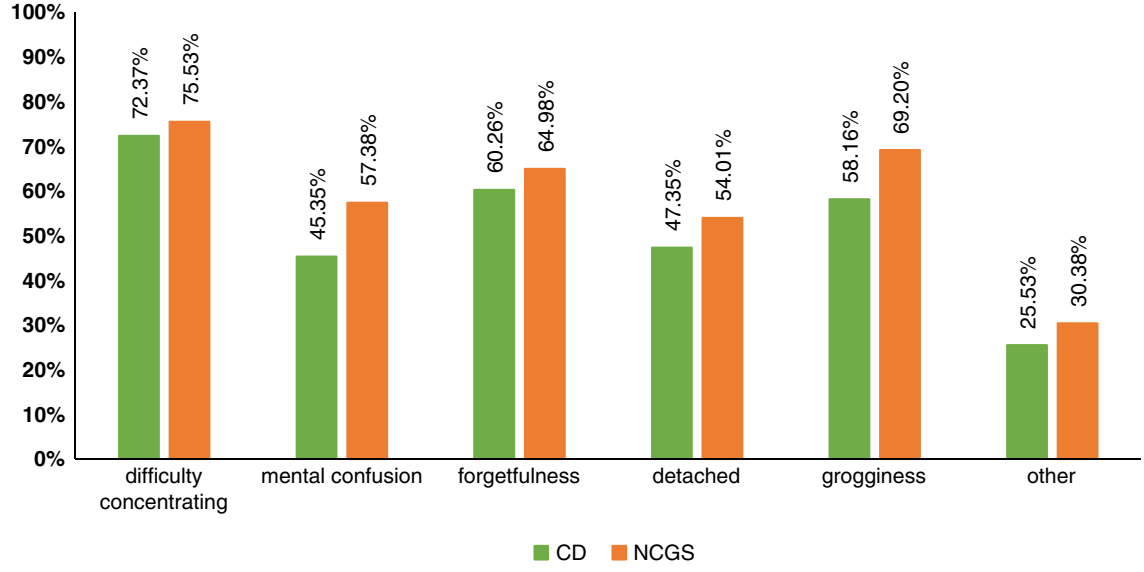

FIGURE 1. Categorization of participants' responses to "please define brain fog as related to your symptoms." CD indicates celiac disease; NCGS, nonceliac gluten sensitivity. full color online

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TABLE 2. Timing of Symptom Onset, Peak, and Resolution for CD and NCGS Participants

Onset of Symptoms (N = 1023)	n (%) CD	n (%) NCGS	χ^2 (*df*)*	*P**
< 30 min	141 (17.2)	33 (16.2)	4.89 (5)	0.43
30 min-1 h	169 (20.6)	47 (23.0)		
1-2 h	122 (14.9)	41 (20.1)		
2-4 h	97 (11.8)	21 (10.3)		
4-12 h	149 (18.2)	31 (15.2)		
> 12 h	141 (17.2)	31 (15.2)		
Symptom peak (n = 1022)				
< 1 h	67 (8.2)	20 (9.8)	4.36 (6)	0.63
1-4 h	230 (28.1)	62 (30.4)		
4-8 h	134 (16.4)	28 (13.7)		
8-24 h	130 (15.9)	38 (18.6)		
1-2 d	182 (22.2)	43 (21.1)		
3-5 d	43 (5.3)	9 (4.4)		
> 5 d	32 (3.9)	4 (2.0)		
Symptom resolution (n = 1022)				
< 1 h	28 (3.4)	1 (0.5)	14.70 (6)	0.02
1-4 h	112 (13.7)	26 (12.7)		
4-8 h	86 (10.5)	27 (13.2)		
8-24 h	95 (11.6)	24 (11.8)		
1-2 d	218 (26.7)	62 (30.4)		
3-5 d	166 (20.3)	50 (24.5)		
> 5 d	113 (13.8)	14 (6.9)		

*χ^2 test for independence.
CD indicates celiac disease; NCGS, nonceliac gluten sensitivity.

node clusters which are clustered by word similarity; Table 4 presents the bottom 10 2-set clusters. Parent nodes that have many words in common were clustered by a similarity metric, in this case the Pearson correlation coefficient, indicating similarities and differences between the nodes.[15]

The clusters shown in Tables 3 and 4 represent relationships between parent nodes based on the similarity of words contained in the text responses to which the thematic codes were assigned. The categories of *things that make symptoms worse* and *duration of symptoms* were the most similar whereas *burden of illness* and *motor impact* were the least similar. (Only parent nodes were included in this analysis and child nodes were aggregated into the parent nodes.) Figure 3 depicts a dendrogram of the top 50 most common words clustered by co-occurrence (ie, words that appear together or are near each other in the text). Using the calculated similarity index between words (ie, Pearson correlation coefficient), items were grouped using the complete linkage (farthest neighbor) hierarchical clustering algorithm.[16] Ten clusters were derived for the dendrogram, and each cluster is depicted by color in Figure 3. In both the node and word cluster analyses, stop words were excluded.[16]

Coder Comparison

Interrater reliability was evaluated using NVivo 11's coding comparison function with text characters as the unit of analysis (total codable characters n = 28,541), and results are presented in Table 5. Interrater reliability was evaluated with percentage agreement metrics and Cohen κ, which accounts for random agreement.[18] Agreement between coders on any given node consisted of the number of text characters coded by both coders, as well as characters not coded by either coder. Disagreement was measured by the number of characters coded by 1 coder but not the other. Agreement based on κ values was poor to excellent across the 9 parent nodes, and on average agreement was good (mean = 0.63). The coders agreed the most on text references to *things that make symptoms better* (κ = 0.85), while they disagreed the most on *burden of illness* text references (κ = 0.02).

A total of 319 disagreements were identified among the 590 references (54.1%), and 292 of them were eventually

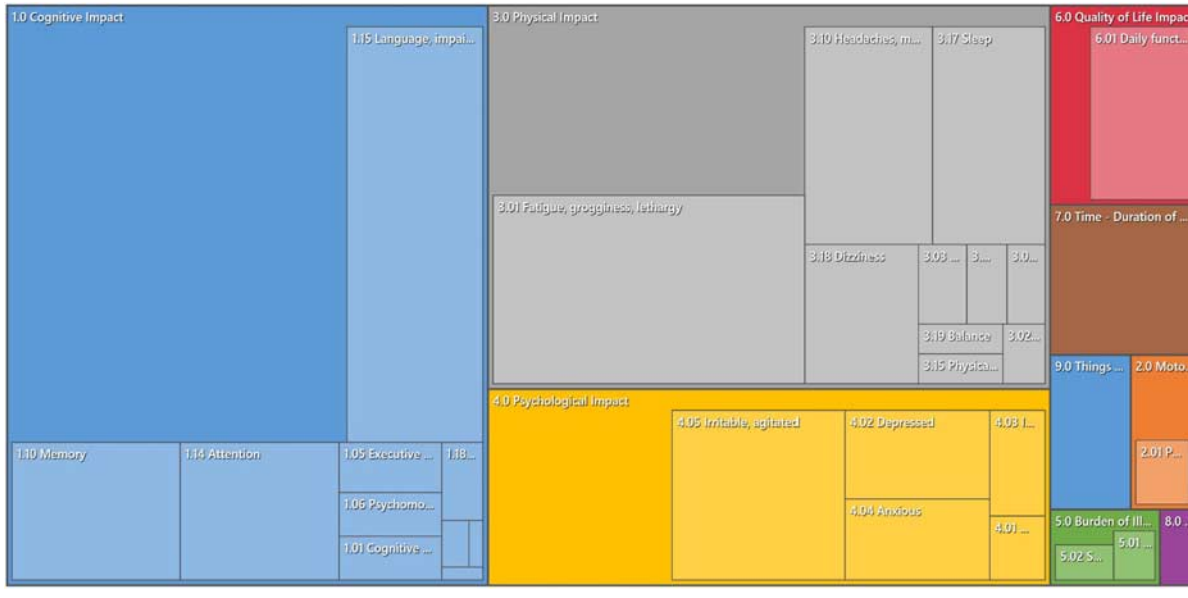

FIGURE 2. Hierarchy of node coding relative to number of text references assigned to the node. Hierarchy of child nodes depicted within parent nodes. As it is defined on NVivo's help website, "size indicates amount" and "map is scaled to best fit the available space so the sizes of the rectangles should be considered in relation to each other, rather than as an absolute number"[3(para2)]. Thus, this figure represents which nodes and child nodes received the most coding references based on the number of characters assigned to the node.

TABLE 3. Top 10 2-set Parent Node Clusters

Node A	Node B	*r*
Things that make symptoms worse	Time—duration of symptoms	0.449
Things that make symptoms worse	Things that make symptoms better	0.352
Quality of life impact	Cognitive impact	0.345
Psychological impact	Physical impact	0.253
Things that make symptoms better	Time—duration of symptoms	0.213
Things that make symptoms worse	Physical impact	0.206
Things that make symptoms worse	Quality of life impact	0.203
Cognitive impact	Physical impact	0.203
Things that make symptoms worse	Burden of illness	0.185
Quality of life impact	Physical impact	0.164

Nodes that have a higher degree of similarity based on the occurrence and frequency of words are shown clustered together.
Similarity determined by Pearson correlation coefficient.

reconciled (92%). Final agreement for the entire data set was 95.4%. Furthermore, new codes (n = 18) were added on several occasions when coders deemed it necessary. Finally, most irreconcilable differences (n = 27) were the result of responses considered to be ambiguous by both coders. While they made grammatical sense, many of these responses used vague words or colloquialisms that did not embody any specific coding category. For example, 1 responder wrote "used to feel like a black cloud blocked reality." One coder considered the full response to be a *psychological impact*, while the other found it to be a *cognitive impact*. Both coders eventually agreed to code it with *psychological impact*, but 1 coder still felt it necessary to label it with *cognitive impact*. Consequently, agreement was not achieved on that particular reference.

DISCUSSION

In this cross-sectional study of individuals with CD and NCGS, 90% reported acute neurocognitive symptoms as a result of gluten ingestion. The 3 most frequent symptoms reported were trouble concentrating, forgetfulness, and grogginess which are consistent with the lay terminology of "brain fog" to describe this phenomenon. The clinical significance is demonstrated by the finding indicating that more than half of the respondents reported that symptoms lasted

TABLE 4. Bottom 10 2-set Parent Node Clusters

Node A	Node B	*r*
Burden of illness	Physical impact	0.047
Burden of illness	Psychological impact	0.044
Quality of life impact	Motor impact	0.034
Things that make symptoms better	Psychological impact	0.033
Things that make symptoms better	Cognitive impact	0.025
Time—duration of symptoms	Motor impact	−0.004
Time—duration of symptoms	Psychological impact	−0.009
Things that make symptoms better	Motor impact	−0.020
Things that make symptoms worse	Motor impact	−0.021
Burden of illness	Motor impact	−0.041

Nodes that have a higher degree of similarity based on the occurrence and frequency of words are shown clustered together.
Similarity determined by Pearson correlation coefficient.

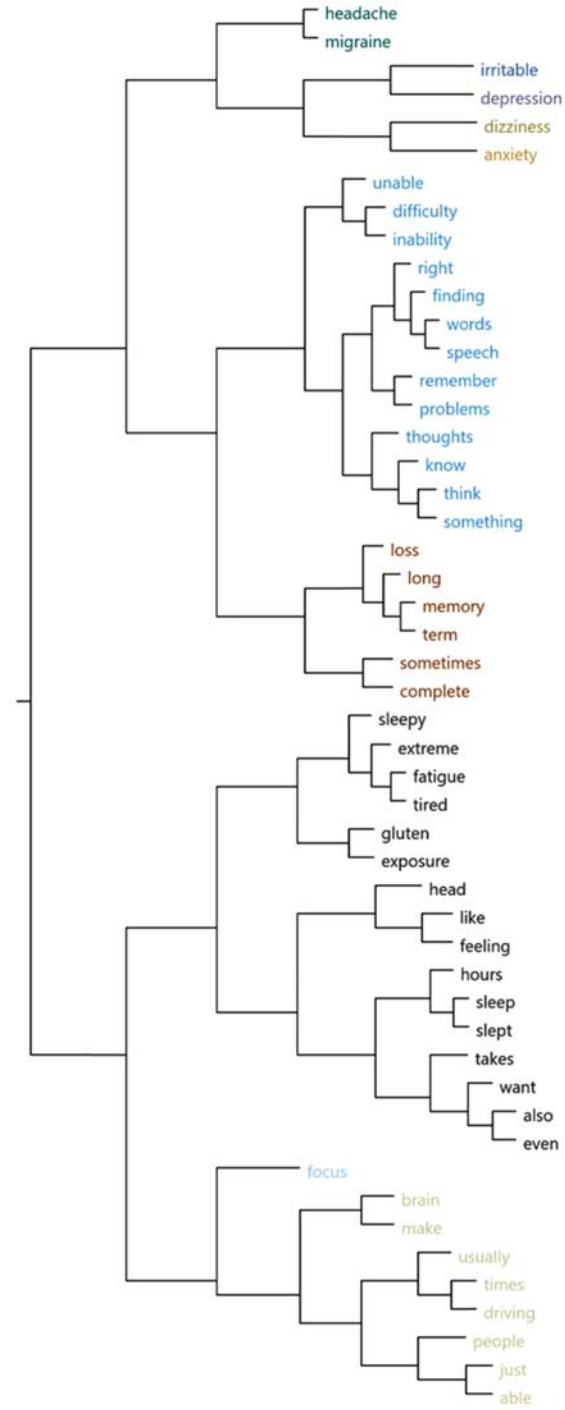

FIGURE 3. Cluster map of top 50 most common words clustered by co-occurrence (ie, words that appear together or are near each other in the text). Clusters were determined using a similarity index between words (ie, Pearson correlation coefficient), and items were grouped using the complete linkage (farthest neighbor) hierarchical clustering algorithm.[16,17] full color online

1 to 2 days or longer, suggesting a potential significant impact on activities including work and school. The majority of respondents also indicated their symptoms started within 2 hours of gluten ingestion. While the true

TABLE 5. Inter-rater Reliability Analysis

Parent Node	κ (0.95 Confidence Interval)	Agreement (%)	A and B (%)	Not A and Not B (%)	Disagreement (%)	A and Not B (%)	B and Not A (%)
1.0	0.66 (0.653-0.670)	83.22	36.84	46.38	16.78	8.74	8.04
2.0	0.43 (0.379-0.492)	98.66	0.52	98.14	1.34	0.00	1.34
3.0	0.65 (0.641-0.664)	88.99	14.13	74.87	11.01	3.41	7.60
4.0	0.40 (0.381-0.423)	92.17	3.06	89.11	7.83	0.93	6.90
5.0	0.02 (0.000-0.066)	94.70	0.12	94.58	5.30	1.78	3.52
6.0	0.13 (0.099-0.156)	89.31	0.96	88.35	10.69	0.61	10.08
7.0	0.68 (0.669-0.703)	95.54	5.24	90.30	4.46	1.28	3.17
8.0	0.85 (0.832-0.905)	99.80	0.58	99.21	0.17	0.00	0.17
9.0	0.27 (0.236-0.306)	94.93	1.02	93.91	5.07	0.52	4.54
Average	0.63	93.04	6.94	86.10	6.96	1.92	5.04

Text characters were the unit of analysis (total codable characters n = 28,541). Interrater reliability was evaluated with Cohen's κ, which accounts for random (by chance) agreement. Definitions of metrics are as follows: A and B = the percentage of words coded to the selected node by both coders; not A and not B = the percentage of words coded by neither coder; Agreement = sum of columns A and B and not A and not B; A and not B = the percentage of words coded by coder A but not coder B; B and not A = the percentage of words coded by coder B but not coder A; Disagreement = sums of columns A and not B and B and not A.

rate of NCGS and CD patients with neurocognitive impairment from gluten ingestion cannot be determined from a self-selected group of survey respondents, the large number of respondents reporting similar symptoms suggests that GINI may be a common manifestation of gluten related disorders. This result highlights the importance of including GINI clinical assessment as part of routine follow-up care in individuals with CD/NCGS.

These findings are consistent with other recent data providing evidence that neuropsychiatric effects may be frequent in a representative CD population. In a prospective cohort, 67% of patients who were newly diagnosed with CD were found to have neurological abnormalities based on clinical evaluation and magnetic resonance imaging findings.[19] Those with antitissue transglutaminase (tTG-6) autoantibodies were found to have significant loss of gray

TABLE 6. Coding Categories (Nodes) Derived From the Development of the Coding Schema

1.0 Cognitive Impact	1.09 Visual attention - vigilance	1.14a Attention and calculation	3.0 Physical Impact	3.09 Low energy	3.18 Dizziness	5.01 Medical burden
1.01 Cognitive ability - IQ	1.10 Memory	1.14b Attention and working memory	3.01 Fatigue, grogginess, lethargy	3.10 Headaches, migraines	3.19 Balance	5.02 Social burden
1.02 Disinhibition	1.10a Visual learning - memory	1.15 Language, impaired speech, expressive aphasia	3.02 Pain or discomfort in upper abdomen or the pit of the stomach	3.11 Food cravings	4.0 Psychological Impact	6.0 Quality of Life Impact
1.03 Hyper-excitability	1.10b Verbal learning and memory	1.16 Repetition	3.03 Nausea	3.12 Appetite	4.01 Detached	6.01 Daily functioning
1.04 Visual motor function	1.10c Recall	1.17 Complex commands	3.04 Rumbling in the stomach	3.13 Health related to celiac disease	4.02 Depressed	7.0 Time Duration of Symptoms
1.05 Executive function	1.11 Orientation to time	1.18 Confusion	3.05 Bloating	3.14 Health in general	4.03 Intoxicated	8.0 Things that make Symptoms Better
1.06 Psychomotor function	1.12 Orientation to place	2.0 Motor Impact	3.06 Diarrhea	3.15 Physical pain	4.04 Anxious	9.0 Things that make Symptoms Worse
1.07 Detection tasks	1.13 Registration	2.01 Psychomotor speed	3.07 Sensation of not completely emptying bowels while going to the bathroom	3.16 Physical comfort	4.05 Irritable, agitated	
1.08 Spatial problem solving	1.14 Attention	2.02 Basic motor skills	3.08 Hunger pains	3.17 Sleep	5.0 Burden of Illness	

Green nodes are parent nodes, which establish an overall thematic category. Orange nodes are child nodes, which further refine the parent node (note: child nodes 1.10 and 1.14 also contain child nodes). Gray nodes are child nodes that were not assigned to any text references by either coder. Parent nodes serve both as a codable node and an aggregate of itself and child nodes.

matter in the thalamus, a region responsible for consciousness and alertness. Anti-tTG-6 autoantibodies have also been observed to be elevated in CD patients with other neuropsychiatric conditions including schizophrenia and ataxia.[20,21]

Results from our qualitative analysis shows that the most referenced themes in open-ended responses concerned *cognitive* (node 1.0 in Table 6), *physical* (3.0), *psychological* (4.0), and *QoL* (6.0) impacts. Coding for *things that make symptoms worse* and *duration of symptoms* had the highest degree of similarity, whereas coding for *burden of illness* and *motor impact* diverged the most. This result provides potential insight into the impact of neurocognitive symptoms on QoL and aligns with common frameworks for evaluating similar symptoms in other diseases/illnesses where impairment in both cognitive functioning and activities of daily living are present. Results of the coding comparison show moderate agreement across most primary thematic categories, with the highest agreement on coding for *things that make symptoms worse*. Weak κ values on coding for *burden of illness* and *QoL* indicated low interrater agreement for these thematic categories. Reconciliation of qualitative codes resulted in 92% agreement on previously disagreed coding.

The coding schema developed through this qualitative analysis allows for increased clarity for health professionals in identifying GINI and assessing its impact on individuals with CD/NCGS. In addition, this framework may be utilized to enable effective patient-provider communication in other disease areas where neurocognitive symptoms are also significantly impacted, novel, and not yet well-understood. Findings from this study may be critically relevant for uncovering the disease burden of the SARS-CoV-2 pandemic and COVID-19 illness, where neurocognitive impairment is increasingly recognized as substantial and long-term. For example, 1 cross-sectional (preprint) study found that 58.7% of hospitalized COVID-19 survivors exhibited neurocognitive impairment in at least 1 cognitive domain, while low mental component QoL was detected in 39.1% of patients.[22] Our finding may assist in improved assessment of neurocognitive symptoms and consequently improved patient-provider communication of such symptoms in individuals with CD and NCGS, as well as other complex diseases, with neurocognitive symptoms.

This study used a self-report, retrospective design and as such an inherent limitation of this study is the potential for voluntary response bias as individuals who believe they experience, have experienced or regularly experience GINI may have been more motivated to participate in the survey. As a result, the prevalence and frequency of neurocognitive symptoms after gluten exposure described here may not be representative of the general CD clinical patient population. Despite this, we believe that the themes revealed allow for improved understanding of GINI and can be used in guiding the design of future studies. Standardized, norm-referenced neurocognitive assessment in biopsy-confirmed CD patients at baseline and after controlled gluten-exposure should be utilized with control groups for comparison to best understand GINI individuals with CD. In addition, extensive collection of demographic and disease-specific characteristics of the sample should occur to determine whether the individuals in the study are a representative sample of the target population for generalization purposes. Nonetheless, this study can help to improve the limited understanding that clinicians and researchers may currently have regarding the postgluten ingestion "brain fog" experiences that individuals with CD/NCGS regularly describe clinically.

Up to this point, GINI has received very little attention in the medical literature. Lichtwark et al[23] studied 11 newly diagnosed patients with CD and found improvement in several neurocognitive tests from baseline to follow-up at 1 year, but there was no assessment of the degree of acute impairment following gluten ingestion. Yelland,[12] in reviewing the literature on acute neurocognitive impairment referred to these types of problems as "subclinical." Yet our data indicates that the neurocognitive impairment is not simply an inability to perform at the normal level on neurocognitive testing but is of sufficient severity to impact an individual's functioning.

This discrepancy between what individuals with CD and NCGS are reporting and what has been studied so far highlights several important points. First, there needs to be more investigation of these symptoms to determine the true prevalence of GINI and the mechanisms by which gluten can induce these symptoms in both CD and NCGS. Second, as part of such research, it is important to be aware that patients use a variety of terms to describe their neurocognitive symptoms and not all patients or their health care providers will interpret words such as "feeling groggy" or "detached" in the same way. Next, as part of this research the impact of GINI on individual's educational, work, and social functioning as well as on societal domains, such as health economics, should be further explored. Finally, as we look forward to clinical trials evaluating therapies for CD beyond the GFD, it is important to include acute neurocognitive impairment symptoms as part of patient-reported outcomes assessment measures in clinical trials.

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