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Severity and Correlates of Brain Fog in People with Traumatic Brain Injury

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Abstract

Brain fog is one symptom that has been underexplored in traumatic brain injury (TBI). We explored the cognitive and affective correlates of brain fog in people with symptomatic mild TBI (n = 15), moderate-to-severe TBI (n = 15), and a healthy control group (n = 16). Measures across the studies assessed "brain fog" (Mental Clutter Scale), objective cognition (Useful Field of View® and Cogstate Brief Battery®), post-concussive symptoms (Post-Concussion Symptom Scale), and depressive symptoms (Profile of Moods Scale). Brain fog was higher in symptomatic mild TBI and moderate-to-severe TBI compared to healthy controls. Greater brain fog corresponded to greater depressive symptoms in symptomatic mild TBI. Greater brain fog corresponded to poorer episodic memory and working memory in moderate-to-severe TBI. Brain fog appears to reflect challenges in recovery, including depressive symptoms and worse cognitive function. Screening for brain fog might be worthwhile in people with brain injuries.

Keywords

traumatic brain injury; concussion; cognition symptoms; depression

Every year, two million people in the United States suffer external, kinetic force to the brain causing traumatic brain injury (TBI) (Frost et al., 2013), which can be either mild, moderate, or severe. As defined by the Mayo Clinic classification system, one of many taxonomies, moderate-to-severe TBIs involve injuries that result in significant loss of consciousness (>30 minutes) and posttraumatic amnesia (>24 hours), while mild TBI remain less severe or even asymptomatic (Malec, 2007). In symptomatic mild TBI and moderate-to-severe TBI considerable difficulties arise for cognition, involving trouble remembering or learning information, thinking quickly, paying attention, and everyday problem solving (Schretlen & Shapiro, 2003). Considerable research has described the wide array of performance-based cognitive difficulties experienced after a TBI. Still, we know less about the full profile of

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self-reported cognitive symptoms, which may provide useful information about a patient before in-depth assessment.

Self-reported cognitive symptoms can range across multiple abilities and likely depend on injury severity (Schmand et al., 1996). For mild TBI, common symptoms include trouble remembering, concentrating, and slowed thinking (de Boussard et al., 2005; Ponsford et al., 2011). While most objective cognitive problems resolve weeks to months after injury, self-reported cognitive symptoms endure up to 8 years after injury and are greater than in uninjured controls ($d = .75$) (Dean et al., 2012). Enduring self-reported cognitive symptoms can indicate cognitive deficits or other functional difficulties due to brain damage. In moderate-to-severe cases, self-reported cognitive symptoms typically indicate difficulties in memory and problem solving (Corrigan et al., 2004) that can last anywhere from two ($d = .62$) to 24 years ($d = .12$) post injury (Corrigan et al., 2004; Gardner et al., 2017; Hart et al., 2005).

One self-reported cognitive symptom receiving increased attention is “brain fog,” which has been revived in the clinical literature due to being a hallmark feature of SARS-Cov-2 infection (e.g., Asadi-Booya et al., 2022). Brain fog is a common colloquial term used in patient groups and clinics and has been operationalized as self-reported problems in memory, attention, and processing speed coupled *with a lack of mental clarity* (Katz et al., 2004; Nelson & Esty, 2015; Theoharides et al., 2015). Evidence for this self-reported cognitive symptom comes from post-concussion symptom screeners originally asking about feeling “fogginess” or “in a fog,” which showed a broad range of prevalence in the symptomatic mild TBI period (17 to 81.2%). Clinicians have labeled brain fog as a significant health challenge in patients with mild TBI and a key symptom for diagnosis by the International Conference on Concussion in Sport (McCrory et al., 2009). However, more research is needed to determine if this symptom is more severe in people with symptomatic mild TBI by inclusion of control group comparison. Also, there is a lack of understanding of how this symptom is manifested in persons with moderate-to-severe TBI, likely due to practical reasons. Studies on the effects of TBI on brain fog likely exclude moderate-to-severe cases due to substantial awareness deficits, which may render self-reported symptoms unreliable. However, self-reported symptoms may be useful during the phase where they may indicate functional issues (Nakase-Thompson et al., 2005; Stuss et al., 1999; Sherer et al., 2005). Hence, there is a need to detail the severity of brain fog during periods where it would be most advantageous to assess, i.e., symptomatic mild TBI and moderate-to-severe TBI.

Nurses have a critical role in caring for inpatients and outpatients with mild and moderate-to-severe TBIs, involving primary responsibilities for patient assessment, coordinating and communicating care, and providing care (Oyesanya, Thomas, Brown, & Turkstra, 2016). As such, nurses would benefit from application of symptom science to better understand the nature of brain fog. Symptom science is essential in nursing, involving investigation of self-reported health problems to inform early identification and treatment of health conditions. Assessing symptoms is important as they can occur across multiple conditions and often involve similar biological mechanisms, enabling the use of similar treatment approaches. Brain fog, for example, has been studied in multiple conditions also involving

neuroinflammation such as chemotherapy receivers, fibromyalgia, lupus, HIV, chronic fatigue syndrome, celiac disease, postural tachycardia syndrome, and thyroid disorders (Alford et al., 2022; Mackay, 2015; Ross, Medow, Rowe, & Stewart, 2013; Samuels & Bernstein, 2022; Theoharides, Stewart, Hatziagelaki, & Kolaitis, 2015). Most recently, brain fog has been denoted as a major and long-term symptom of SARS-Cov-2-19 infection (Asadi-Pooya et al., 2022; Callan, Ladds, Husain, Pattinson, & Greenhalgh, 2022) also attributed to neuroinflammation. However, so far, studies have not been able to characterize the severity of brain fog and how it corresponds to differing degrees of neurological disorder and other major clinical symptoms.

To date, investigations of brain fog have relied on one-item assessments not capturing brain fog as a whole. Most studies of subjective cognitive function have relied on measures of self-rated memory problems or concentration problems, which do not capture difficulties in multiple cognitive abilities or a lack of mental clarity (Asadi-Pooya et al., 2022). Other studies directly ask people to indicate brain fog using only one item (Ross et al., 2013), which may not adequately capture the extent of brain fog symptoms. Furthermore, the term “brain fog” can be interpreted differently by each person, especially based on language and cultural differences, so an effort to provide a measure based on an operational definition is needed. One such measure is the Mental Clutter Scale, which assesses cognitive problems in multiple areas as well as mental clarity (Leavitt & Katz, 2011). Although validated in people with fibromyalgia, this instrument may help also differentiate severity of neurological disorders such as TBI. Such a tool would be helpful in indicating the need for more intensive clinical assessment.

To close this critical knowledge gap, our investigatory aims were two-fold: One, we sought to use a comprehensive measure of brain fog to compare symptom severities in people with symptomatic mild TBI and moderate-to-severe TBI to a healthy control group. Second, we strived to understand what major clinical factors contribute to these reports. Brain fog self-reports may help detect ongoing cognitive deficits that could potentially be ameliorated. Brain fog may also help identify people with major clinical issues to be resolved such as ongoing physical symptoms and depressive symptoms. Analyses involved integrating data from two recent studies on mild and moderate-to-severe traumatic brain injury conducted with harmonized measures. Findings provide nurses with knowledge of how brain injury corresponds to level of brain fog and how brain fog may relate to other clinical symptoms.

METHODS

Participants

The first dataset was obtained from an IRB approved study at the University of Alabama at Birmingham (Protocol Number: X160830007) seeking to identify cognitive correlates of return to driving after mild TBI. Written consent was obtained for all participants 18 years and older, and written assent was obtained for those under the age of 18 alongside consent from their legal guardians. From Fall 2016 to Summer 2018 15 individuals ages 16 to 25 within two weeks of mild TBI were recruited from local concussion clinics. We defined mild TBI using the criteria from the American Congress of Rehabilitation Medicine which requires at least one major symptom of concussion (e.g., loss of consciousness ≤

30 minutes; loss of balance or motor coordination; disorientation or confusion; loss of memory; or dizziness; Kay et al., 1993). For this design, we selected individuals at the higher end of the mild TBI spectrum, with substantial symptoms on the Post-Concussion Symptom Scale (PCSS; individuals scoring ≥ 13) (Lovell et al., 2006). Such patients are of primary interest as they show poorer functional recovery and require continued clinical care compared to those with asymptomatic mild TBI (Collie, Makdissi, Maruff, Bennell, & McCrory, 2006). Eligibility criteria were reviewed and approved by one of our co-authors, a physician specializing in mild TBI (RDD). In addition to these participants, the first study recruited 16 healthy controls via community advertisements matching the mild TBI group on age and gender characteristics.

The second dataset was derived from a study (IRB Protocol Number: X160907003) seeking to identify the cognitive predictors of fitness to drive after moderate-to-severe TBI. All participants provided written consent with consultation of their caregivers. In the second study, we recruited 15 adult participants within 24 months of a moderate-to-severe TBI, ages 21 to 50 years, referred from the UAB Traumatic Brain Injury Model Systems. Diagnosis was based on criteria generated by the Mayo Classification System which defines a moderate-to-severe TBI as kinetic force to the brain that involves 30 minutes or greater of lost consciousness, posttraumatic amnestic greater than or equal to 24 hours, and a Glascow Coma Scale score of less than 13 (Malec et al., 2007). We additionally were able to verify moderate-to-severe TBIs using MRI and CT imaging to confirm the presence of brain injury. Our classification is generally aligned with other criteria such as from the National Institute of Neurological Disorders (NINDS) that defines a moderate-to-severe TBI as sudden damage to the brain resulting in major neuropsychological difficulties (NIH, 2018). Diagnosis of moderate-to-severe TBI was made by our co-author (TN), a clinical psychologist specialized in TBI who administered neuropsychological assessment and reviewed brain imaging results. There was no exclusion of individuals due to other underlying conditions or disorders, but people were excluded if they had had neurological conditions other than TBI that might have contributed to brain fog. All procedures were ethically approved by our Institutional Review Board. Further details about these studies have been published elsewhere (McManus, Bell, & Stavrinos, 2019; McManus, Cox, Vance, & Stavrinos, 2015; Newton et al., 2018; Stavrinos et al., 2019).

Measures

In each parent study, information was collected on demographics, brain fog, objective cognition, depressive symptoms, and post-concussive symptoms via harmonized measures described below:

Demographics.—From telephone screening, participants provided information on their age, gender, race, and ethnicity. Lastly, we collected the date of the most recent TBI.

Brain fog.—Brain fog was measured by the 16-item Mental Clutter Scale (MCS) (Leavitt & Katz, 2011). The MCS was developed to provide a detailed scale of brain fog over two dimensions: self-reported symptoms of general cognitive problems and lack of mental clarity. Questions asked participants to rate how much they have experienced different issues

from 1 “Not at all” to 10 “All the time.” Example items for general cognitive symptoms included trouble with “concentration,” “memory,” or “mental speed,” whereas mental clarity included self-reported problems with “spaciness,” “fogginess,” or “information overload.” The research revealed that these two dimensions (8-items each) contained good factor stability (Leavitt & Katz, 2011). However, a one-factor score also produces strong reliability while mirroring criteria for brain fog, i.e., both subjective cognitive problems and a lack of mental clarity (Leavitt & Katz, 2011). Our study demonstrated high reliability for a total score across groups (αs ranged from .95 to .96). This total score ranges from 16 to 160, where higher values indicate greater brain fog.

Objective cognition.

Cogstate Brief Battery.®: An objective evaluation of cognitive performance was obtained by the Cogstate Brief Battery® (Collie et al., 2003). This battery is derived from the general Cogstate Battery®, which is comprehensive and tests several domains (see www.cogstate.com). However, for brevity, the current study used a brief battery, which only takes 10 to 15 minutes to complete. The Cogstate Brief Battery® consisted of four tasks:

1. The Detection task was a simple reaction time task in which participants pressed a “YES” key (Letter K) when they saw a card turned face-up on the screen.
2. The Identification task was a choice-reaction time task in which participants determined if a car was red or black and pressed the appropriate key.
3. The One-Back task is a working memory task like the n-back; in this task, participants selected if the card presented to them was the same as the one just before.
4. Lastly, in the Learning task, participants selected if a card presented was ever presented in the deck before; this required intact memory and learning ability.

Each task had a set of 1 to 3-minute practice trials to ensure comprehension of the task. To ensure optimum performance, participants wore a headset for auditory performance feedback (e.g., which makes a harsh tone for wrong answers and a light sound for correct answers). Scores were calculated using a proprietary algorithm incorporating speed, accuracy, hits, misses, and anticipations. Tests show strong construct validity with other neuropsychological measures (Maruff et al., 2009).

Useful Field of View.®: Useful Field of View (UFOV®) (Ball & Owsley, 1993) also captured objective cognition and has been used previously in persons with TBIs (Novack et al., 2006). UFOV® consisted of four tasks capturing processing speed and forms of executive function.

1. UFOV®1 – Stimuli Identification: Participants quickly determined if they viewed a “car” or “truck” within milliseconds of exposure. This task captured speed of processing.
2. UFOV®2 – Divided Attention: Participants shifted between identifying a car or truck in the center and remembering the location of a car in the periphery. The location of the car in the periphery occurred anywhere on an eight-spoke spiral

around the center stimuli. As named, this task estimated divided attention but partly captured set-shifting ability.

3. UFOV®3 – Selective Attention I: Participants completed the same task as UFOV®2 but in the presence of distracting stimuli (47 triangles) across the screen.

4. UFOV®4 – Selective Attention II: The fourth subtest also tested selective attention in the presence of distractors (47 triangles) but with a new task involving the center stimuli. Participants decided if two stimuli in the center were the same (two cars or two trucks shown) or different (car and truck shown) while determining the location of the peripheral car as before. However, it involved the introduction of a novel task that increased difficulty.

Each subtest comprised visual demonstrations and a 2-minute practice to verify task comprehension. During their performance, the software provided an exposure threshold where 75% of responses were correct. These scores approximated optimal ability for each cognitive domain.

Depressed mood.—The Profile of Mood States (POMS) captured depressive symptoms for both injury and healthy control groups. The POMS was a 37-item instrument that allowed participants to denote feelings “since their injury” for the mild and moderate-to-severe TBI groups and “in the last two weeks” for the healthy control group. Participants rated how frequently they experienced various symptoms using the following Likert-type scale: “1-not at all,” “2-a little,” “3-moderately,” “4-quite a bit,” and “5- extremely.” This format provided a quickly answerable instrument with high factorial, face, and construct validity (McNair et al., 1971). To control for between- and within-group differences in negative affect, we used the depression (POMS-Dep) subscale from this instrument. This subscale includes feelings of being unhappy, sad, hopeless, discouraged, miserable, helpless, and worthless. POMS-Dep scores range from 8 (no depressive symptoms) to 40 (severe depressive symptoms) with excellent internal consistency in the current study (αs ranged from .88 to .94).

Post-Concussive Symptoms.—The Post-Concussion Symptom Scale (Lovell et al., 2006) measured injury severity. For 22 listed symptoms, participants rated their occurrence from none (0) to severe (6). Symptoms entailed cognitive (4 items), somatic (14 items), and mental/psychological difficulties (4 items). Summed responses ranged from 0 (no concussion symptoms) to 132 (high concussion symptoms). For healthy controls, scores represent general health problems. Internal consistency was high (αs ranged from .89 to .95).

Procedure.

Participants were assessed within two weeks to confirm symptomatic mild TBI and within 24 months for moderate-to-severe TBI. After verifying eligibility, we scheduled participants for an appointment in the laboratory. At this session, participants reported their level of brain fog (MCS), depressive symptoms (POMS-DEP), and post-concussive symptoms

(PCSS). Afterward, participants completed the Cogstate Brief Battery® and UFOV®. We remunerated participants for their time.

Data analysis—For our first set of analyses, we calculated descriptive statistics on all variables using SPSS version 25 (see Tables 1 to 2). An ANOVA then examined the effect of group (healthy controls, symptomatic mild TBI, and moderate-to-severe TBI) on the continuous measure of brain fog (MCS total). If provided a significant omnibus test, Tukey's post-hoc tests were then conducted to determine pairwise differences (control versus symptomatic mild TBI, control versus moderate-to-severe TBI, symptomatic mild TBI versus moderate-to-severe TBI). Because of the small sample and possible non-normality of brain fog, this was followed by a Kruskal–Wallis test, which inspected group differences based on rank. Secondly, because the moderate-to-severe TBI group was older and had greater time since injury based on the original study aims, a sensitivity analysis using a generalized linear model tested if group differences in brain fog remained after accounting for group differences in age and time since injury (value is 0 for controls). Furthermore, we examined whether group differences in brain fog could be accounted for by differences in depressive symptoms and post-concussive symptoms in sensitivity analyses. Group comparisons on demographics, objective cognition, depressive symptoms, and post-concussive symptoms are provided in Table 2.

Next, we tested group-specific relations between brain fog with objective cognition (speed of processing [UFOV®1], divided attention [UFOV®2], selective attention [UFOV®3 and UFOV®4], processing speed time [Cogstate® Detection task], processing speed accuracy [Cogstate® Identification task], working memory [Cogstate® One-Back task], and episodic memory [Cogstate® Learning task]), depressive symptoms, and postconcussive symptoms using Spearman correlations. Area under the curve analyses were conducted with non-parametric assumptions to determine how well brain fog discriminated healthy controls from people with symptomatic mild and moderate-to-severe TBI. Area under the curve analyses were also made to examine how post-concussive symptoms and depressive symptoms discriminated healthy controls from people with symptomatic mild and moderate-to-severe TBI. Associations between brain fog and objective cognition included adjustment for depressive symptoms for our second aim. For all analyses, pairwise deletion was used rather than listwise deletion to preserve sample size. We reported *p*-values and effect sizes for all analyses and determined significance at the .05 level.

Results

Descriptives

Demographics.—Participant demographics are shown in Table 1. For the symptomatic mild TBI group ($n = 15$), the average participant age was 16.73 years ($SD = 0.80$, range: 16 to 19). This group was predominately female (60.0%, $n = 9$) and Caucasian (80.0%, $n = 12$). The healthy control group ($n = 16$) appeared successfully matched to the symptomatic mild TBI group. Meanwhile, individuals with a moderate-to-severe TBI were predominately young to middle-aged adults ($M_{age} = 33.19$ years, $SD = 8.74$, range = 20 to 50) – significantly older than our symptomatic mild TBI and control samples ($F(2,43) = 51.72$,

$p < .001$, $\eta^2 = .71$). Regarding other personal characteristics, the sample consisted of a slight male majority (56.3%, $n = 9$) who were predominantly Caucasian (73.3%, $n = 11$). The moderate-to-severe TBI group were similar on sex ($X^2(2) = 1.33$, $p = .514$) and race proportions ($X^2(2) = .20$, $p = .905$) compared to the symptomatic mild TBI and healthy control groups. Because age was the only significant difference across groups, age was included as a covariate in later our descriptive comparisons.

Group differences in brain fog.

After conducting a one-way ANOVA, we found a significant effect of group on brain fog ($F(2,43) = 6.29$, $p = .004$; $\eta^2 = .23$; 95%CI[.03 to .40]) (shown in Figure 1 and Table 2). Post-hoc tests confirmed that individuals with symptomatic mild TBI reported higher brain fog compared to healthy controls ($M_{Diff} = 24.64$, $p = .014$; $d = .96$) as did individuals with moderate-to-severe TBI ($M_{Diff} = 34.84$, $p = .004$, $d = 1.25$). No significant difference emerged between individuals with symptomatic mild TBI and moderate-to-severe TBI ($M_{Diff} = 10.20$, $p = .327$). Sensitivity analyses showed that these patterns of results were similar after nonparametric testing using a nonparametric Kruskal-Wallis test as well as adjustment for age, time since injury, depressive symptoms, and post-concussive symptoms (ps < .05).

Area under the curve analyses.—Next, AUC models examined the ability of brain fog, post-concussive symptoms, and depressive symptoms, as continuous variables, to discriminate healthy controls from symptomatic mild TBI and moderate-to-severe TBI. Overall, brain fog discriminated healthy controls from individuals with symptomatic mild TBI well (AUC = .74; 95%CI: .56 to .92). Post-concussive symptoms (AUC = .64; 95%CI: .44 to .84) and depressive symptoms did poorly at discriminating healthy controls from individuals with symptomatic mild TBI (AUC = .52; 95%CI: .32 to .73). Brain fog better discriminated healthy controls from those with moderate-to-severe TBI well (AUC = .85, 95%CI: 70 to .99) as did post-concussive symptoms (AUC = .76; 95%CI: .58 to .93). Depressive symptoms did poorly at discriminating healthy controls from individuals with moderate-to-severe TBI (AUC = .62; 95%CI: .42 to .82).

Correlates of brain fog in healthy controls.

Brain fog was significantly related to depressive symptoms in healthy controls ($r_{sp} = .65$, $p = .006$). After adjusting for depressive symptoms, brain fog did not associate with any scores on UFOV® or Cogstate® in healthy controls ($|rs_{sp}|$ range: .02 to .36, all ps > .10), as shown in Table 3.

Correlates of brain fog in symptomatic mild TBI.

Brain fog was significantly related to depressive symptoms in people with symptomatic mild TBI ($r_{sp} = .66$, $p = .008$, see Figure 2). After adjusting for depressive symptoms, brain fog was related to slower processing speed on UFOV®1 ($r_{sp} = .72$, $p = .003$) but not other scores on UFOV® or Cogstate® ($|rs_{sp}|$ range: .06 to .27, all ps > .10) .

Correlates of brain fog in moderate-to-severe TBI.

Brain fog was unrelated to depressive symptoms in people with moderate-to-severe TBI (r_{sp} = .26, p = .349). After adjusting for depressive symptoms, brain fog was related to objective cognition as shown in Table 5. Regarding objective cognition, greater brain fog significantly related to worse scores on the Learning (r_{sp} = −.62, p = .023) and One Back task (r_{sp} = −.58, p = .014; see Figure 3 and 4).

Discussion

"Brain fog" may indicate neurological disorder, making it of great clinical interest. Brain fog has been implicated in multiple conditions linked to neuroinflammation, most recently SARS-Cov-2. To date, nurses and other healthcare practitioners have few tools to measure brain fog severity, mostly relying on ratings of cognitive abilities unspecific to brain fog or one-item assessments of brain fog. This is particularly true in studies of brain injuries (Dean et al., 2012; Lovell et al., 2006). In this study, we examined the Mental Clutter Scale, a measure of brain fog validated in people with fibromyalgia (Leavitt & Katz, 2011), to capture brain fog severity. As described below, brain fog was more severe in people with mild and moderate-to-severe TBI than controls and related to other clinical symptoms differently within each group.

First, group comparisons established higher brain fog in people with symptomatic mild TBI (d = .96) and moderate-to-severe TBI (d = 1.25) than in healthy controls. Area under the curve analyses found that brain fog was able to acceptably discriminate symptomatic mild TBI (AUC = .74) and moderate-to-severe TBI from healthy controls (AUC =.85). Overall, these results are in line with the idea that brain fog captures the presence of a neurological disorder. Results are also consistent with previous work showing greater frequency of brain fog in mild TBI compared to controls, while also expanding this work to show greater *severity* of brain fog and to expand this finding to people with moderate-to-severe TBI (Dean et al., 2012; Lovell et al., 2006).

Second, within-group analyses revealed different clinical correlates of brain fog severity in mild and moderate-to-severe TBI. Brain fog was related to depressive symptoms and slower speed of processing in people with mild TBI. Unexpectedly, there were scant associations between brain fog and other measures of objective cognition, although this finding is consistent with the literature more broadly. Previous studies have failed to find significant associations between self-reported cognitive symptoms and objective cognitive difficulties after mild TBI (Karr et al., 2019; Spencer, Drag, Walker, & Bieliauskas, 2010; Stenberg et al., 2020), with only one other study finding an association between self-reported cognitive symptoms and slower processing speed (Schiehser et al., 2011). Furthermore, studies have found that negative affectivity, such as found in those with high depressive symptoms, contributes to the lack of correspondence between self-reported cognitive symptoms and objective cognition after mild TBI (Caplan et al., 2021). A significant correlation between brain fog and depressive symptoms in the mild TBI group may contribute to a lack of alignment between brain fog and objective cognition in people with mild TBI.

Furthermore, mechanisms underlying the association of mild TBI with depressive symptoms are likely multifactorial, involving psychological and biological components. Psychologically, depressive symptoms may arise from reduced self-efficacy resulting from being unable to keep oneself safe. Another reason could be general worries about recovery and return to normal function extending to symptom reports. Indeed, self-efficacy and general worries show strong links with self-reported cognitive symptoms in the broader literature (Aben et al., 2011; Dux et al., 2008). Biologically, depressive symptoms may correspond to inflammation related to brain damage that also underlies brain fog (Bodnar et al., 2018). In human models, blood markers of neuroinflammation (IL-6, TNFalpha, IL-10, and CRP) have been linked to depressive symptoms (Juengst, Kumar, & Wagner, 2017). In animal models, mild TBI results in neuroinflammation corresponding to anxiety-like behavior (Broussard et al., 2018). This may also explain why brain fog is related to slower processing speed, as processing speed shares negative associations with inflammation (Heringa et al., 2014). People with high brain fog severity and depressive symptoms after mild TBI may be experiencing unaddressed neuroinflammation. Further research will be needed to discover the psychobiological underpinnings of brain fog in symptomatic mild TBI.

Contrasting with the mild TBI group, reports of brain fog aligned with problems in episodic memory and working memory (as opposed to processing speed and depressive symptoms) in people with moderate-to-severe TBI. Although few studies exist in this severity group, this is consistent with one previous research showing that mental fatigue coincided with reduced working memory (Johansson et al. 2009). Thus, despite possible awareness issues, ratings of brain fog might identify persons with moderate-to-severe TBI with residual issues in episodic memory and executive function. Regarding biological mechanisms, as posited for mild TBI, brain fog may be due to persistent neuroinflammation after moderate-to-severe TBI. Recent studies have highlighted the possible role of long-term chronic neuroinflammation in explaining ongoing difficulties after moderate-to-severe TBI, including higher risk of other neurological disorders such as Parkinson's and Alzheimer's disease (Faden & Loane, 2015; Schimmel, Acosta, & Lozano, 2017). Brain fog, as a possible correlate of neuroinflammation, may help flag individuals having continuous difficulties in cognitive function who may also be at risk for other neurodegenerative diseases. Biomarkers of neuroinflammation may be informative in future studies.

Overall, these results have important implications for nursing, including in the area of SARS-Cov-2 infections. According to symptom science, brain fog may have similar biological mechanisms across conditions, despite different etiologies (McCall et al., 2018; Page et al., 2018; Saligan, 2019). This would explain why a measure of brain fog severity validated in people with fibromyalgia was also able to differentiate people with brain injury from controls in this study, as one common mechanism across these conditions is possible neuroinflammation (Bäckryd, Tanum, Lind, Larsson, & Gordh, 2017; Simon et al., 2017). This seems further likely as SARS-COV-2, which also involves reports of brain fog, can result in significant brain neuroinflammation (Kempuraj et al., 2020). Like investigations done in other conditions, most studies assessing brain fog in SARS-Cov-2 have relied on single item measures unable to assess severity or focus on indirect indicators of brain fog (Asadi-Pooya et al., 2022; Caspersen, Magnus, & Trogstad, 2022; Graham et al., 2021).

Here we provide a measure that may be able to capture severity of brain fog which might also help differentiate those with neurological disorder after SARS-COV-2 infection. If not due to SARS-COV-2, these patients might have other contributing conditions such as brain injury which should be considered. According to the National Institutes of Health Symptom Science model, developed by the National Institute of Nursing Research, the next step for such work would be to continue phenotypic characterization of brain fog in conditions such as SARS-COV-2, followed by research on biomarker discovery and treatment application within these conditions (Cashion, Gill, Hawes, Henderson, & Saligan, 2016). The field of nursing and its focus on symptom science is well-positioned to lead such investigations.

Limitations

This study was not without limitations. First, although the symptomatic mild TBI group and healthy controls were comparable on age, the moderate-to-severe TBI cohort was much older. Therefore, descriptive comparisons involving this group should be considered with some caution. Fortunately, considerable research shows that age does not significantly affect reports of cognitive symptoms before older adulthood (Devolder & Pressley, 1991), minimizing this concern. Furthermore, differences in brain fog remained after adjusting for age differences. Second, definitions of TBI may influence results. For mild TBI, we recruited highly symptomatic mild TBI cases (> 13 on the PCSS) as these individuals are more likely to have poorer functional recovery and require continued clinical care (Collie et al., 2006). Results may not be generalizable to asymptomatic mild TBI. It is also important to note that high symptomology might influence reporting on other symptom scales like brain fog, especially if due to personality differences (Lange et al., 2010). However, adjustment for depressive symptoms lessens this concern. Furthermore, our definition of moderate-to-severe TBI was based on the Mayo Classification System, although several other definitions such as NINDS can be applied. Third, medical histories of each participant were not available for analyses of other conditions, such as mood disorders. This is particularly relevant in mild TBI where comorbid major depressive disorder and posttraumatic stress are particularly explanative of self-reported cognitive symptoms (Chamelian & Feinstein, 2006; French, Lange, & Brickell, 2014). Our analyses, however, noted no significant differences in depressive symptoms across the groups and adjusted for depressive symptoms to account for any mood differences across and within the groups. Lastly, sample sizes were modest but bolstered by the well-designed methodology to include representative clinical cases when self-reported brain fog might be most valuable. We used nonparametric statistical techniques which provide conservative testing for small samples.

Conclusions

After a TBI, individuals may experience a plethora of self-reported cognitive symptoms, some of which outlast objective cognitive impairments and may reflect residual functional concerns. Brain fog is one commonly reported symptom that has been largely overlooked despite its consideration as a common symptom of mild TBI. Here we validated the ability of a brain fog scale to differentiate people with symptomatic mild TBI from controls, providing further evidence for this measure as a potentially important diagnostic symptom. Moreover, we showed that brain fog is associated with greater depressive symptoms and

slower speed of processing, outcomes that might benefit from interventions. Meanwhile, in the moderate-to-severe TBI group, brain fog appeared to represent enduring problems in episodic memory and executive function rather than depressive symptoms. In sum, the MCS appears a worthwhile tool to measure brain fog and detect the need for further clinical assessment in people with suspected head injury. Future work is needed to unravel the contributing biological mechanisms of brain fog that may be informative to other conditions, including SARS-Cov-2 infection, which is an area of heightened interest due to the pandemic.

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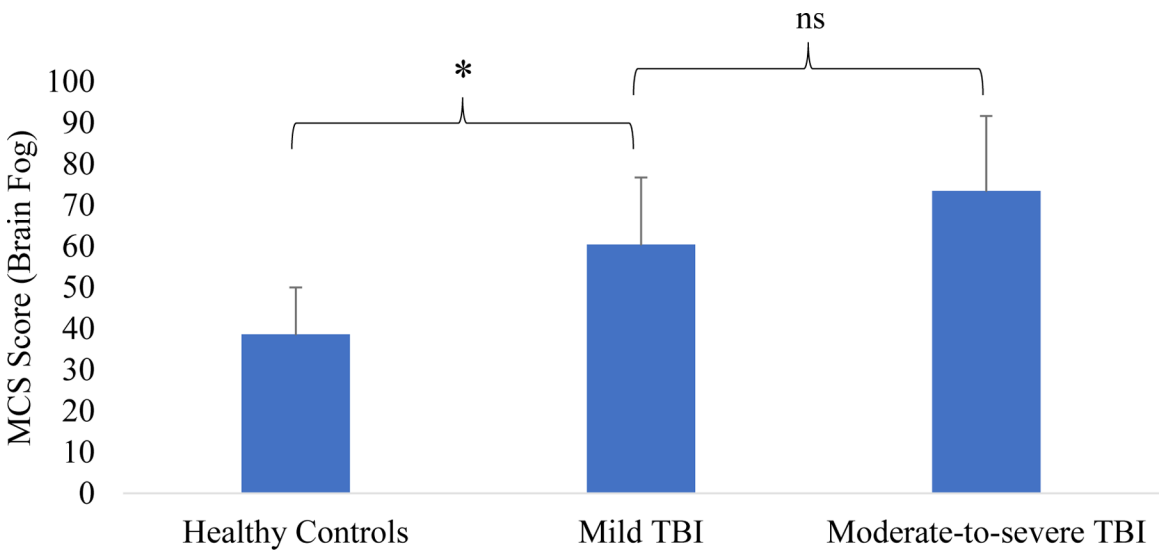

Figure 1.

Group differences on brain fog. Notes. TBI = traumatic brain injury; asterisk represents significant differences between groups (*p*s < .05).

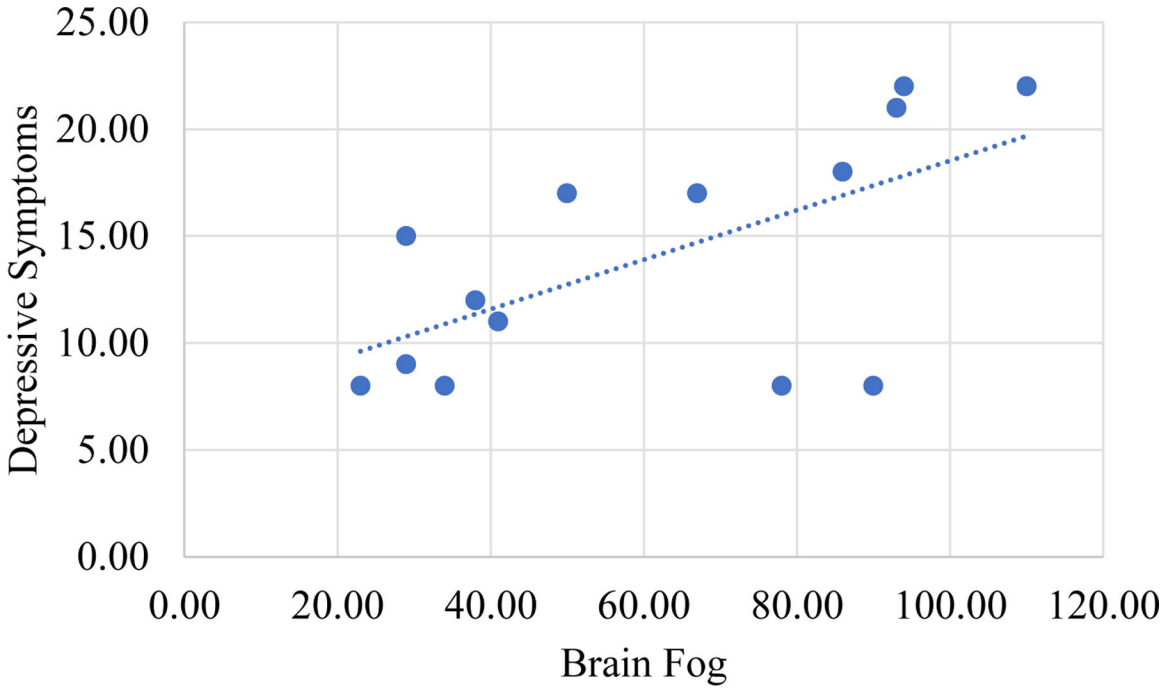

Figure 2.
Correlation between brain fog and depressive symptoms in mild traumatic brain injury.

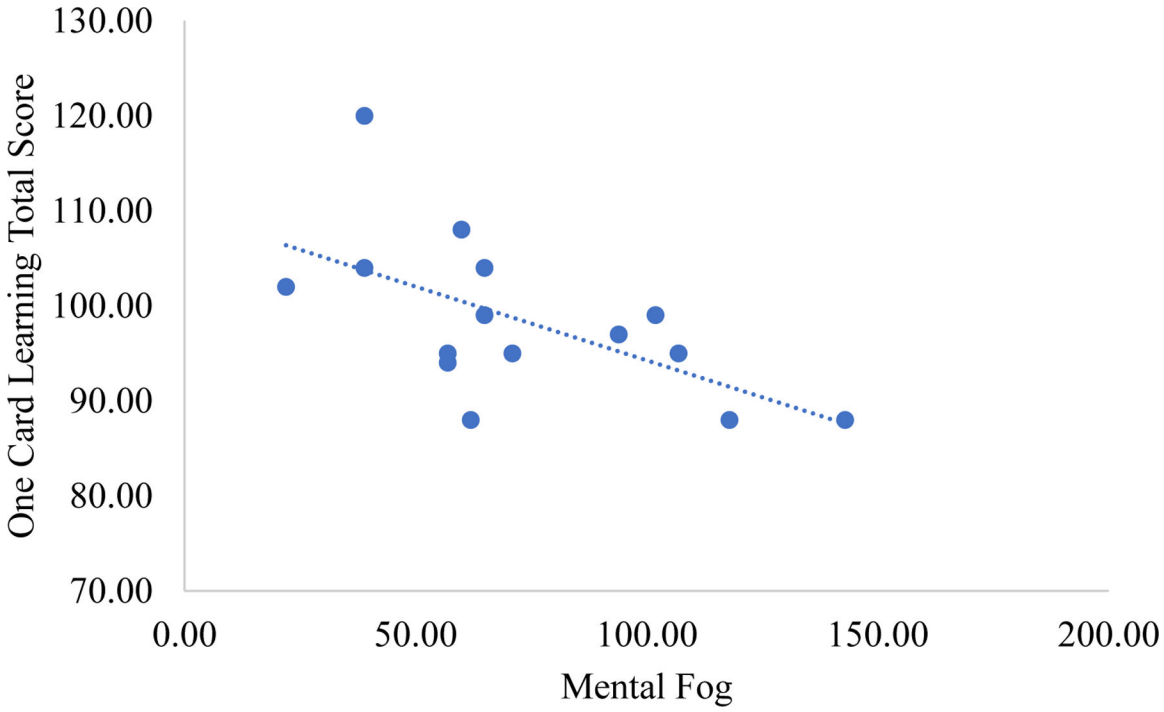

Figure 3.
Correlation between brain fog and the Cogstate® Learning task in moderate-to-severe traumatic brain injury.

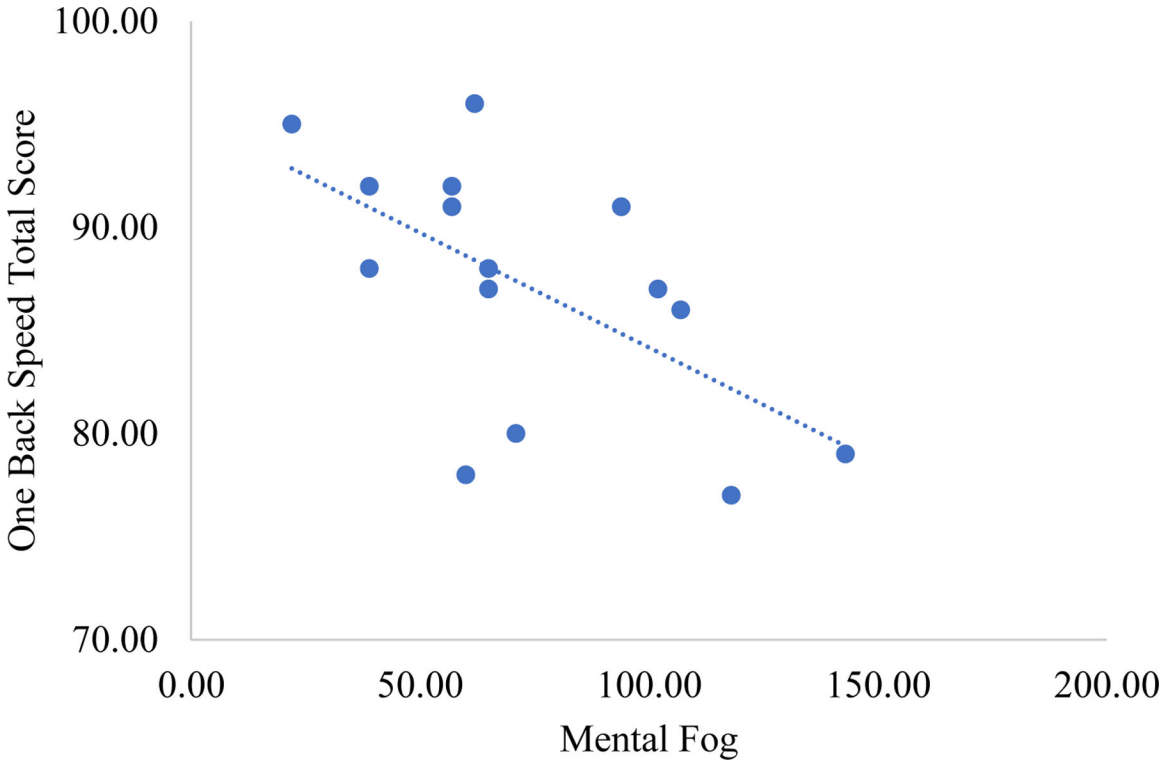

Figure 4.
Correlation between brain fog and the Cogstate® One Back task in moderate-to-severe traumatic brain injury.

Table 1.

Participant Demographics.

Characteristic	Healthy Controls [a] *n* = 16		Symptomatic Mild TBI [b] *n* = 15		Moderate-to-severe TBI [c] *n* = 15					
	***M*/%**	***SD*/*n***	***M*/%**	***SD*/*n***	***M*/%**	***SD*/*n***	**X^2/ANOVA *p*-value**	**a vs. b**	**a vs. c**	**b vs. c**
Demographics										
Gender							.514			
Female	62.5	10	60	9	43.8	7				
Male	37.5	6	40	6	56.3	9				
Race								.441		
Caucasian	75.0	12	80.0	12	73.3	11				
African American	25.0	4	13.3	2	26.7	4				
Asian	0.0	0	0.0	0	0.0	0		.513		
Bi-racial	0.0	0	6.7	1	0.0	0				
Age (years)	**17.06**	**1.57**	**16.73**	**0.80**	**33.19**	**8.74**	**<.001**	.472	**<.001**	**<.001**
Time Since Injury (mo.)	**–**	**–**	**0.40**	**0.13**	**44.26**	**36.84**	**<.001**			

Table 2.

Differences in cognitive function, brain fog, post-concussive symptoms, and depressive symptoms across groups.

Characteristic	Healthy Controls[a] *n* = 16		Symptomatic Mild TBI[b] *n* = 15		Moderate-to-severe TBI[c] *n* = 15					
	M	***SD***	***M***	***SD***	***M***	***SD***	**ANOVA *p*-value**	**a vs b**	**a vs c**	**b vs c**
UFOV®										
UFOV®1 - Speed of Processing	17.00	0.00	30.29	48.95	47.87	54.06	.130			
UFOV®2 - Divided Attention	**17.38**	**1.50**	**52.63**	**101.99**	**119.13**	**100.74**	**.005**	.202	**.004**	**.073**
UFOV®3 - Selective Attention I	**52.00**	**24.82**	**99.33**	**114.38**	**215.00**	**141.36**	**<.001**	.117	**<.001**	**.012**
UFOV®4 - Selective Attention II	**94.63**	**58.25**	**173.42**	**141.46**	**306.20**	**123.08**	**<.001**	.091	**<.001**	**.007**
Cogstate®										
Detection	**99.67**	**4.08**	**89.29**	**13.15**	**91.60**	**9.17**	**.010**	**.011**	.057	.783
Identification	**102.81**	**5.12**	**95.8**	**11.16**	**92.53**	**9.86**	**.009**	.089	**.008**	.585
Learning	101.69	7.66	95.13	12.26	98.40	8.52	.179			
One Back	**95.25**	**6.76**	**94.07**	**10.61**	**87.13**	**6.12**	**.016**	.913	**.020**	.058
MCS	**38.56**	**21.39**	**63.20**	**29.43**	**73.40**	**32.96**	**.004**	**.014**	**.004**	.587
Mental Clarity	**17.81**	**10.31**	**31.73**	**15.89**	**32.73**	**19.23**	**.016**	**.008**	**.027**	.983
Cognitive Problems	**20.75**	**11.42**	**31.47**	**14.44**	**40.67**	**16.13**	**.001**	**.031**	**.001**	.185
PCSS	**19.94**	**15.66**	**30.67**	**22.54**	**38.60**	**22.84**	**.049**	.133	**.039**	.545
POMS-Dep	14.06	6.14	14.27	5.40	16.67	7.37	.459			

Notes. MCS = Mental Clutter Scale; PCSS = Post Concussive Symptom Scale; POMS-Dep = Depression subscale from Profile of Mood States; UFOV® = Useful Field of View. Boldened variables indicate significant differences.

Table 3.

Correlations between Mental Fog and Objective Cognitive Tasks in Healthy Controls ($n = 16$).

	1	2	3	4	5	6	7	8	9	10	11	12
1. MCS[a]	1	−.03	−.04	−.20	.02	−.09	.18	−.03	<.01	.36	.29	.19
2. PCSS		1	−.08	−.49†	.19	−.01	−.17	−.06	<.01	.08	.10	.05
3. Age			1	−.23	.22	.13	−.17	−.13	<.01	.33	−.08	.31
4. Sex				1	−.10	−.10	.07	−.02	<.01	−.20	−.25	−.42
5. Detection					1	.67*	.33	.53**	<.01	−.03	−.22	−.29
6. Identification						1	.44	.27	<.01	−.19	.24	−.05
7. Learning							1	.07	<.01	−.16	−.25	−.43
8. One Back								1	<.01	−.19	−.14	−.35
9. UFOV®1									1	<.01	<.01	<.01
10. UFOV®2										1	.06	.42
11. UFOV®3											1	.59*
12. UFOV®4												1

Notes. All correlations are Spearman rho. MCS = Mental Clutter Scale; PCSS = Post-Concussive Symptom Scale; POMS-Dep = Depression subscale from the Profile of Mood States; UFOV = Useful Field of View.

† $p < .10$

* $p < .05$

** $p < .01$

[a] Pre-adjusted for association with depressive symptoms using residuals from a linear regression.

Table 4.

Correlations between Mental Fog and Objective Cognitive Tasks in Persons with Symptomatic Mild TBI ($n = 15$).

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. MCS[a]	1	.28	.4	−.03	−.21	−.27	−.11	−.06	.16	.72***	.50	.23	.09
2. PCSS		1	.18	.32	−.24	−.41	.12	−.47†	.09	.56*	.22	.35	.50
3. Time Since Injury			1	−.03	−.32	−.58*	−.65**	−.10	−.42	.37	.65**	.36	.39
4. Age				1	.04	.18	.35	.06	.25	.02	.03	.43	.12
5. Sex					1	.61*	.32	−.25	.49	−.26	−.22	−.43	−.22
6. Detection						1	.69**	.18	.55*	−.48†	−.51†	−.33	−.77**
7. Identification							1	.09	.65**	−.21	−.51†	−.12	−.42
8. Learning								1	.13	−.10	−.02	.27	−.19
9. One Back									1	−.16	−.30	−.49	−.56†
10. UFOV®1										1	.82***	.45†	.48
11. UFOV®2											1	.41	.30
12. UFOV®3												1	.57†
13. UFOV®4													1

Notes. All correlations are Spearman rho. MCS = Mental Clutter Scale; PCSS = Post-Concussive Symptom Scale; POMS-Dep = Depression subscale from the Profile of Mood States; UFOV = Useful Field of View.

† $p < .10$

* $p < .05$

** $p < .01$

[a] Pre-adjusted for association with depressive symptoms using residuals from a linear regression.

Table 5.

Correlations between Mental Fog and Objective Cognitive Tasks in Persons with Moderate-to-severe TBI (n = 15).

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. MCS[a]	1	−.08	.06	−.20	.25	−.4	−.31	−.62*	−.58*	.12	.03	−.22	−0.22
2. PCSS		1	−.25	.30	.09	−.13	−.31	.20	−.20	.27	.09	.23	−0.12
3. Time since injury			1	.18	.13	.01	.32	−.03	.10	−.27	−.29	−.32	−.24
4. Age				1	.24	−.12	.09	−.02	.40	−.13	−.09	.13	.10
5. Sex					1	.30	−.16	−.14	−.16	.15	.17	.06	.17
6. Detection						1	.46†	.36	.08	−.30	−.10	−.18	.19
7. Identification							1	.25	.69**	−.28	−.24	−.28	.05
8. Learning								1	.13	−.58*	−.39	−.14	−.19
9. One Back									1	.13	−.03	.04	.29
10. UFOV®1										1	.80***	.66**	.62*
11. UFOV®2											1	.80***	.77***
12. UFOV®3												1	.68**
13. UFOV®4													1

Notes. All correlations are Spearman rho. MCS = Mental Clutter Scale; PCSS = Post-Concussive Symptom Scale; POMS-Dep = Depression subscale from the Profile of Mood States; UFOV = Useful Field of View.

† $p < .10$

* $p < .05$

** $p < .01$

[a] Pre-adjusted for association with depressive symptoms using residuals from a linear regression.