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Feature Review

Defining brain fog across medical conditions

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'Brain fog' is commonly reported in more than a dozen chronic diseases, but what is it? We review research across conditions which has characterised brain fog and evaluate its definitions and objective correlates. Brain fog has been used to refer to a variable set of overlapping symptoms implicating cognition, fatigue, and affect. It has been defined as a distinct symptom, a syndrome, or a nonspecific term. We consider the evidence that brain fog is a transdiagnostic entity with a common phenomenology and profile of objective cognitive deficits. We discuss where these commonalities arise and argue that linguistic ambiguity, shared cognitive impairments, and noncognitive factors are more likely than shared neurobiology. We suggest how future research might apply existing tools to disambiguate the phenomena that brain fog conflates.

Highlights

The term 'brain fog' is used to convey a broad but characteristic set of symptoms, implicating cognition (particularly attention, memory, and language), affect, and fatigue.

Brain fog is related to, but dissociable from, cognitive performance. Fatigue and affect influence subjective brain fog and mediate cognitive performance deficits across diagnoses. Divergent neural correlates suggest a heterogeneous aetiology.

Researchers should provide clear definitions when studying brain fog, preferably replacing or complementing it with more precise terms where possible [e.g., 'post-coronavirus disease 2019 (COVID-19) neuropsychiatric symptoms' rather than 'COVID-19 brain fog'].

We suggest that future research should conduct transdiagnostic comparisons of brain fog using a standardised set of measures to fractionate the distinct constructs that brain fog conflates and enable precise characterisation.

What is brain fog?

Patients, doctors, and researchers are increasingly using the term 'brain fog' across a disparate set of conditions. Examples include coronavirus disease 2019 (COVID-19) [1], myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) [2], fibromyalgia [3], sleep-related disorders [4], menopause [5], hypothyroidism [6], traumatic brain injury (TBI) [7], and systemic lupus erythematosus (SLE) [8]. It is associated with poor quality of life [9] and social and occupational disability [10,11]. But what is brain fog? Is it a problem with attention, memory, cognition generally, or something broader? Does it reflect objectively measurable cognitive deficits or specific neurobiological correlates? When people say they have brain fog, do they all mean the same thing?

Previous reviews have focussed on brain fog in specific conditions [3,4,6,11,12]. However, a transdiagnostic view of the concept is largely lacking. If brain fog has transdiagnostic commonalities, there may be common mechanisms or therapeutic targets that would allow translation of research findings across disorders. Conversely, the term may be impeding research by conflating distinct phenomena.

This narrative review summarises research across conditions which has aimed to characterise and define brain fog. Although the review is not based on strict literature-search criteria, as a general approach we searched the human biomedical literature for research using 'brain fog' as an inclusion criterion or outcome (we discuss some studies which are relevant despite using other terms, as denoted and explained, when relevant, in the text). In the following sections we first use COVID-19 as a case study. We then draw comparisons to other conditions and delineate heterogeneous definitions of brain fog currently in use in research, including as a symptom, a syndrome, and as an inherently ambiguous term. We discuss whether commonalities arise at the level of neurobiology, cognitive function – including the effects of anxiety and fatigue on cognition and metacognitive errors – or linguistic ambiguity. We argue that future research requires more precise terminology, direct transdiagnostic comparisons, and a standard set of measures to understand the mechanisms underlying brain fog.

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Post-COVID-19 brain fog

Characteristics of post-COVID-19 brain fog

COVID-19 provides a useful case study owing to its extensive and recent literature base. Persistent post-COVID-19 brain fog was reported early in the COVID-19 pandemic through patient reports, online support groups, and news media [13]. Qualitative research found that brain fog conveyed difficulties with concentration, memory, planning, decision-making, and/or language [10,14], often co-occurring with fatigue, anxiety, depression, post-exertional malaise, sleep disturbance, and headache [1,10,14–16]. It can be transient, fluctuating, and interrelate with fatigue, guilt, and shame [10,14] (Box 1).

Cross-sectional research established brain fog as one of the most frequent persistent COVID-19 symptoms, with a prevalence of 20–30% [1,17–20]. Cohort evidence suggests that brain fog follows COVID-19 infection temporally and is persistent, that the risk is greater following COVID-19 than after other common respiratory infections [21], and that risk correlates with hospitalisation [22]. Population-level research links COVID-19 to subtle deficits in measured cognition in attention, memory, and executive functions [23,24], particularly in hospitalised or ongoing persistent symptoms groups [22–25]. A human challenge study further solidified this connection by demonstrating that infection is associated with cognitive performance deficits which persist for a year [26].

However, the results of research relating brain fog to cognitive performance deficits are nuanced. While some studies report correlations between subjective cognitive symptoms and performance deficits [27–29], many find no such correlation [30–35], suggesting that subjective brain fog does not always reflect objective cognitive performance deficits. These discrepancies may be explained by differences in the populations being studied – studies of hospitalised patients find a correlation between symptoms and performance [27,29], whereas in most studies finding no correlation, hospitalised participants are not included or make up a small minority.

Recent studies illuminate the relationship between brain fog and cognitive performance by applying high-precision cognitive assessment and subgroup comparisons. A study comparing three groups – no COVID-19, COVID-19 with resolved symptoms, and COVID-19 with persistent symptoms – found the objective deficits were associated with COVID-19 infection, but no difference was noted between the persistent and resolved symptom groups, nor any correlation between subjective cognitive symptoms (including brain fog) and objective cognitive function [35].

Box 1. First-person descriptions of brain fog following COVID-19

The following selection of quotes from qualitative studies exploring persistent post-COVID-19 symptoms illustrates the range of symptoms implicated and their course, including variability through the day, exacerbation by exertion, and interrelation with fatigue.

‘I can’t cope with multiple inputs, like if I’m trying to reply to a message on my phone and one of my boys starts speaking to me or there’s something else happening as well that just really fries my brain. … I’ve got to focus on just one thing or I make massive mistakes and it’s like I forget my intentions all the time’ [10].

‘You know what you want to say but you can’t think what that word is because it doesn’t come to the forefront of your mind’ [10]

‘If I exert myself like cognitively then my Long COVID-19 symptoms sort of exacerbate like shortness of breath, chest tightness. But earlier on I think that it was the other way round … if I exert myself physically – this means going for a 5 min walk on flat – then I get confused, I can’t remember stuff’ [10].

‘In the last week, I'm wondering because my brain fog seems to have lifted and it's feeling possible finally, after nearly six months, that I might one day find a new job’ [15].

A multicentre study comparing post-COVID-19 brain fog and recovered COVID-19 groups found severe cognitive slowing in the brain fog group, which was not seen in the recovered group, suggesting an association between brain fog and a generalised task performance deficit [36]. A study using a detailed cognitive battery in a large general population sample (n = ~113 000) found that post-COVID-19 brain fog was associated with subtle performance deficits [25]. These were primarily mediated by illness severity (aligning with the strong correlations between subjective and objective cognition in hospitalised samples [27,29]). Interestingly, the profile of deficits associated with post-COVID-19 brain fog – affecting memory, attention and executive function – was similar but attenuated in participants with resolved COVID-19. By contrast, brain fog in those without confirmed COVID-19 was associated with negligible performance deficits [25]. Further, across the whole study population, the association between global cognitive deficits and brain fog was no stronger than with other factors such as fatigue, mood swings, and markers of severe inflammation. These results indicate that post-COVID-19 brain fog does reflect a particular pattern of post-COVID-19 cognitive deficits, but the association is modest, and other factors are at play.

More broadly, many studies report that noncognitive factors contribute to post-COVID-19 brain fog, including fatigue [27–29,34,37,38], depression/anxiety [27,29,31,34,37–41], psychological trauma [27,29], poor sleep [34,38], and psychiatric illness [34,42]. Several studies suggest that these factors mediate the relationship between objective and subjective cognition [37,39], or correlate with subjective cognition, while subjective cognition is not correlated with cognitive performance [31,35]. Studies also find that noncognitive factors affect cognitive performance, for example sleep disturbance [38]. Another study found a strong correlation between fatigue and measured attention in COVID-19-negative patients, which was absent in COVID-19-positive patients, suggesting that contributing factors differ by population [30].

Overall, these findings suggest that post-COVID-19 brain fog is multifactorial, and relates to both cognitive performance deficits and noncognitive factors, including fatigue, depression, sleep disruption, and psychiatric illness, which either mediate the relationship between cognitive performance and brain fog, or cause brain fog independently. This is perhaps unsurprising for a generalised subjective symptom (for comparison, in a study recruiting participants who never contracted COVID-19, 34.5% reported increased fatigue during the pandemic [43]). However, mediation remains an important question because the findings are conflicting and could direct research toward psychosocial or biological factors.

Neural correlates of post-COVID-19 brain fog

Several studies have investigated the neural correlates of post-COVID-19 brain fog by using neuroimaging, electroencephalography (EEG), and blood markers. These do not find predictors of brain fog based on differences in standard diagnostic magnetic resonance imaging (MRI) [34,44,45]. Several studies suggest subtle structural changes, although none offers strong evidence that these correlate with brain fog specifically (as opposed to COVID-19 generally). For example, an MRI study comparing three groups – post-COVID-19 brain fog, recovered COVID-19, and no COVID-19 – found reduced brain and white matter volume following COVID-19, but no difference between the brain fog and recovered groups [44]. One study found reduced cortical grey matter volume in patients with persistent neurological symptoms including brain fog, but did not recruit controls [46]. Other studies have analysed by subjective cognitive symptoms rather than brain fog specifically, and found reduced grey matter volume in cortical, limbic, and cerebellar areas, as well as alterations in white matter axial and mean diffusivity, in long COVID compared with controls [47]; other findings include increased volume in the left transverse temporal gyrus [48] and reduced superior temporal gyrus and insula volume [27]. An ultra-high-field MRI study in hospitalised patients shows damage to serotonergic nuclei in the

brainstem, including the inferior medullary reticular formation and the raphe pallidus and obscurus which regulate respiration and cognition [49].

Studies have investigated changes in blood–brain barrier (BBB) permeability in COVID-19 in relation to brain fog. A study using dynamic contrast-enhanced MRI showed significantly increased whole-brain BBB leakage in long COVID with brain fog patients compared with both long COVID without brain fog and recovered COVID-19 [44]. Brain fog during acute COVID-19 in this study was associated with blood markers of inflammation (cytokines), coagulopathy (clotting and growth factors), and BBB dysfunction (protein S100β). Another study assessing BBB permeability using single-photon emission computed tomography (SPECT) did not find a difference between long COVID-19 and controls [50]. However, participants in the first study had cognitive performance deficits, whereas those in the second did not, suggesting that their populations differ.

A small study using magnetic resonance spectroscopy (MRS) found markers of ischaemia in individuals with post-COVID-19 brain fog compared with controls [45], and a study using frequency-domain near-IR spectroscopy found that brain fog was associated with reduced cerebral oxygen saturation [51].

Functional neuroimaging studies have also implicated the limbic cortex in post-COVID-19 brain fog. One positron emission tomography/computed tomography (PET-CT) study found hypometabolism in the cingulate gyrus in two patients with post-COVID-19 subjective brain fog and objective cognitive deficits [52], whereas a later study using functional MRI (fMRI) found hypoconnectivity between left and right parahippocampal areas, and between bilateral orbitofrontal and cerebellar areas, in patients with post-COVID-19 cognitive symptoms (which the authors considered to be synonymous with brain fog) compared with controls [47].

Studies examining the EEG correlates of post-COVID-19 brain fog have found differences when comparing a post-COVID-19 brain fog group with recovered COVID-19 and never-COVID-19 groups [53]. Differences were also found when comparing EEGs in individuals experiencing post-COVID-19 brain fog with recordings made in the same individuals before COVID-19 [54]. Changes include increased theta activity (implicated in subjective cognitive decline [55]) and various subtle regional differences.

Overall, these findings indicate that subjective brain fog may co-occur with changes in brain systems linked to attention and memory. However, larger-scale studies will be necessary to tease apart markers specific to brain fog from those related to COVID-19 infection in general. Post-COVID-19 cognitive symptoms, cognitive performance deficits, and their neural correlates are unlikely to be uniform, as this population is complex and multiple mechanisms are likely to be involved. An analysis of data from a cohort of hospitalised patients illustrates this because it identified two blood biomarker profiles during acute COVID-19 – one predicting both subjective cognitive symptoms and decrements in cognitive performance, the other predicting cognitive symptoms mediated by fatigue [56]. Neither of the predictions by these biomarker profiles were mediated by anxiety or depression. These profiles might indicate distinct aetiological pathways: (i) subjective symptoms relating to microscopic pulmonary emboli via fatigue, and (ii) performance deficits relating to cerebrovascular pathology.

Brain fog beyond COVID-19: symptoms, performance deficits, and neural correlates

Comparing transdiagnostic brain fog research overall (Tables 1 and 2), several themes emerge. First, a similar constellation of symptoms is described across diverse conditions – difficulties

Table 1. Brain fog across conditions: definitions and phenomenology

Condition	Definition and phenomenology	Refs
Fibromyalgia ('fibro-fog')	The subjectively experienced cognitive dysfunction associated with fibromyalgia – mental fogginess or impaired mental clarity, attention and memory impairments	[57,58]
SLE ('lupus fog')	Periods of forgetfulness and confusion related to impaired cognition, as well as to depression and fatigue	[8,59,60]
ME/CFS	Subjective cognitive symptoms and objective cognitive impairments relating to mental fatigue; brain fog is considered to be a cognitive subtype of fatigue	[2,61,62]
Cancer and chemotherapy ('chemofog')	Memory loss, inability to concentrate, difficulty in thinking, and other subtle cognitive changes; diminished quality of life and daily functioning	[63,64]
Chronic pain	Subjective cognitive dysfunction which fluctuates and is associated with disability	[11]
Menopausal transition	The constellation of cognitive symptoms experienced around the menopause – memory and attention difficulties, difficulty retaining and recalling language, difficulty maintaining a train of thought, distractibility, forgetting intentions (reason for coming into a room), and difficulty switching between tasks	[65,66]
TBI	Fatigue and subjective cognitive impairment, including self-reported problems in memory, attention, and processing speed, coupled with a lack of mental clarity	[67,68]
POTS	Subjective cognitive impairment – forgetfulness, difficulty focusing, thinking, and communicating; feeling 'cloudy', lost, or confused; 'thoughts moving too quickly'; triggered by fatigue and standing	[69]
Hypothyroidism	Mental cloudiness or lack of mental alertness; symptoms vary but commonly include fatigue, depressed mood, and difficulties with memory and executive function, sleepiness, anxiety, confusion, and difficulty making decisions	[6,70,71]
Central disorders of hypersomnolence	Cognitive dysfunction that may or may not be linked to excessive sleepiness, related to an underlying neuronal dysfunction, which reduces concentration and impairs information processing, leading to a complaint of lack of clarity of mental thinking and awareness	[4,72]
CDS	Excessive daydreaming, mental confusion, and fogginess; slowed behaviour and thinking	[73]

with cognition, particularly attention and memory, subjectively experienced as 'fogginess' or impaired 'mental clarity'; chronicity; variability; and strong associations with fatigue and depression/anxiety, leading to impaired occupational function and quality of life [4,7,11,57,65,69,71,73].

Second, brain fog appears to be common in various conditions, and prevalences of 15–40% are reported in chronic pain, 68% in perimenopause, 65% in TBI, 96% in postural tachycardia syndrome (POTS), and 74–86% in central narcolepsy/primary hypersomnia [11,66,68,69,72]. In other conditions, while brain fog is reportedly common, prevalences are reported for subjective cognitive symptoms, endorsed by 76–83% in fibromyalgia, 38% in SLE, 85–89% in CFS, and 44% in breast cancer chemotherapy [2,57,58,60,64]. These prevalence data are not comparable across conditions and may be inflated because they mostly derive from binary self-report measures without standardised wording in small, self-selecting samples. High prevalences may reflect a high base rate of symptom endorsement, a well-known finding in symptoms research [95] – in one study, brain fog was endorsed by 22% of control group subjects [96].

Where data relating brain fog to objective cognition is available for different conditions, findings are more mixed. Subtle impairments in cognitive performance are reported in fibromyalgia, SLE, ME/CFS, chronic pain, TBI, menopause, and cognitive disengagement syndrome (CDS) [2,11,67,73,74,82,87,88]. Performance deficits correlate with brain fog in TBI (in attention) [67], and with subjective symptoms in chronic pain (attention) and menopause (memory) [67,87,88], whereas symptoms are unrelated to performance in SLE [60] and healthy controls [7,25].

Table 2. Brain fog across conditions: cognitive performance and correlates

Condition	Cognitive performance domains, correlation with brain fog and noncognitive factors	Refs
Fibromyalgia ('fibro-fog')	Performance deficits in attention, psychomotor speed, memory, task switching, working memory, and executive function; effect sizes small to large Changes in cognitive performance are associated with depression, anxiety, distraction, and somatic symptoms	[74–81]
SLE ('lupus fog')	Performance deficits in memory, attention, and language No correlation between cognitive performance and subjective cognitive symptoms, depression, anxiety, or fatigue Cognitive symptoms correlate with depression, anxiety, fibromyalgia scores, and fatigue	[60,82]
ME/CFS	Subtle performance deficits in visuospatial short-term memory, processing speed, verbal memory, and visual memory recall Inconsistent findings across studies Performance deficits are mediated by fatigue Subjective symptoms correlate with depression, but not performance	[2,62,83,84]
Cancer and/or chemotherapy ('chemofog')	Subtle performance deficits are found in memory recall and executive function Cognitive symptoms in cancer are common, and are associated with cancer type (CNS highest, genitourinary lowest); depression, anxiety, and fatigue	[85,86]
Chronic pain	Performance deficits in attention and executive function associated with cognitive symptoms Performance deficits mediated by anxiety, and correlate with pain and catastrophising	[87]
Menopausal transition	Subtle performance deficits in memory Performance correlated with subjective complaints, depression, anxiety, and insomnia Subjective symptoms associated with age, hot flushes, anxiety, depression, stress, perceived health status, and history of sexual abuse	[88]
TBI	Brain fog in TBI correlates with cognitive performance deficits (processing speed) and depressive symptoms, whereas in a control group without TBI, brain fog correlates with depressive symptoms only Subjective cognitive symptoms correlate with cognitive performance, psychiatric symptoms, insomnia, post-traumatic amnesia, and loss of consciousness	[67,89]
POTS	Evidence is limited to two case series High prevalence of subjective cognitive symptoms but normal neuropsychological test results	[90,91]
Hypothyroidism	Hypothyroidism is associated with cognitive performance deficits, particularly in memory, but also in attention, executive function, and language	[6,92]
Central disorders of hypersomnolence	Performance deficits in attention, but normal memory scores, despite a high prevalence of subjective memory complaints	[4]
CDS	Mixed evidence for performance deficits in sustained attention, processing speed, and motor speed CDS is correlated with internalising symptoms, especially depressive symptoms, and is dissociable from inattention in ADHD	[73,93,94]

Findings are mixed in ME/CFS [84,97,98]. No objective deficits have been found in POTS, to our knowledge, although evidence is limited to small case series [69,91]. There is evidence that noncognitive factors (depression and/or fatigue) were associated with brain fog (or cognitive symptoms) in all populations where this was assessed (fibromyalgia, ME/CFS, SLE, cancer, chronic pain, menopause, and TBI, and healthy controls [2,60,67,77,85,87,88]), and noncognitive factors were associated with cognitive performance in fibromyalgia, ME/CFS, chronic pain, menopause, and TBI [2,67,78,81,87,98,99]. Overall, this is consistent with brain fog reflecting both cognitive performance deficits and noncognitive factors, including depression, anxiety, and fatigue, which have mediating or independently causal roles.

A limitation across this literature is inconsistency in the cognitive testing protocols used. This is exacerbated as cognitive performance deficits associated with brain fog are often small, unlike in dementia, which is defined by clinical impairment at an individual level. While some studies set a threshold for impairment of for example, 1 or 1.5 standard deviations below the mean, a lack of standardisation means that impairment prevalences are not comparable [100,101]. Many studies assess a difference in scores between 'brain fog' and 'no brain fog' groups, which avoids the need for a threshold, but may detect clinically insignificant differences, limit inter-study comparability, and introduce confounding.

Comparing the neural correlates of brain fog across conditions, studies which specifically analyse brain fog are scarce. However, several trends are apparent. A wide range of neural correlates that could plausibly underlie brain fog have been identified, but heterogeneity both within and between disorders is substantial.

Functional neuroimaging studies in ME/CFS during cognitive tasks report decreased caudate nucleus activity, an inactive ventral anterior cingulate cortex during errors compared with control subjects, and recruitment of additional cerebral regions [62]. In TBI, it is reported that subjective fatigue and cognitive symptoms are associated with deficits in growth hormone, and that these respond to growth hormone supplementation [7]. In menopause, studies suggest that vasomotor symptom ratings are associated with subjective cognitive complaints, but not with objective cognitive performance [102]; while objective vasomotor symptom measures are associated with objective cognitive performance [99].

Considering the correlates of cognitive impairment in individual underlying conditions, the list becomes long and diverse. Some factors are shared amongst conditions – BBB dysfunction, which is implicated in brain fog after COVID-19, has also been found in SLE [103] and is associated with cognitive impairment following acute respiratory distress syndrome and mechanical ventilation [104]. Other factors appear to be condition-specific. In menopause, cognitive impairment is thought to relate to reduced brain volume in frontal, hippocampal, and temporal areas via oestrogen depletion [65,105], whereas in ME/CFS and POTS, studies implicate altered cerebral blood flow and autonomic dysfunction [106].

Overall, this divergent pattern of results accords with a multifactorial neurobiology for brain fog, with both shared and distinct causes within and between conditions. This is perhaps unsurprising given the distributed neurobiology of cognition and affect. A key limitation of the current literature is that direct comparative evidence is largely lacking, leaving the extent of transdiagnostic similarities unclear because of confounds in measurement methodologies, sample sizes, and study designs.

Finally, we note that brain fog has been reported in an even broader range of conditions than those discussed here, including neurological, endocrine, and neuroimmune diseases such as multiple sclerosis [4], hypoparathyroidism [107], and hepatitis C [108]. Studies on brain fog in these conditions are scarce and often investigate 'cognitive dysfunction' or 'subjective cognitive symptoms' rather than 'brain fog' specifically. However, there may be phenotypic similarities [109], and research into brain fog in these conditions using a standardised approach may be a valuable future direction.

How has brain fog been defined?

The studies discussed earlier generally measure brain fog as a binary self-report variable (either present or absent). However, several studies have sought to define brain fog with more precise self-report scales (Table 3). Comparison of these scales shows a heterogeneous construct. Although there are commonalities, the scales generally place emphasis on different symptoms.

Table 3. Brain fog measures or scales

Scale	Population	Construct
Mental clutter scale [110]	Fibromyalgia	One cognitive symptom ('fogginess')
Multidimensional inventory of subjective cognitive impairment [111]	Fibromyalgia	Cognitive symptoms (clarity, memory, learning, concentration, multitasking, language)
BF-COVID questionnaire [112]	COVID-19	Cognitive symptoms [language, attention (multitasking), memory (registration and recall), orientation (time and space)]
Fatigue and altered cognition scale [7]	TBI	Cognitive symptoms (forgetting, concentrating, 'spaced out', processing, indecision) Fatigue
Brain fog scale [113]	General population	Cognitive symptoms (processing, memory, communication, concentration, planning, multitasking, indecision, mistakes) Fatigue Affective symptoms Sleep
Brain fog scale [114]	University students	Cognitive symptoms (slowness, memory registration, word-finding, concentration, logical thinking, reading, rushing thoughts) Fatigue Dissociation
Brain fog assessment and severity scale (BFASS) [115]	Coeliac disease	Cognitive symptoms (slowness, cloudiness, brain buzzing, fatigue) Fatigue Affective symptoms (anxiety, irritability) Dissociation

The concept of brain fog in these scales ranges from a single, distinctive cognitive symptom, to a set of cognitive symptoms, to a broader collection of symptoms including fatigue, mood, and sleep. None of these scales has entered widespread use, and to our knowledge only one has been validated outside its development population [116].

Relatedly, there is substantial heterogeneity in use of the term brain fog in the current scientific literature [117,118]. Implicitly or explicitly, in these scales and the literature discussed earlier, definitions of brain fog fall into three categories conceptualizing brain fog as (i) a symptom, (ii) a syndrome (bounded set of symptoms), or (iii) an inherently ambiguous term (unbounded set of symptoms) (Table 4 and Figure 1).

Table 4. Brain fog definitions and examples

Concept	Definition	Example
Symptom	One cognitive symptom May be either distinctive or synonymous with existing symptoms	Mental 'fogginess'/clarity [110] Brain fog symptom differentiated from attention or memory symptoms [119]
Syndrome	A 'constellation' or cluster of several symptoms Often disorder-specific: a term for the neurocognitive/neuropsychiatric features in a specific disorder	"Brain 'fog' is a constellation of symptoms that include reduced cognition, inability to concentrate and multitask, as well as loss of short- and long-term memory" [120] 'The subjectively experienced cognitive dysfunction associated with fibromyalgia' [57]
Nonspecific term	An inherently ambiguous term, with a nonspecific definition, or an 'umbrella' term, including any neuropsychiatric symptom or objective deficit	"A colloquial expression indicating a phenomenon whose clinical impact may be detrimental to an individual's psychological, occupational, and social life" [117] 'Cognitive deficit (known as brain fog)', 'a composite of several ICD-10[a] F, G, and R codes to capture so-called brain fog', including 'cognitive symptoms', 'encephalopathy', 'dementia', 'stupor' [121]

[a]Abbreviation: ICD, International Classification of Diseases.

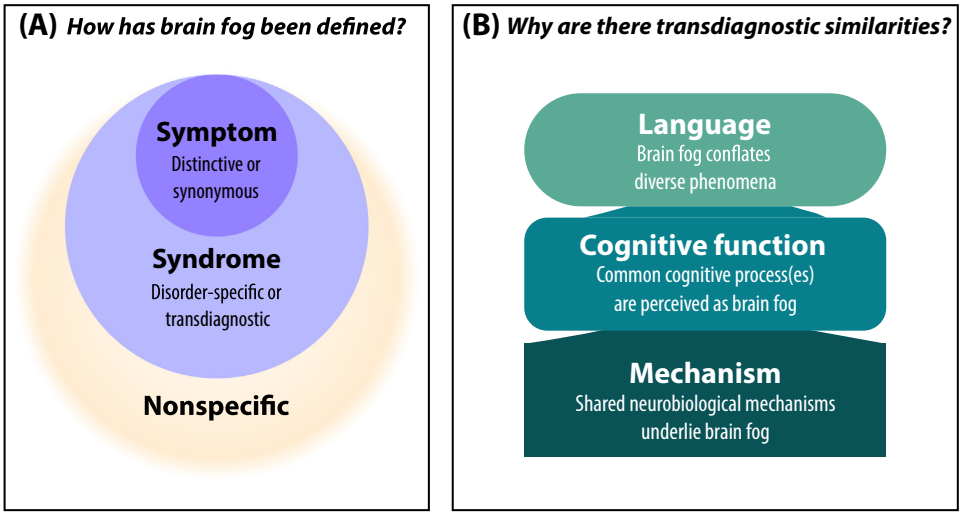

Figure 1. How has brain fog been defined, and why are there transdiagnostic similarities? (A) Heterogeneous definitions of brain fog are used in research and can be broadly divided into three categories: (i) brain fog as a symptom. Some definitions imply a distinctive quality ('fogginess' or 'impaired mental clarity'), whereas in others brain fog is used as a synonym for other symptoms ('difficulty concentrating'). (ii) Brain fog as a syndrome (bounded set of symptoms). Some definitions are 'disorder-specific', using brain fog to refer to neuropsychiatric features of a specific disorder (e.g., fibro-fog, or COVID-19 brain fog), while others are transdiagnostic. (iii) Brain fog as a nonspecific/inherently ambiguous term (unbounded set of symptoms). In these broader usages brain fog refers to any related feature. (B) The transdiagnostic commonalities in brain fog likely arise at several levels: (i) mechanism – many conditions share mechanisms which underlie brain fog, such as neuroinflammation or blood–brain barrier dysfunction. (ii) Cognitive function – many mechanisms lead to shared cognitive processes which underlie the perception of brain fog, such as a specific domain or profile of impairments (e.g., attention or processing speed), or metacognitive errors, fatigue, or affect. (iii) Language – many phenomena share the term brain fog as a linguistic descriptor. In this context, brain fog conflates phenomena which are in fact distinct, suggesting transdiagnostic similarities which might not exist. Abbreviation: COVID-19, coronavirus disease 2019.

This heterogeneity presents several challenges. First, discrepancies in the use of brain fog between or within participants and researchers may reduce external validity. Second, the process under investigation, and the validity of the approach used, depend on which definition is used. For example, if brain fog is an inherently ambiguous term (unbounded set of symptoms), then attempts to understand its underlying mechanisms may be misguided without precise characterisation and subclassification. In the following sections we discuss each definition and highlight its strengths and weaknesses, which we also summarise in Table 5.

Brain fog as a cognitive symptom

The narrowest definition of brain fog used in the literature is as a single cognitive symptom. This is either distinctive [110] or equivalent to an existing symptom such as impaired concentration [25,122–124]. However, the empirical data on brain fog universally find that it overlaps with many cognitive and other symptoms. Surveys characterising brain fog have found associations with >20 symptoms, including depression, anxiety, dissociation, and somatic symptoms (a feeling 'inside the head'), as well as difficulties with concentration, communication, and memory [125,126].

Does brain fog have a distinctive phenomenology? The literature supporting this notion is scarce and sometimes difficult to interpret. The clearest example of a systematic attempt to distinguish brain fog from other cognitive symptoms may be the mental clutter scale [110]. The development of this scale was motivated by clinical observations and survey data in fibromyalgia suggesting that the 'fibro-fog' reported by patients had a unique 'foggy' quality – like 'looking at life as if

Table 5. Brain fog definitions – strengths and weaknesses

Definition	Strengths	Weaknesses
Symptom – synonym of existing symptom term	Unclear	Unnecessarily ambiguous; the existing term is preferable Widespread use of brain fog encompasses multiple symptoms
Symptom – distinctive	Prerequisite for studying unique subjective qualities	Conceptual difficulties with defining and communicating this unambiguously; limited evidence for distinctive qualities
Syndrome – disorder-specific	Unclear	Unnecessarily ambiguous; a descriptive term is preferable Multiple overlapping 'brain fogs' Frequent comorbidity between disorders
Syndrome – transdiagnostic	Pragmatic response to transdiagnostic similarity of phenomena described as brain fog Promotes the identification of transdiagnostic mechanisms for cognitive symptoms	May mask subtle differences between neurocognitive syndromes
Nonspecific term	Most aligned with widespread use of the term Broad sensitivity for impaired quality of life	Heterogeneous category; greater precision may aid mechanistic research

through a haze' or 'functioning with a mind full of cotton' – which was not captured by existing scales and was specific to fibromyalgia [58]. The authors found that a subscale of 'mental fogginess'-related items could be separated via factor analysis from one containing general cognitive symptoms, suggesting that these two measures captured distinct constructs [110].

Although the idea that 'fibro-fog' has a unique phenomenology is intriguing, we would argue that it has poor face validity. Comparing the 'fog' and 'cognition' subscales of the mental clutter scale, items appear to overlap – 'confusion', 'rushing thoughts', and 'information overload' sit within the fogginess scale, whereas 'thinking clearly', 'perceptual clarity', and 'mental speed' sit within the general cognitive symptoms scale. In later work, the group suggested that 'mental clutter' alone is too narrow to capture the 'fog' of fibromyalgia, which includes difficulties with memory, attention, and language [57] – motivating the development of a broader measure, the multidimensional inventory of subjective cognitive impairment [111]. Attempts to distinguish brain fog from other symptoms in other conditions would probably face similar issues.

Brain fog as a disorder-specific syndrome

Most brain fog research defines brain fog as a syndrome or constellation of symptoms that are associated with a specific disorder (Table 1). With this definition, studies recruit participants with the index diagnosis and research brain fog using interview, survey, or objective cognitive measures.

There are several issues with this approach. First, it could lead to any neuropsychiatric symptom in the selected population being labelled 'brain fog' (e.g., in narcolepsy/primary hypersomnia, is 'excessive daytime sleepiness' part of brain fog or the primary disorder? [4]). It is also unclear how to categorise cognitive symptoms in patients who do not endorse 'brain fog' but may nonetheless experience similar symptoms [2]. For example, fatigue and cognitive impairment are reported in primary adrenal insufficiency, but the published literature does not refer to 'brain fog', and phenomenological detail on cognitive symptoms is lacking [127] – a clear gap, given the evidence potentially implicating hypocortisolism in post-COVID-19 brain fog [128,129].

A disorder-specific approach also invites the assumption that brain fog is pathophysiologically related to the disease in question. However, this may not be true. For example, in a study on hypothyroidism, half of the participants reported brain fog preceding their hypothyroidism [71].

A final issue is that this approach may lead to a plethora of subtly different definitions of brain fog across different disorders. This might exacerbate confusion and miscommunication for researchers, clinicians, and patients. This issue is further exacerbated by frequent comorbidity between conditions in which brain fog is prevalent. For example, several studies have highlighted the overlap between ME/CFS and long COVID in aetiology and symptoms [106,130,131], and some estimate that 13–45% of long COVID patients fulfil the criteria for ME/CFS [132]. Overlap is also reported between long COVID, POTS, and ME/CFS [133], and between fibromyalgia and ME/CFS [134].

Brain fog as a transdiagnostic syndrome

Direct cross-conditional comparisons to assess whether brain fog is a transdiagnostic entity are currently lacking. However, brain fog does appear to be similar across diagnoses, both in phenomenology [7] and objective cognitive correlates (Table 2). We suggest that a way to understand the commonalities in brain fog across diagnoses is to consider whether they arise at any of 3 levels – (i) shared neurobiological mechanisms, (ii) shared impairments in cognitive function, or (ii) ambiguities/overlap in language and symptom definitions (Figure 1). We now consider each of these.

Shared neurobiological mechanisms offer the potential to translate insights between several conditions with limited available treatment options. However, although there is evidence that a wide range of mechanisms are associated with brain fog, few are shared, and many appear to be disorder-specific. While there may be shared mechanistic factors further down the causal chain, such as neuroinflammation [120], BBB dysfunction [44,103], or impaired cerebral perfusion homeostasis [51,62], current evidence for these is limited to specific conditions. A broad syndromic definition of brain fog means that it is likely to be highly multifactorial, and the range of mechanistic hypotheses is extremely broad, leaving viable translational targets unlikely – at least without a precise system for subclassification.

Moving to the level of cognitive function, shared impairments here appear *a priori* to be more likely and are better supported by the available evidence. Several studies have identified cognitive performance impairments that are shared across multiple diagnoses, and are consistent with descriptions of brain fog such as slowed processing speed [36] and increased fatigability/decreased sustained attention [135]. The characteristic clustering of brain fog symptoms may also result from interrelations between (perceived) cognition and depression, anxiety, fatigue, and distraction by somatic symptoms or rumination [80,136]. This would be consistent with the findings of a systematic review of subjective cognitive symptoms in nonneurological chronic diseases which reported a strong association between self-reported cognitive function and noncognitive factors including depression and fatigue, but no correlation between self-reported cognitive symptoms and neuropsychological test results in most studies [137].

Finally, considering language, it is also possible that the similarities in brain fog across conditions are due to ambiguous definitions that result in conflation of related but distinct phenomena. Moreover, the underlying phenomena may partly overlap; it would be mistaken to assume that there is a 1:1 mapping of symptom terms/descriptors to distinct mental phenomena. For example, the construct of mental fatigue has striking similarities to brain fog [7]. While the mental fatigue questionnaire [138] has not been used to our knowledge in recent brain fog research, the three items – concentration difficulties, fatigue, and affective features – appear to converge. Brain fog in CFS

has been defined as 'mental fatigue' [61,62], and brain fog following COVID-19 is strongly associated with fatigue [28,29,37]. Fatigue has a remarkably similar prevalence to brain fog in symptom survey studies in COVID-19 [1,18–21,118], ME/CFS [2,62], hypothyroidism [6,71], TBI, and other conditions [89]. In a study validating the fatigue and altered cognition scale in long COVID, a correlation of $r = 0.85$ was found between the fatigue and altered cognition subscales [116], and an fMRI study in post-COVID-19 syndrome suggests that fatigue and cognitive symptoms share some neural structural and functional correlates that are similar to the substrates of fatigue in ME/CFS [139].

Brain fog may also overlap with several other mental symptoms, including dissociation and the cognitive symptoms described in depression/anxiety ('difficulty in making decisions, lack of concentration and loss of clarity [or] general fuzziness in thinking') [140]. As outlined, brain fog is associated with depression/anxiety across conditions. There are also similarities with subsyndromal delirium, sometimes referred to as 'clouding of consciousness' or 'mental fog' [140–142]. It is unclear whether the executive/attention deficits associated with brain fog lie on a continuum with delirium – this is essentially unresearched, perhaps because subsyndromal delirium is undefined and lacks measures [143].

The entity CDS (formerly 'sluggish cognitive tempo') is an interesting comparator with transdiagnostic definitions of brain fog. CDS is conceptualised as a neurodevelopmental disorder that has brain fog as its primary feature [144,145]. CDS is assessed using a self-rated symptom scale whose items include 'mental fogginess' and 'fuzzy brain'. Factor analysis studies suggest that scores on this scale are separable from scores of hyperactivity and inattention in attention deficit hyperactivity disorder (ADHD) [94,144]. The occurrence of CDS in children, and its separability from other traits, situates susceptibility to mental fogginess as a universal trait – analogous to some conceptions of fatigue [146].

Brain fog as an inherently ambiguous or colloquial term, or an idiom of distress

Brain fog functioning as a linguistic 'final common pathway' for a broad and heterogeneous group of phenomena is consistent with the third type of definition we identify – brain fog as an inherently ambiguous term. Several studies use brain fog to refer to an (essentially) unbounded set of symptoms/phenomena; for example, 'an umbrella term used to describe a wide variety of cognitive symptoms' [37], or 'a colloquial expression indicating a phenomenon [which is] detrimental to an individual's psychological, occupational, and social life' [11].

A study of 141 first-person descriptions of brain fog from the online forum Reddit suggests the term may be used in this way by the general population – brain fog described 'an overlapping set of cognitive, emotional and physical symptoms', including a sensation of mental 'fuzziness' or pressure, fatigue, and dissociation [126]. Descriptions were heterogeneous, and brain fog occurred in many non-disease states.

Another factor suggesting that brain fog has broad popular usage is its etymology. The word 'fog' itself has been used metaphorically to denote 'confused' or 'obscured' since circa 1600 ('in a fog', 'fog of war', etc.).[i,ii] To many anglophones, brain 'fog' would therefore serve as a natural metaphor for an inability to think clearly or comprehend, but has connotations even broader than nonspecific medical terms such as 'confusion' or 'cognitive dysfunction'.

In this broader sense, brain fog is comparable with 'thinking too much' – an 'idiom of distress' that is used across many cultures to refer to ruminative, intrusive, and anxious thoughts. This has wide

intra- and intercultural variation, and overlaps with common mental disorders and non-disease states [147]. We did not identify any research conceptualising brain fog as an idiom of distress, but suggest that this lens might offer insight.

This open-ended definition is problematic for researchers. In this broad sense, brain fog may be too nonspecific an entity for many research questions, as diverse phenomena would be captured when attempting to measure it. However, this does not mean that it is not useful in other contexts – for example, to communicate cognitive quality of life. One definition of long COVID includes brain fog as a core symptom, as defined by a cognitive quality of life measure, the Neuro-QoL v2.0 cognition short form, which includes slow thinking and difficulties with reading, concentrating, learning new tasks, and managing time [148].

Brain fog is similar and prevalent across many disparate conditions – why?

This transdiagnostic review of brain fog suggests that it is a prevalent feature of chronic diseases and refers to a similar cluster of symptoms – cognitive, fatigue, affective, and even quasi-somatic symptoms – which are chronic and have day-to-day variability. It is often associated with subtle decrements in cognitive performance that share a broad but characteristic profile implicating attention, executive function, memory, and language. Noncognitive factors often mediate the relationship between subjective and objective cognition or account for subjective symptoms independently. However, direct transdiagnostic comparisons are lacking, meaning that the extent of similarities in phenomenology, correlates, and aetiology remains unclear.

The commonalities in brain fog might exist at one of three levels (Figure 1) – neurobiological mechanisms, cognitive function, and language/symptom definition. While there are many plausible low-level biological mechanisms for brain fog, some of which are shared across conditions [2,8,12,103,131], the mechanisms overall appear to be highly heterogeneous. A more parsimonious account is that the commonalities reflect shared and commonly co-occurring symptoms: for example, cognitive impairments related to fatigue that are detectable in measures such as sustained attention [135] and processing speed [2,36,67,76]. The broad and ambiguous definition of brain fog means that it is also likely to conflate phenomena. Brain fog may offer an easy shorthand to communicate a set of common and overlapping symptoms which occur following COVID-19 and many chronic illnesses [149]. It thereby presents a 'many-to-many mapping' problem for research because multiple mechanisms and symptoms converge via the term.

The study of brain fog reflects difficulties in researching subjective symptoms generally – qualia are inaccessible to direct measurement, meaning that the separation of a mental symptom from the totality or 'gestalt' of subjective experience is somewhat arbitrary [150]. As brain fog, empirically, occurs alongside several other affective, neuropsychiatric, and somatic symptoms [1,20,33,118,122], difficulty in circumscribing it within these is unsurprising.

Network analysis may provide a useful model to understand the relations between the various factors implicated in brain fog [151]. These models posit that COVID-19 is a trigger that activates a causally interconnected network of symptoms, such as depression, fatigue, and insomnia. Comparison of connectivity patterns between conditions or states could elucidate the mechanisms and role of brain fog in persistent syndromes such as long COVID.

Metacognition is another research direction which may be fruitful. Research on metacognition in brain fog is scarce, despite the ostensible relationship between the two. A primary impairment of metacognition – in which perceptions/expectations of cognitive dysfunction cause distress and dysfunction, despite (near-)normal cognitive performance – has been proposed to explain brain

fog in ME/CFS and fibromyalgia, as well as the cognitive symptoms in functional cognitive disorder (FCD) [136]. While this has some empirical support in FCD [79], research into this mechanism in other conditions remains to be conducted. Some features of post-COVID-19 brain fog resemble the hallmarks of FCD – subjective impairments in excess of performance deficits [39,149], variability of symptoms, heightened attention to normal memory lapses (e.g., forgetting what to do next after parking [14]), and potential internal inconsistency (e.g., inability to drive in urban, but not rural, areas [14]).

Finally, the links between brain fog and somatoform disorders may offer insights. Brain fog frequently co-occurs with multiple somatic symptoms, and somatic symptom disorders frequently feature cognitive symptoms and mild performance deficits [152]. Distractibility, which is implicated in performance deficits in fibromyalgia [80], may be relevant to brain fog in other conditions. Some suggest deeper shared mechanisms – for example, one model [149] suggests that long COVID, including brain fog, is a functional somatic symptom disorder, using a Bayesian hierarchical predictive processing (BHPP) framework [153,154]. BHPP is a general model of cortical function which proposes that the key function of the cortex is to represent the external environment by modelling expected sensory inputs. In functional somatic symptom disorders, an overly strong expectation of a symptom is encoded, leading to the perception of persistent symptoms despite absent or contradictory sensory input. Insights from this framework might refine or extend the model of FCD described earlier. BHPP accounts have also been advanced for functional neurological disorder [155], chronic pain [156], and chronic fatigue in depression [157].

Concluding remarks and future perspectives

Future research on brain fog requires greater conceptual clarity. Our review highlights issues with the present definitions of brain fog and research characterising it – there is limited evidence that brain fog has distinctive features versus existing constructs; it may conflate multiple phenomena which, although potentially interrelated, are meaningfully distinct, and it suggests transdiagnostic commonalities that are currently unclear.

Therefore, at present, we suggest that researchers and publishers should complement the term brain fog with more specific definitions. Neuropsychiatric symptoms in a specific disorder should be given descriptive names (e.g., 'post-COVID-19 neuropsychiatric symptoms' rather than 'COVID-19 brain fog'). The term brain fog itself may have greatest utility as an item in patient-reported quality of life measures.

For research, before attempting to formally define brain fog, further investigation will be necessary to understand the characteristic syndrome of cognitive, affective, and fatigue symptoms and the mild objective cognitive deficits it refers to (see Outstanding questions). A standardised and comprehensive measurement strategy is required that uses scales to fractionate the constructs that it most commonly conflates. This should capture the essential transdiagnostic features while being more precise and operationalizable via more detailed subjective and, ideally, objective measures.

We suggest that, rather than developing new tools, a standardised set of well-validated existing measures should be used wherever possible. This should enable researchers to precisely characterise brain fog subjectively and objectively and to differentiate between the contributions of objective cognitive impairment, metacognitive errors, fatigue, and affect. Assessment should include a high-precision cognitive battery that covers the major cognitive domains (attention, memory, reasoning, language, visuospatial) with accuracy and speed metrics, objective fatigue metrics (such as sustained attention), and metacognitive accuracy metrics. These have unique value in

Outstanding questions

How does the phenomenology of brain fog compare between conditions? Does brain fog have distinctive phenomenological qualities?

How does the cognitive performance profile associated with brain fog compare across conditions – is there an essential transdiagnostic profile? How does it compare with the deficits observed in depression and anxiety?

Considering cognitive correlates, is mental fatigability, or cognitive slowing, correlated with brain fog outside COVID-19 and ME/CFS?

How do subjective brain fog, cognitive performance, and noncognitive factors such as affect, fatigue, and apathy interrelate? Is this consistent across conditions? Is brain fog associated with increased distractibility outside fibromyalgia? Are metacognitive errors increased in brain fog outside ME/CFS and fibromyalgia?

Are there shared neural correlates of brain fog across conditions? Are BBB disturbances implicated in brain fog outside long COVID-19 and SLE?

Can a clinically useful (objective) instrument be developed to subtype or fractionate aspects of brain fog by differentiating between cognitive performance, fatigability, metacognitive errors, and anxiety/depression?

Do cognitive rehabilitation or 'brain-training' interventions, or treatments for depression/anxiety, benefit brain fog?

determining the multidomain profile of cognitive impairment associated with brain fog and in identifying a unifying cognitive signature, if this exists [135]. Protocols to harmonise results across different neuropsychological test procedures, such as the IC-CODE for epilepsy, also adapted for post-COVID-19 cognitive dysfunction, may help here, although precision would be lower [158]. We suggest that noncognitive factors are also measured – affect (e.g., using the generalised anxiety disorder questionnaire, GAD-7 [159] and the patient health questionnaire, PHQ-9 [160]), fatigue (e.g., the fatigue severity scale [161]), sleep quality (e.g., the Pittsburgh sleep quality index, PSQI [162]), and somatisation (e.g., the 15-item patient health questionnaire, PHQ-15 [163]). Studies using large sample sizes and standardised assessment protocols will be necessary to detect subtle performance deficits and to conduct the subgroup comparisons necessary to understand the relationships between brain fog and underlying disorders.

Future goals include the development of biomarkers of brain fog and clinical recommendations for its assessment and treatment. Existing recommendations, including a personalised, multidisciplinary assessment [122], and optimising lifestyle and cardiovascular risk factors (diet, exercise, social activity, etc.) [65,122], while sensible, are nonspecific. In our view, research to characterise brain fog and elucidate its subtypes is a prerequisite for progress in this domain, as brain fog likely conflates heterogeneous pathologies. While treatment approaches such as hyperbaric oxygen therapy, noninvasive brain stimulation, methylphenidate, bupropion, and atomoxetine have been trialled [164–167], these require further testing and validation. The design and targeting of effective treatments, including cognitive rehabilitation approaches, will ultimately require the development of more refined stratification tools, biomarkers, and assessment methods.

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Declaration of interests

A.H. is founder and director of Future Cognition Ltd, and cofounder and codirector of H2CD Inc which are developing custom online assessment software and provide automated online assessment technology as a service to third parties primarily in the academic and healthcare sectors. M.H. is a consultant for NeuHealth. P.D. and S.Z. declare no competing interests.

Resources

[i] www.oed.com/dictionary/brain-fog_n

[ii] www.etymonline.com/word/fog

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