# Eating behaviour and metabolism in amyotrophic lateral sclerosis and frontotemporal dementia: providing insights for neurodegeneration.

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**Search Strategy:**

We searched medline (1966 to 31st October 2015) using terms neurodegeneration, amyotrophic lateral sclerosis, frontotemporal dementia and metabolism in combination with eating, neuroendocrine, diet, insulin resistance, cholesterol and lifestyle factors. Further articles were included from reference lists, review articles, and major textbook chapters. Abstracts and reports from relevant meetings were also included. The final reference list was generated on the basis of originality and relevance to the topics. Emphasis was placed on publications from the past 5 years, but did not exclude commonly referenced and highly regarded older publications. Only papers published in English were considered in our search.

**Abstract**

Metabolic changes incorporating changes in weight, insulin resistance and cholesterol levels have been identified across a number of neurodegenerative conditions. It remains unknown how these changes arise, whether they represent the result of the process of neurodegeneration affecting critical brain regions involved in metabolic regulation, or are causative, driving the process. In amyotrophic lateral sclerosis (ALS) metabolic changes have been linked to disease progression and prognoses. Changes in eating behaviour affecting metabolism have been incorporated into the diagnostic criteria for frontotemporal dementia (FTD), which shares a significant clinical and pathological overlap with ALS. Given the spectrum of metabolic and eating changes observed in ALS and FTD, these two conditions may potentially provide a model to better understand the pathophysiology of metabolic change and to further study the interplay between systemic metabolism and the process of neurodegeneration**.**

## Introduction

Increasing evidence suggests that metabolic change, including fluctuations in weight, insulin resistance and cholesterol has an increased incidence across a range of neurodegenertive conditions[1,2-5]. It remains to be clarified how these changes may modulate the process of neurodegeneration and indeed how they may affect disease progression and thereby prognosis. Typically insulin resistance and metabolic changes have been viewed as consequences of obesity.[6] However increased peripheral insulin resistance and diabetes occur more frequently in neurodegenerative disease,[1,2-5] despite significant weight loss occurring in many of these disorders, often prior to diagnosis[7,8] As such insulin resistance may be considered independently related to the

processes of neurodegeneration.[9,10] (Figure 1) Common mechanisms associated with both metabolic dysfunction and neurodegeneration include oxidative stress, inflammation and vascular dysfunction.[10] Whether these or alternate mechanisms promote metabolic dysfunction and neurodegeneration remains unclear.

While there is limited *in vivo* evidence for the exact metabolic mechanism/s that may enhance neurodegeneration, there is emerging data on the metabolic variability associated with different neurodegenerative phenotypes. This is best highlighted by recent research in amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) that suggests a spectrum of phenotypic metabolic changes that can be used as a model for studying such changes across other neurodegenerative conditions. The present article examines the eating and metabolic changes across the ALS and FTD spectrum and proposes a way forward for investigating metabolic disorders in these conditions in order to answer the critical question, namely whether metabolic derangements are the result, or conversely promote neurodegeneration.

****Figure 1****

**The ALS and FTD clinical spectrum**

Mounting evidence points towards an overlap between ALS and FTD at clinical and neuropathological levels.[11] These two conditions may be conceptualised as representing the extremes of a disease spectrum.[12,13] Patients diagnosed with ALS typically exhibit limb or bulbar symptoms at initial presentation. (figure 2)[14-16] There are varying reports on the incidence of cognitive changes in ALS (behavioural, cognitive, language) with estimates upwards of 5%[17,18], while up to 15% of patients may satisfy the criteria for a diagnosis of concomitant FTD.[19] Conversely, 10-15% of FTD patients have ALS, with varying estimates of motor neuron dysfunction in FTD insufficient to reach criteria for ALS, at between 25-30%.[12,20.] FTD and ALS often

share a common pathology, TDP-43 protein deposition, which is present in the majority of ALS patients and in up to 50% of cases of FTD.[21] This overlap has been further reinforced with the discovery of the *C9orf72* gene abnormality in individuals with familial FTD and ALS.[22] Recent research has suggested that these conditions may potentially result from a contiguous (almost 'prion like') spread [23],[24,25] in a recognised centrifugal pattern with 4 stages of spread in ALS beginning in the motor neocortex, progressing to the spinal cord and brainstem, with involvement of frontal-parietal regions and finally the temporal lobes.[26] Such a pattern of spread may further potentially explain the development of cognitive symptoms in ALS. In behavioural variant FTD (bvFTD) spread has been suggested to develop with a fronto-occipital gradient involving initially the frontal region, and then pre-motor, primary motor, parietal and occipital cortex.[27] How this spread of pathology may occur and how it may further explain the spectrum of ALSFTD and the effect that metabolism may play, remains to be determined. The available evidence for eating and metabolic changes in ALS and FTD and potential affects on disease pathology, progression and survival is now reviewed.

**Figure 2**

## Amyotrophic lateral sclerosis

### *Eating behaviour and Nutritional intake in ALS*

Traditionally ALS has been regarded as a disease associated with malnutrition, with recent suggestions that nutritional intake decreases as the disease progresses, with decrease intake in those with lower functional levels,[28] such that a high calorie diet and supplements may often be prescribed, with nutritional advice one of the major aspects of a multidisciplinary care model of management of ALS patients.[29-31] Despite these recommendations, empirical evidence regarding optimal food intake levels in

ALS remains to be defined. It has been accepted that ALS patients may develop a reduced intake secondary to dysphagia,[32] loss of appetite [33] and difficulty consuming food due to weakness of their hands. Recently it has also been determined that presymptomatic ALS patients may have increased total daily energy consumption compared to control subjects.[34] Nutrition in ALS is arguably far more complex than these factors alone. The insufficient food intake typically reported by ALS patients may reflect increased catabolic demand and a state of hypermetabolism, and ALS patients may have increased caloric intake to overcome this. In extreme situations, some patients may develop severe complications of malnutrition including Wernicke's encephalopathy.[35]

There is limited evidence as to whether particular diets may slow progression of ALS. A high caloric diet is generally promoted and a recent study has shown that a high caloric, high carbohydrate diet is safe and tolerated by patients, but its effect on progression is yet to be identified. [36] Small studies have reported that a high carbohydrate diet and high fat diet results in stabilization of BMI, with no effect on functional decline (ALS functional rating scale -ALSFRS) and muscle mass.[37] Studies in the SOD-1 mouse model[38] have suggested that a high fat diet may be beneficial, but given that TDP-43 is the predominant pathology in this disease, generalizability to humans is limited. A number of clinical trials utilizing a high fat diet are currently underway to help address this question (Clinical trial reference numbers NCT02306590, NCT02152449 www.clinicaltrials.gov). A recent study utilizing protein supplementation resulted in increased BMI and stabilization of the ALSFRS suggesting a possible role for protein supplementation that requires further investigation as to whether the benefit was from the protein supplementation per se or the increased caloric intake that resulted.[39]

Percutaneous endoscopic gastrostomy (PEG) is offered to many ALS patients with bulbar involvement, in an effort to maintain nutrition and prevent further weight loss[40]. Despite this clinical approach, evidence of an overall benefit on survival remains limited, and the timing of insertion needs to be considered closely with the need to maintain nutrition and BMI against a typical backdrop of worsening respiratory function. It was recently determined by a multi-centre observational study that PEG tube placement was safe, even in those ALS patients with low forced vital capacity and that a slow increase in caloric rate and long term high caloric diet was associated with prolonged survival.[41] Currently we are unable to advise patients on the ideal diet to slow progression in ALS, nor the effects that diet may have on metabolic changes.

***Metabolic changes in ALS***

Energy balance is a combination of intake (including food intake and nutrient absorption) and energy expenditure. Energy homeostasis is also intrinsically linked to glucose and lipid metabolism, with insulin being integral to cellular uptake of nutrients, and insulin resistance resulting in decreased sensitivity of peripheral cells (e.g. muscle) to nutrient uptake leading to decreased energy stores. ALS patients are generally lean and lose body mass, muscle mass and fat as the disease progresses leading to decreased energy store.[42] These patients are also hypermetabolic, resulting in a complex interaction between energy metabolism, insulin and glucose homeostasis, lipid levels and BMI.

*Hypermetabolism*

Patients with ALS are consistently hypermetabolic, with increased resting energy expenditure evident in up to 50% of patients.[43,44] This finding seems somewhat paradoxical, given that as the disease progresses patients develop denervation, muscle

atrophy, decreased muscle mass and decreased free fat mass, all of which would be expected to decrease energy expenditure.[43] Several variables have been hypothesized to contribute to this hypermetabolic state, including uncontrolled fasciculations,[42] increased respiratory muscle work[45] and mitochondrial dysfunction.[46] It is also possible that the hypermetabolic state is intrinsically linked to the process of neurodegeneration with several genetic animal models exhibiting hypermetabolism and weight loss.[38,47-49] Further compounding the issue are recent findings that energy expenditure in ALS patients using the doubly labeled water method are dependent on body composition and physical activity, meaning that some ALS patients may have reduced energy expenditure in advanced ALS. It remains to be determined what factors may modulate energy expenditure and how such factors may be incorporated into a clinical management paradigm.[50]

*Lipids*

The significance of hypercholesterolemia in ALS remains an ongoing source of debate, with questions remaining on whether there is an increased prevalence of hyperlipidaemia in ALS and its effect on progression and survival, with variations of reported results potentially secondary to factors including gender, ethnicity and BMI. In a French cohort of 369 patients with ALS, two thirds of patients had increased LDL cholesterol, decreased HDL concentration or a combination of the two.[51] In the same cohort 38% had an elevated LDL to HDL ratio and increased concentrations of apolipoprotein E.[51] In a German cohort elevated triglyceride and total cholesterol levels were associated with a positive effect on survival.[52] Other studies have suggested that increased cholesterol levels may be associated with slower functional decline and increased survival,[53] but these elevations in cholesterol levels may be gender specific, e.g. present only in females in a Japanese cohort.[53]

Alterations in lipid metabolism in ALS have been inconsistent, with several other studies suggesting that dyslipidaemia does not occur in ALS,[54-56] and is not associated with a benefit on survival,[55] whilst in other studies, although patients were not dyslipidemic, having a higher HDL/LDL ratio was correlated with improved survival.[56] In an Italian cohort poorer respiratory function was associated with lower cholesterol levels.[55] These differences may be secondary to ethnic group, with low cholesterol levels or hypolipidemia being found in a population of Asian ethnicity.[54] Adding support to the hypothesis that cholesterol may play a modulating role in ALS is the finding in a number of epidemiological studies that treatment with statins results in an increased incidence of ALS.[57,58]

The direct relationship between BMI and lipid levels has not being extensively investigated. One study has found that whilst LDL/HDL cholesterol ratio did not correlate with survival, the levels did not change over time or decrease with BMI, suggesting that for a given BMI the levels may remain elevated.[59]

Why some ALS patients develop hyperlipidaemia and the effects on prognoses and pathogenesis remains unclear. Hyperlipidaemia could result from higher caloric intake and studies are needed correlating intake and cholesterol levels. Currently we do not know how lipid levels vary with BMI, gender and ethnicity and their subsequent effect on survival.

*Insulin resistance*

ALS was one of the first neurodegenerative conditions in which an association with insulin resistance was identified.[60] Since then controversy has surrounded whether there is an increased incidence of diabetes and insulin resistance in ALS or whether diabetes may be protective for the onset of ALS and affect disease progression. The majority of the studies examining diabetes and ALS have been cross sectional and

single centre, meaning that the conclusions that can be derived are limited. Several studies[61,62] have shown insulin resistance or diabetes may be protective with later onset of ALS in those with diabetes.[61] A large Danish case control study found the estimated odds ratio (OR) for ALS in association with diabetes was 0.61 (95% Confidence Interval CI, 0.46-0.80).[63] In a large Swedish case control study, type 2 diabetes was associated with a decreased risk of ALS (OR 0.79, CI 0.68-0.91), whereas type 1 insulin dependent diabetes was associated with an increased risk (OR 5.38, 95% CI 1.87-15.51), suggesting protective effects may be restricted to type 2 diabetes which is associated with insulin resistance, rather than type 1 which has an autoimmune pathophysiology and may drive ALS. [64,65]

Recently a phase II clinical trial showed that pioglitazone, an oral anti-diabetic drug, as an add on therapy to riluzole, did not result in improved survival in ALS, and, in fact, resulted in a 21% increased hazard risk for mortality.[66] It was hypothesized that this drug would be effective due to its anti-oxidant and anti-inflammatory properties. One reason why this effect was not seen could be secondary to its effect on insulin resistance and glucose homeostasis.[67]

Despite these findings a number of other studies have suggested that whilst there may be an increased incidence of diabetes, it is not protective or a prognostic factor associated with ALS.[68] A systematic review recently found an increased incidence of diabetes and insulin resistance, yet no effect on disease progression or survival.[69] Adding further controversy, a recent study in a Japanese population[70] suggested an increased incidence of ALS in diabetics over a 9 year period with a HR of 1.35 (95% confidence interval [CI], 1.10– 1.67). This effect could be secondary to diabetes being an early marker of neurodegeneration, rather than driving the neurodegenerative

process, and further, that ALS patients may develop insulin resistance as a protective mechanism early on in the disease prior to diagnoses.

In order to determine the association of diabetes and insulin resistance with ALS and whether this metabolic change drives neurodegeneration or is protective, large prospective longitudinal multiple centre studies will be required across multiple countries and ethnic groups.

*Body Mass Index*

Patients with ALS typically have a normal or low BMI[71] and lose weight and body fat as the disease progresses,[72,73] which in turn negatively affects prognosis.[74] Low BMI in ALS has been attributed to a number of causes including loss of muscle mass,[42] swallowing difficulties, decreased nutritional intake[32] and a state of hypermetabolism.[42] It has also been suggested that the effect of BMI on survival in ALS may form a U–shaped relationship, with both low BMI and BMI > 35 associated with increased mortality, perhaps secondary to an increased incidence of cardiovascular disease.[59] There are anecdotal reports of fat redistribution in ALS, with patients developing muscle wasting, loss of subcutaneous fat and increased abdominal fat with the amount of subcutaneous fat correlating with functional status and survival in ALS.[75]

*Lifestyle factors*

Premorbid BMI has been linked to the development of ALS, with lean individuals, those with high levels of increased leisure physical activity,[76] and low premorbid BMI,[77,78] at higher risk of ALS. Increased prediagnostic body fat has also been associated with decreased risk of ALS mortality.[73] Whether prediagnostic BMI is predictive of the evolution of the disease in individuals diagnosed with ALS remains unknown..

Several studies have suggested that dietary modifications could decrease the risk of developing ALS and be protective. Interestingly, a high carbohydrate diet and low polyunsaturated fatty acid diet has been associated with an increased prevalence of ALS.[79] These results seem counterintuitive given that a high carbohydrate diet would be expected to be related to a higher caloric intake and BMI, which should be protective. A more recent study has suggested that a diet high in omega -3 polyunsaturated fatty acids decreases the risk of ALS, suggesting that the results in the previous study may have been secondary to the low polyunsaturated fatty acid content.[80] At this stage, no clear evidence exists as to which is the best diet to adopt to protect against ALS or change disease progression. Further large center studies are required to examine the effect of diet on preventing ALS.

## Frontotemporal dementia

### *Eating behavior and nutritional intake in FTD*

The following sections focus on eating and metabolic changes in the other disease extreme FTD, where research when compared to ALS has focussed more on eating abnormalities and less on their metabolic effect thus far. FTD is characterized by atrophy of the frontal and anterior temporal lobes. Three main clinical syndromes of FTD are generally reported, namely bvFTD and two language presentations, based on the predominant features at initial presentation. BvFTD is characterized by a marked deterioration in social function and personality. The language presentations are divided into fluent (semantic variant of primary progressive aphasia -svPPA) or nonfluent (nonfluent variant of PPA- nfPPA) variants, depending on the pattern of language and speech output deficits.[81,82]

Hyperorality and dietary changes form one of the six criteria for the diagnosis of bvFTD[83] and are reported in over 60% of patients at initial presentation[84] and prove

304 helpful in diagnosing bvFTD and in discriminating this condition from other
305 dementias such as Alzheimer's disease.[85] The changes in eating habits vary across the
306 clinical subtypes of FTD. Alterations in bvFTD patients have been characterized by
307 gluttony, hyperphagia, indiscriminate eating, and increased preference for sweet
308 foods,[86-88] as well as changes in appetite, food preference, eating habits and other oral
309 behaviours compared to patients with Alzheimer's disease.[89] It is accepted that these
310 changes in eating behaviour in FTD are complex and may be further confounded by
311 cultural and ethnic factors that may influence eating behaviour.[90]
312 In contrast, eating behaviour in svPPA has not been systematically examined until
313 recently, perhaps reflecting the longstanding tradition of conceptualising svPPA as
314 predominantly a language disorder. Typically svPPA patients have increased
315 selectivity and food fads in their eating behaviour [88] and prominent changes in food
316 preference and eating habits.[89,91]
317 Swallowing abnormalities have been reported in all three subtypes of FTD, and are
318 thought to be separate from compulsive eating behaviours and to reflect disruption of
319 cortical and subcortical brain pathways connecting to the brainstem swallowing
320 centre.[92] They may also indicate early ALS, and have been found to influence
321 prognosis.[92,93]
322 The effects of changes in eating behaviour on carer stress and on the patients' every
323 day functional activity have not been investigated. Anecdotally, many carers report
324 having to limit intake and place locks on fridge doors to limit patient intake. Our
325 recent systematic examination of the eating changes in FTD using carer surveys
326 revealed increased energy consumption in both bvFTD and svPPA patients.[91]
327 Compared to controls, bvFTD patients had significantly increased carbohydrate
328 intake, whereas svPPA patients displayed significantly increased sugar intake. Hunger

and satiety did not differ between bvFTD patients and controls, suggesting that alterations in hunger and satiety are not solely responsible for the abnormal eating behaviour in FTD. Other factors including cognitive behavioural changes, changes in reward processing, and pathological changes in neuro-endocrine systems are likely to contribute to alterations in eating behaviour in FTD.

*Proposed regional degeneration contributing to eating behaviour in FTD*

A number of studies have attempted to identify brain regions with greater neurodegeneration in bvFTD and svPPA patients, associated with abnormal eating behaviour. In bvFTD consistent regions identified were in a distributed set of frontoinsular and anteromedial temporal brain areas.[86,94] These areas are similar to the areas involved in bvFTD,[95,96] The pattern of change relating to eating behaviour suggests the disintegration of several networks rather than a specific structure being solely responsible for the behavioural change.

Some studies have examined further specific eating behaviours and deficits in FTD. Binge eating in bvFTD patients has been associated with atrophy of the ventral aspects of the right insula, striatum and orbitofrontal cortex,[86] which overlaps with regions involved in sweet preference (right anterior insula and bilateral orbitofrontal cortex)[94] and reward seeking (right ventral putamen and pallidum). [97]Patients with bvFTD and svPPA have been found to have deficits in flavour and odour identification, which link with degeneration in the left entorhinal cortex, hippocampus, and temporal pole.[98] The hypothalamus is known to be critical for the regulation of food intake as it is integral to both the neuroendocrine and autonomic control systems of the brain.[99,100] Atrophy of the posterior hypothalamus has been

associated with increased eating abnormalities in bvFTD[101,102], however this atrophy is not present in sv-PPA patients with eating abnormalities.[103]

Overall, these data support the concept that more than a single region is involved in the eating behaviours observed in FTD and that FTD subtypes may have degeneration in different parts of the same system producing overlapping behavioural abnormalities..

*Gut hormones and hypothalamic neuropeptides regulating food intake in FTD*

The hypothalamus is influenced by circulating hormones and locally-produced neuropeptides that mediate appetite and eating behaviour: hormones and neuropeptides key to the appetite stimulating pathway include ghrelin (released peripherally) and agouti-related peptide (AgRP- released in the hypothalamus),[104] while key substances to the appetite suppressing pathway include peripheral hormones leptin, peptide tyrosine tyrosine (PYY) and cholecystokinin (CCK)[105] and key central neuropeptides pro-opiomelanocortin (POMC).[106-108]

Studies on the appetite stimulating neuropeptides have found elevated levels of AgRP in both bvFTD and sv-PPA, and that AgRP levels were significantly associated with body mass index (BMI).[103] This is consistent with the increased food intake and potential hyperphagia described as one of the main eating behaviours observed. AgRP is known to be a strong promoter of food intake,[104] with administration of AgRP intracerebroventricularly in rats resulting in long-lasting hyperphagia.[109] In addition to increasing total food intake in rats, AgRP may also lead to a preference for fat enriched food,[110] and sucrose in the context of a high fat diet.[111]

Two studies have examined the role of the appetite suppressing hormone leptin in FTD. The first found that women with FTD who were hyperphagic had higher circulating levels of leptin compared with women with Alzheimer's disease. In

contrast, men with these disorders did not differ from controls in their leptin levels.[112] A second study found increased leptin levels in bvFTD patients exhibiting overeating.[113] The increase in leptin should increase satiety and decrease food intake, however leptin is produced in adipose fat with its levels increasing secondarily to an increase in adipocyte mass and higher BMI, resulting in central leptin resistance, and this seems a more likely explanation for increased leptin levels found in FTD.

It has been suggested that gut and hypothalamic hormonal changes in FTD may offset reward circuit dysfunction by regulating dopaminergic "top- down cognitive circuits" in compensation to overeating.[113] Overall changes in the levels of these regulating peptide hormones in FTD subtypes may assist with understanding differences in the eating behaviours observed. The interaction between these central and peripheral systems (Figure 3 and Table 1) regulating eating behaviour (peptide hormones influencing the hypothalamus, neurons in the hypothalamus, networks impacting on the hypothalamus and reward pathways) will be important to determine for the different FTD phenotypes.

***Table 1***

****Figure 3*****

***Metabolic changes in FTD***

Given the prominent changes in eating behavior in FTD it is not surprising that patients exhibit changes in BMI, insulin and cholesterol levels.

*Body Mass Index*

Recently it has been shown that both bvFTD (BMI= 29.65) and svPPA (BMI= 28.71) patients have increased BMI and waist circumference compared to normal controls (BMI= 24.05).[91] It has been suggested that this weight gain is associated with their eating habits.[87] Given the level of eating abnormalities in FTD, the question has been

raised in the literature as to why these patients do not have a higher BMI.[86] It has been suggested that concomitant changes in metabolic rate similar to that seen in ALS may be present in FTD and may counteract some of the effect of these abnormal eating behaviours on BMI.[86]

Lower body weight is observed in mouse models of FTD and ALS driven by a variety of genetic mutations, suggesting a secondary metabolic phenomenon from degenerative changes in a common set of vulnerable neurons.[114,115,116,117] Eating behaviours in these mice have not been determined. Mouse models of FTD and ALS could have similar eating disturbances with increased food intake that results in lower body weight due to their increased metabolic rate. In humans a reduction in weight with increased caloric intake and increased metabolic rate could be observed.

Changes in eating behavior with disease progression in bvFTD and sv-PPA may be further considered as metabolic change although evidence remains limited, and similarly how eating changes may progress longitudinally in FTD and their long-term effect on metabolism and BMI.

*Insulin resistance and lipids*

Insulin resistance has been identified in both bvFTD and svPPA with increased insulin and triglycerides and lower HDL cholesterol (reflecting a state of insulin resistance).[118] Importantly, more severe insulin resistance was associated with more severe eating abnormalities and higher BMI, and the changes in triglyceride and HDL cholesterol levels increase with disease progression.[118] Increased insulin resistance is a risk factor for diabetes, and FTD patients also have an increased incidence of diabetes.[119] The overall impact of these changes on disease progression and survival has not been explored, but is an important issue to consider, given the potential to

easily modify insulin and cholesterol levels with currently widely available medications.

**Could eating behavior and metabolic change influence survival in FTD and ALS?**

Given the clinical and pathological overlap between FTD and ALS,[12,120] it would be reasonable to consider whether metabolic changes represented additional components of the overlap spectrum.[121] At one end of the continuum, ALS patients develop weight loss, hypermetabolism, malnutrition, hyperlipidemia and insulin resistance. At the other end, patients with FTD develop insulin resistance, and potentially less weight gain than would be expected in light of their increased caloric intake.[86] Further supporting the notion of the continuum between ALS and FTD (Figure 4), is the observation that ALS patients who develop additional cognitive deficits have an increased BMI compared to ALS patients without cognitive deficits.[121] As such, these cognitively impaired ALS patients may mirror the eating changes described as typical in bvFTD, resulting in increased caloric intake and BMI.[122]

In further support, it has recently been suggested that the structures involved in eating behaviour in bvFTD may also play a role in ALS, with pathological studies identifying TDP-43 pathology in the lateral hypothalamus in ALS that correlates with reduced BMI.[123] It seems plausible that changes in the hypothalamus may reduce weight in ALS, and that patients who develop cognitive impairment in ALS may develop a spectrum of eating changes similar to those observed in bvFTD. This aspect may seem further enticing given that patients with the combination of FTD and ALS have a more rapid disease progression and poorer survival,[124,125] suggesting a more aggressive disease process.

It remains to be determined how diet, ethnicity and BMI correlate with insulin, lipid and metabolic rate, perhaps contributing to the variation in results reported in the literature to date; and how such relationships may in turn influence disease progression and survival in FTD and ALS. Metabolic changes may reflect and also potentially modulate pathological progression along the clinical spectrum between ALS and FTD.[23] Development of more exact animal models[126] may promote examination of the process by which eating and metabolism affect pathological spread.[23] Further understanding is required to determine whether metabolic differences vary with neuropathology, such as between TDP-43 which is most commonly identified in sv-PPA and ALS, when compared to bvFTD, which appears to be a mixture of TDP-43 and tau pathology. Given that many patients and carers ask about modifiable factors such as diet and lifestyle, clarification of these areas will enable the provision of targeted and accurate clinical advice.

***** Figure 4*****

## Conclusion

### Are metabolic changes the result of or do they exacerbate neurodegeneration?

The central question remains as to whether metabolic changes are the result or alternatively exacerbate neurodegeneration in ALS and FTD. These metabolic changes may represent an effect occurring secondarily to the process of neurodegeneration in critical brain regions, with some behavioural changes potentially serving as a protective influence. For example, the eating changes (hyperphagia) described in FTD may act as an adaptive mechanism to stave off a hypermetabolic state. Without more targeted research empirical evidence supporting either of these positions remains elusive. Further studies are required to document the relationship between eating behaviour and metabolic change in ALS and FTD.

Furthermore, critical analyses of disease progression and survival combining methods that examine the interaction between peripheral changes such as BMI, cholesterol and insulin levels, with central changes in brain structures, and the neuroendocrine changes,[127] may bridge a better understanding between these factors. It remains to be determined how premorbid lifestyle factors and genetic factors interact and affect phenotypical expression, for example whether patients with high premorbid BMI go on to develop a phenotype with cognitive deficits whilst those with a low BMI develop pure ALS. We propose that targeted studies adopting a longitudinal approach across multiple disease groups, including affected and presymptomatic mutation carriers examining both eating behaviour and metabolism, should yield critical insights into the complex relationship between eating, metabolism and neurodegeneration.

**Declaration of interests**

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**Author's contributions**

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**Table 1: Neural and hormonal correlates of eating behaviour in FTD**

| Study | Factors implicated in eating behavior in FTD | Measures used |
|---|---|---|
| Miller and colleagues, 1995 [87] | Hypothesis: ? reduced hypothalamic serotonin release | Carer questionnaire: weight gain, sweet/carbohydrate preference |
| Ikeda and colleagues, 2002 [89] | Hypothesis: eating changes related to atrophy in ventral (orbito-basal) frontal lobe, temporal pole and amygdala | Carer questionnaire: measuring 5 domains swallowing, appetite change, food preference, and eating habits |
| Woolley and colleagues, 2007[86] | Outcome: binge eating associated with atrophy in the right ventral, insula, striatum and orbito-frontal cortex. | Patient observation: Number of sandwiches eaten over 1 hour. Imaging: structural, Voxel Based Morphometry (VBM) |
| Whitwell and colleagues, 2007[94] | Outcome: sweet tooth associated with grey matter loss in a distributed network including bilateral postero-lateral orbitofrontal cortex and right anterior insula. Hyperphagia associated with grey matter loss in anterolateral orbitofrontal cortex bilaterally | Carer questionnaire: Manchester and Oxford Universities Scale for the Psychopathological Assessment of Dementia (MOUSEPAD) assessing hyperphagia and sweet preference. Imaging: structural, VBM |
| Piguet and colleagues, 2011[101] | Outcome: those with high feeding disturbance had significant posterior hypothalamic atrophy | Carer questionnaire: measuring 5 domains swallowing, appetite change, food preference, and eating habits Imaging: structural, manual tracing of hypothalamus Pathology: Hypothalamic volumes |
| Omar and colleagues, 2013[98] | Outcome: flavour identification in the combined Frontal – | Patient observation: New test based on cross modal matching of flavours to |

| | | |
|---|---|---|
| | temporal lode degeneration cohort was associated with grey volume in the left entorhinal cortex, hippocampus, parahippocampal gyrus and temporal pole. | words and pictures.<br>Imaging: structural, VBM |
| Perry and colleagues, 2014[97] | Outcome: overeating and sweet preference related to right hemispheric reward circuits including putamen, globus pallidus, insula and thalamus. | Case note review: documenting hyperphagia and sweet preference<br>Imaging: structural, VBM |
| Woolley and colleagues 2014[113] | FTD associated with decreased ghrelin, cortisol and increased insulin. Patients who overate exhibited increased leptin levels | Standardized lunch feeding session- total caloric intake calculated.<br>Blood serum: neuroendocrine measures |
| Bocchetta and colleagues, 2015[102] | Outcome: atrophy of the superior parts of the anterior and tuberal regions and the posterior region, with a trend to association with abnormal eating behaviours | Carer questionnaire: Cambridge behavioural inventory<br>Imaging: structural, multi-modal segmentation of hypothalamus on imaging |
| Ahmed and colleagues, 2015[103] | Outcome: abnormal eating behaviours related to posterior hypothalamic atrophy. Elevated levels of Agouti-related protein in bvFTD and sv-PPA | Carer questionnaire: measuring 5 domains swallowing, appetite change, food preference, and eating habits<br>Imaging: manual tracing of hypothalamus<br>Blood serum: neuroendocrine measures. |

**Figure 1: Metabolic changes in neurodegeneration**

Figure showing the metabolic changes documented in several neurodegenerative conditions and cross over between conditions, with multiple conditions showing insulin resistance and weight loss.[1-10]

**Figure 2: Patterns of involvement in ALS.**

Figure showing the classical patterns of involvement in ALS[15,16]

Figure A: Atrophy affecting the first dorsal interossei (grey arrow), with sparing of the adductor digiti minimi (ADM- black arrow) and the classical split hand syndrome. Figure B: Wasting of the tibialis anterior and intrinsic muscles of the feet. Figure C: MRI brain (T1 and T2 sequences) showing hyperintensity of the cortical spinal tracts (grey arrow), suggesting upper motor neuron involvement as described in the original description of ALS by Charcot.

**Figure 3: Structures implicated in eating changes in FTD and control of eating in the normal individual**

Figure showing structures implicated in eating behavior in FTD and pathways controlling eating behavior in normal individuals. Structures implicated in FTD include orbito-frontal cortex, right sided reward structures including putamen, paillidum and striatum and posterior hypothalamus.[86, 97-103]

Normal eating behavior is controlled by an appetite stimulating pathway (shown in green) which results from ghrelin being released peripherally and targeting neurons of the arcuate nucleus (ARC) of the hypothalamus that contain neuropeptide Y (NPY) and agouti related peptide (AgRP). An appetite suppressing pathway involves leptin (shown in red) being released from peripheral adipocytes which then acts on pro-opiomelanocortin (POMC) and the cocaine and amphetamine related transcript (CART) neurons in the hypothalamus. Peptide tyrosine tyrosine (PYY) and cholecystokinin (CCK), released peripherally also suppress appetite. AgRp, NPY, POMC and CART neurons in the hypothalamus project to act on melanocortin receptors (MCR). POMC is cleaved into alpha and beta melanocyte stimulating hormone that act on melanocortin receptor subtypes 3 and 4 (MCR 3 and 4) to

950 decrease food intake. AgRP stimulates food intake by antagonism of MCR 3 and 4
951 receptors.[106-108] In both bvFTD and sv-PPA elevated levels of AgRP have been
952 found.[103] Autonomic pathways (black arrow) are also involved in food intake through
953 projections via the brainstem and cerebellum to the hypothalamus, PVN:
954 paraventicular nucleus
955
956
957 **Figure 4: Eating and metabolic changes across the spectrum of ALS and FTD**
958
959 Visual representation of eating and BMI changes across the ALS and FTD spectrum.
960 With decreased BMI and metabolic changes in ALS[42], and as patients develop
961 increasing cognitive impairment in ALS, increased BMI.[121] FTD patients have
962 increased BMI, but in the literature it has been suggested that this is less than
963 expected for their caloric intake.[86] Areas requiring further work (marked with ?)
964 include the levels of caloric intake in ALS and whether FTD patients are also
965 hypermetabolic. ALS plus refers to ALS patients with cognitive and behavioural
966 changes that do not yet meet the diagnostic criteria for FTD.
967