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Apathy: a neurocircuitry model based on frontotemporal dementia

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Abstract

Apathy is a symptom shared among many neurological and psychiatric disorders. However, the underlying neurocircuitry remains incompletely understood. Apathy is one of the core features of behavioural variant frontotemporal dementia (bvFTD), a neurodegenerative disease presenting with heterogeneous combinations of socioaffective symptoms and executive dysfunction. We reviewed all neuroimaging studies of apathy in frontotemporal dementia (FTD) attempting to refine a neurocircuitry model and inform clinical definitions. Levels of apathy have been consistently shown to correlate with the severity of executive dysfunctions across a wide range of diseases, including FTD. Some authors view 'energisation'—the loss of which is central in apathy—as a core executive function. Apathy in FTD is most robustly associated with atrophy, hypometabolism and/or hypoperfusion in the dorsolateral prefrontal cortex, the anterior and middle cingulate cortex, the orbitofrontal cortex and the medial and ventromedial superior frontal gyri. Data also suggest that abnormalities in connecting white matter pathways and functionally connected more posterior cortical areas could contribute to apathy. There is a lack of consistency across studies due to small samples, lenient statistical thresholds, variable measurement scales and the focus on apathy as a unitary concept. Integrating findings across studies, we revise a neurocircuitry model of apathy divided along three subcomponents (cognition/planning, initiation, emotional-affective/motivation) with specific neuroanatomical and cognitive substrates. To increase consistency in clinical practice, a recommendation is made to modify the bvFTD diagnostic criteria of apathy/inertia. More generally, we argue that bvFTD constitutes a disease

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model to study the neurocircuitry of complex behaviours as a 'lesion-based' approach to neuropsychiatric symptoms observed across diagnostic categories.

INTRODUCTION

Frontotemporal dementia (FTD) is a clinical descriptor for a group of neurodegenerative diseases including both a behavioural variant and language variants (primary progressive aphasia (PPA)). Behavioural variant frontotemporal dementia (bvFTD) is a progressive neurodegenerative disease presenting with a heterogeneous combination of socioaffective symptoms and executive deficits[1] due to dysfunction in neuronal networks subserving social cognition, motivation, emotion regulation, decision-making and others.[2] While bvFTD is a complex clinical challenge, it constitutes an interesting disease model to understand the neurocircuitry of many human behaviours ascribed to frontal neural systems.

Apathy is one of the six core symptoms of the 2011 International Consensus Criteria for bvFTD (see box 1).[1] However, there is still debate about the best definition of apathy, and its boundaries are unclear. The bvFTD diagnostic criteria II.B can be met if the subject has apathy *or* inertia,[1] without specifying the distinction between these concepts. Unsurprisingly, apathy/inertia was found to be the bvFTD criterion with the least inter-rater reliability (mean κ=0.47)[3] and specificity.[4]

Apathy is a symptom shared between many neurological and psychiatric disorders including Parkinson's disease (PD), Alzheimer's disease (AD), cerebrovascular disease, major depressive disorder (MDD) and schizophrenia. It is one of the most salient behavioural and psychological symptoms of dementia, having been associated with more rapid cognitive and functional decline,[5] increased mortality in AD[6] and worse outcomes across a number of neurological diagnoses.[78] Despite the ubiquitous nature of apathy, the underlying neurocircuitry remains incompletely understood. We postulate that bvFTD is an excellent model to study the neurocircuitry of apathy for several reasons. In bvFTD, changes in behaviour are the central clinical feature in the early stage of the disease and arise from neuronal dysfunction associated with measurable cortical atrophy, in contrast to more difficult to localise functional abnormalities in primary psychiatric disorders. Moreover, symptoms are less confounded by other related symptoms such as dysphoria in AD,[9] perceptual disturbances in schizophrenia (eg, command hallucinations influencing behaviour) and depressed mood in MDD. In this article, we systematically review FTD neuroimaging studies of apathy attempting to refine a neurocircuitry model of apathy in FTD, postulating that it could serve as a model to understand apathy in other neuropsychiatric disorders. We first provide a brief overview of clinical aspects of apathy.

BACKGROUND

Phenomenology and definitions

We generally think of apathy as a symptom of a disease such as FTD or AD or as a symptom that is an element of a disorder such as MDD, but some authors consider apathy to be a primary neuropsychiatric syndrome in some settings.[10] Operationalised criteria for an

apathy syndrome were proposed in 1991,[10] with lack of motivation compared with a previous baseline being the core symptom. Motivation is defined by the Oxford English Dictionary as the reason(s) an individual behaves in a particular way, as well as the general desire or willingness of someone to do something. Lack of motivation can be evidenced by diminished goal-directed behaviour (eg, lack of initiative), goal-directed cognition (lack of interest in new things) and emotional concomitants of goal-directed behaviour (eg, lack of affective reactivity to evocative events).[10] These criteria were revised in 2009, including a 4-week duration criterion (box 2).[11] Symptoms are divided into goal-directed behaviour, cognition and emotion, each domain including one example of self-initiated action/cognition/emotion and one related to responsiveness to external stimuli.[11] Despite this division into cognitive, affective and action-oriented components, studies have generally found substantial overlap between the three subcomponents.[912]

Some authors have criticised the emphasis on motivation, suggesting that apathy is best described in behavioural terms by the absence of responsiveness to internal or external stimuli, leading to decreased self-initiated actions.[1314] Levy and Dubois[13] suggested redefining apathy more ‘objectively’ as ‘the quantitative reduction of self-generated voluntary and purposeful behaviour’.[13] While we agree that a reduction in self-initiated and sustained behaviour is a central feature, we believe that change in the subjective motivation state is a dissociable component. Indeed, some patients with bvFTD report an intact sense of motivation but engage in little productive activity, while others express remarkable indifference but still perform tasks. Integrating these different contributions, Massimo and Evans recently revised the definition of apathy in the context of FTD as being a reduction in goal-directed behaviour stemming from any combination of deficits in initiation, planning and motivation.[15]

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) does not include operationalised apathy criteria. Apathy is listed as a behavioural disturbance in mild/major neurocognitive disorders, as a symptom of frontotemporal neurocognitive disorder and as a form of personality change due to another medical condition. DSM-5 has adopted a definition of apathy including both subjective motivation changes and reduced observable behaviour, stating that ‘apathy is typically characterised by diminished motivation and reduced goal-directed behaviour, accompanied by decreased emotional responsiveness.’

Comparative terminology

Further challenges arise from the use of different terms to describe related phenomena across disciplines and diseases.[16] In psychiatry, apathy has been historically and arbitrarily reserved for disorders with structural abnormalities (eg, dementia, ‘organic personality’), as opposed to idiopathic syndromes. However, symptoms of MDD such as ‘lack of interest’, ‘lack of pleasure’ and ‘lack of energy’ are in part related to apathy. Despite some overlap, patients can have apathy without MDD and vice versa.[1718] The clinical distinction is made based on the presence of these symptoms within a broader negative affective syndrome in depression, including low mood, neurovegetative symptoms, guilt/worthlessness and suicidal thoughts. Whereas anhedonia (reduced experience of pleasure) can be a feature of both depression and apathy,[19] it is usually accompanied by distress in the former, as opposed to

indifference in the latter. Negative symptoms of schizophrenia also overlap with apathy but are described by distinct terms such as avolition, alogia (impoverishment in thoughts) and asociality. These overlaps across diagnostic categories open the possibility of cross-informative neuroscientific studies.

In neurological nosology, apathy overlaps with abulia and akinetic mutism. Abulia usually implies a poverty of spontaneous movements and speech, in addition to the usual features of apathy.[20] Milder forms of abulia have been historically referred to as abulia minor.[21] Akinetic mutism is the complete absence of spontaneous behaviour and speech in an individual who appears alert. While akinetic mutism clearly has added descriptive value, we postulate that the distinction between apathy and abulia is not conceptually clear and that the latter term should be eliminated and replaced by a severity specification for apathy.

Neuropsychological perspective

Levels of apathy have been shown to correlate with the severity of executive dysfunctions in a wide range of diseases, including FTD,[2223] AD,[24] mild cognitive impairment (MCI),[25] PD,[2627] late-life depression[28] and psychotic disorders.[2930] It has been most consistently associated with impaired performance on letter fluency (F-A-S),[25282931] Trail Making part B[232829] and the Wisconsin card sort test,[2728] independent of depressive symptoms.[23–252732] A few studies have also found links between apathy and short-term recall[2732] and social cognition.[23]

Based on neuropsychological studies and patients with brain lesion, Stuss and Alexander categorised frontal cognitive processes into task setting, monitoring and energisation.[1433] Energisation, defined as the process of initiation and sustaining a response, is particularly relevant to apathy. Deficits in energisation can be measured by, for example, lexical fluency tasks (eg, total number of words produced in a finite period of time)[3334] and have been most consistently associated with lesions of bilateral supplementary motor area (SMA).[33] When a clinician is evaluating a patient with suspected apathy, generative tasks such as this may provide the simplest performance-based correlate of the symptom of apathy.

Apathy scales

The most frequently used scale is the Apathy Evaluation Scale (AES), an 18-item scale completed by the patient, caregiver or clinician.[16] In dementia, the informant-rated version has the most reliable psychometric properties.[35] The Apathy Scale is a briefer version that can be administered with a structured interview. Another scale, the Apathy Inventory, assesses the three dimensions of apathy (behavioural, cognitive, emotional blunting) on a simple one-question frequency/severity Likert scale.[36] Apathy is also an item of the Neuropsychiatric Inventory (NPI), graded for both frequency and severity based on nine standard questions after a positive screening item.[37] A clinician-rated version including 12 apathy items (NPI-C) was also developed.[38] The Frontal Behavioural Inventory (FBI) includes some apathy items (apathy, aspontaneity, emotional flatness, logopenia, personal neglect)[39] as part of the ‘negative symptoms’ cluster. The specific apathy item corresponds to the cognitive component (lack of interest). The Frontal Systems Behaviour Scale (FrSBe) is a self-rated or informant-rated scale to assess apathy, disinhibition and executive

dysfunction in patients with frontal lobe injuries.[40] For a comprehensive review of psychometric properties of scales, see Clarke *et al*[3541] and Starkstein *et al.*[516] Although most measures of apathy involve questionnaires such as these, some investigators have developed performance-based tests such as the Philadelphia Apathy Computerized Test (PACT) to objectively assess apathy along three dimensions: initiation, planning and motivation.[42]

METHODS

Neuroimaging review

A Pubmed search of all English language original research articles with keywords 'Frontotemporal Dementia' AND 'Apathy' was conducted through December 2016. We did not include imaging search terms to identify articles of potential interest that did not have imaging component for the general review, in addition to neuroimaging studies that were the focus of the review. The search produced 168 abstracts that were systematically reviewed to identify neuroimaging studies of apathy in FTD across all imaging modalities, excluding case reports. Articles were included in the study if they were either:

1. Group analyses comparing the neuroimaging correlates of apathy in FTD to other disorders.
2. Correlation analyses between apathy severity and neuroimaging measures in FTD.

Fourteen articles met the inclusion criteria. Articles were reviewed to extract key findings and determine methodological validity. Reviewing references from the identified articles and a complementary Google Scholar search did not yield additional articles.

RESULTS

Apathy is the most common initial symptom of FTD[43] and is present to some degree in almost all patients suffering from bvFTD.[912] It is more frequent and severe in FTD than in AD[1243] and constitutes a major burden for caregivers.[44] Apathy is attributed more predominantly to loss of motivation in FTD, as opposed to dysphoria in AD.[912]

Structural neuroimaging

Most structural imaging studies of apathy have used MRI voxel-based morphometry (VBM) (table 1). In the largest study including only subjects with bvFTD (n=48) or PPA (n=14), FrSBe apathy scores were associated with increased atrophy of the right dorsolateral prefrontal cortex (DLPFC) ($p<0.05$, whole brain family-wise error correction), with trends of association in the right lateral orbitofrontal cortex (OFC), right anterior cingulate cortex (ACC), right temporoparietal junction (TPJ) and right putamen.[22] In a more recent study, Eslinger *at al* (bvFTD=12, primary non-fluent aphasia (PNFA)=7, semantic dementia (SD)=7) reported an association between AES score and atrophy of the right head of the caudate (including the ventral striatum), right TPJ, the posterior part of the right inferior and middle temporal gyri, left frontal operculum and left anterior insula.[23] However, the statistical threshold was lenient ($p<0.025$, uncorrected, >100 voxels/clusters). In another study (bvFTD=26, PPA=14), NPI apathy was correlated with atrophy in bilateral medial,

orbital, inferior and dorsolateral prefrontal areas, in addition to the right middle temporal gyri and right caudate nucleus ($p<0.01$,false discovery rate corrected after masking areas without atrophy, clusters ≥40 adjacent voxels).[44] One study found no difference in basal ganglia volume in subjects with high compared with low NPI apathy.[45] Finally, in one of the rare white matter studies, apathy severity was associated with reduced fractional anisotropy (FA) of the temporal part of the uncinate fasciculus.[46]

In a large study of mixed neurodegenerative diseases (n=148), including FTD (bvFTD=39, PNFA=13, SD=23), NPI apathy was associated with VBM atrophy in predominantly right-sided frontotemporal areas, including the lateral OFC, ACC, ventromedial superior frontal gyrus (vmSFG, ie, medial PFC area anterior to the ACC), caudate head and ventral striatum, but there was major overlap with other neuropsychiatric symptoms. When controlling for other variables, apathy was specifically associated with atrophy in the right vmSFG only in the FTD/SD subgroup (less stringent small volume region of interest (ROI) correction).[47]

Massimo and colleagues recently analysed the grey and white matter correlates of apathy along the three subcomponents of initiation, planning and motivation as measured by the PACT (n=18 bvFTD).[42] Impaired initiation was associated with decreased grey matter density in the ACC along with reduced FA in various related white matter tracts (cingulum, inferior longitudinal fasciculus, uncinate fasciculus, corpus callosum). Planning deficits were linked to atrophy in the DLPFC and decreased FA in the superior longitudinal fasciculus. Reduced motivation was associated with decreased grey matter in the OFC and ACC, along with reduced FA in the uncinate fasciculus. These results provide the best support for partially distinct circuits underlying subcomponents of apathy.

Functional neuroimaging (table 2)

Using single-photon emission computed tomography (SPECT), McMurtray et al. (2006) reported that apathy (single item Likert scale) was associated with bilateral frontal hypoperfusion, as opposed to temporal hypoperfusion for “hypomania-like” behaviors.[48] Sample size was relatively large (n=74 bvFTD), but hypoperfusion was assessed with a semiquantitative method with poor anatomical resolution. Le Ber *et al* compared 17 subjects with a predominant apathetic bvFTD to 28 age-matched controls and reported the strongest degree of hypoperfusion in medial SFG, ACC, middle cingulate cortex (MCC), pre-SMA/SMA and DLPFC.[49] The authors do not mention controlling for disease severity, so these findings may not be specific to apathy.

Using fluorodeoxyglucose positron emission tomography (FDG-PET), Peters *et al* did not find correlation between NPI apathy score and metabolism in 41 bvFTD subjects.[50] When comparing the 13 subjects with predominant apathy to controls using a more lenient statistical threshold ($p<0.001$, uncorrected, masking hypometabolic areas in non-apathetic subjects), there was hypometabolism in the posterior medial OFC (gyrus rectus). Franceschi *et al* compared 12 subjects with predominantly apathetic bvFTD to 24 age-matched controls and 6 disinhibited bvFTD.[51] The apathetic subjects unsurprisingly showed widespread differences with controls, while compared with disinhibited subjects controlling for disease duration ($p<0.01$, uncorrected) they had less uptake in bilateral DLPFC, medial PFC and

insula. The disinhibited subgroup had predominant hypometabolism in posterior OFC, inferior temporal cortex, ACC, hippocampus/amygdala and nucleus accumbens.[51]

In an FDG-PET study of a mixed sample of early dementia, MCI and subjective cognitive concerns (13/54 with FTD), apathy, disinhibition and abnormal eating were all associated with hypometabolism of the ACC, MCC, medial PFC and the left anterior and medial SFG.[52] Controlling for age and dementia severity (but not diagnosis), NPI apathy was specifically associated with hypometabolism in the left medial, inferior temporal gyri and the ventral tegmental area, a crucial node of the dopaminergic system.[52]

Two studies have used fMRI intrinsic connectivity. In a small sample (n = 8 bvFTD+8 SD) independent component analysis, there was an association between apathy and increased dorsal PFC connectivity, even when controlling for atrophy.[53] In bvFTD subjects only, increased right angular gyrus connectivity, a central node of the default mode network, was also linked to apathy.[53] Of note, the FBI negative symptoms score was used as a proxy of apathy; however, this subscale includes unrelated items (eg, apraxia, aphasia). Another study from the same group in 15 subjects (5 bvFTD+10 SD) found no association between baseline resting state fMRI and FBI negative symptoms score.[54] Authors reported that fractional amplitude of low-frequency fluctuation (a measure of network integrity) in the left insula predicted worsening of apathy, but this finding is difficult to interpret given the very short 8-week time frame.

DISCUSSION

Although there are considerable variations between studies, some patterns seem to emerge. Atrophy, hypometabolism and hypoperfusion localise predominantly to the DLPFC,[2242444951] ACC/MCC,[2242474951] OFC[224244475051] and medial SFG.[444749] Other areas less consistently implicated included the ventromedial SFG,[47] pre-SMA/SMA,[4951] insula[2351] and temporal areas,[234452] with possibly a right-sided predominance in structural imaging studies.[2247] The lack of consistency across studies is not surprising given the small samples and the often lenient statistical thresholds. The most statistically robust structural correlations were found in the right DLPFC[22] and right vmSFG (the medial area rostral to the ACC),[47] which are associated with executive dysfunctions.[2223]

These results partially overlap with findings in AD that have most consistently linked apathy to the ACC and OFC, but less with the MCC, vmSFG, SMA, ventrolateral PFC and DLPFC.[5556] Studies in PD have suggested a possible reduction in cathecholaminergic transmission in the mesolimbic pathway as one of the causes of apathy.[57–59] This dovetails with the finding of VTA hypometabolism on FDG-PET in a mixed sample of neurodegenerative disease, although this is an isolated finding requiring replication.[52]

Levy and Dubois proposed a frontostriatal neurocircuitry model of the three subcomponents of apathy. Cognitive features were attributed to damage in the DLPFC and connections to the ‘cognitive territory’ of basal ganglia (dorsal caudate nucleus); emotional-affective aspects to the vmPFC/OFC and connections to the ‘limbic territories’ of the basal ganglia (ventral striatum and ventral pallidum); and behavioural/auto-activation deficits to the ACC,

MCC and medial SFG and connection to both cognitive and limbic basal ganglia territories. Although there is overlap between these components,[912] this model was partly supported by findings from Massimo and Evans[15] linking planning to the DLPFC, initiation to the ACC and motivation to the ACC/OFC.[42]

We agree in large parts with the biological plausibility of this model,[13] with a few additional updates as illustrated in figure 1A. DLPFC atrophy is predominantly related to the cognitive component (planning) and associated with deficits in set-shifting, task setting and abstraction. Neuronal loss in the dorsomedial frontal areas (ACC, MCC, medial SFG, SMA) is most likely linked to the initiation component and to energisation deficits. The SMA/pre-SMA was not included in the original Levy and Dubois model, but this is potentially an important area given its role in energisation[3360] and intentional movement planning.[61] Finally, dysfunction in ventral prefrontal areas (SgACC, medial and lateral OFC) would be predominantly responsible for the emotional/affective components (subjective motivation) and accompanying problems in social cognition tests. The anterior insula could also have a role in the subjective motivation state across all subcomponents[23] given its role in the perception of emotionally significant stimuli, integration of interoceptive inputs and close connections with prefrontal structures.[62]

These cortical areas have specific anatomical connections and functional correlations with the striatum (figure 1B,C).[63] Lesions/dysfunction in these striatal areas (and possibly in their thalamic nuclei) could lead to similar symptoms to their cortical counterparts, as supported by the presence of apathy in neuro-degenerative diseases with predominant subcortical involvement (eg, PD, Huntington's disease) and subcortical strokes.

The few studies on white matter support the idea that apathy could also stem from lesions in pathways connecting these corticostriatal areas to each other and to wider networks (figure 1D).[63–65] Indeed, apathy was related to FA of the uncinate fasciculus, which is a key white matter tract connecting the limbic system to the OFC.[4246] The main intrinsic connectivity network related to the DLPFC, dorsal medial PFC and pre-SMA/SMA is the frontoparietal executive control network, while the ventral medial PFC is integrated as part of a wider limbic network.[6366] These long-range connections could explain a more minor contribution to apathy of posterior areas with functional connections to the PFC. Indeed, a few studies in FTD have suggested associations between apathy and the TPJ or lateral temporal areas.[222344] Although this remains to be tested, the severity of the different domains of apathy could evolve over time within a single patient as the disease propagates from core frontomedial deficits to more lateral frontal and temporal areas.[67]

It is important to note that the networks involved in this model are closely related to other core behavioural symptoms of bvFTD. Indeed, Shroeter *et al* and Rosen *et al* have demonstrated the significant overlap of cerebral regions across behavioural symptoms. For example, the dorsomedial PFC circuitry plays a key role in theory of mind,[68] and the anterior insula is part of the salience functional network, which has been shown to be disrupted in the stages of the disease.[69] However, not all regions involved in executive dysfunction, such as the inferior frontal area, overlap with the neurocircuitry of apathy.[70]

A few factors contribute to our limited understanding of the neurocircuitry of apathy. First, there remains some debate regarding the optimal definition of apathy. Although lack of motivation was identified as the central component of the syndrome,[11] observable lack of initiation and sustainability of goal-directed actions are also core features in our opinion. Indeed, patients with FTD are often unable to communicate a subjective lack of motivation or may report a normal degree of subjective motivation while not engaging in any productive behaviour. The wording in the 2011 bvFTD criteria[1] and DSM-5 is not consistent with this current definition of apathy. Indeed, 'inertia', if interpreted as a lack of behavioural initiative/auto-activation, is a subcomponent of apathy, not a separate symptom. Consequently, we suggest the modification in box 3 to the bvFTD diagnostic criteria.

Some patients with bvFTD and many with SD may have excessive motivation for compulsive non-productive interests or rituals but neglect day-to-day productive activities. In our view, some of these patients do not exhibit what we would describe as apathy—in fact, they may keep themselves quite 'busy'—but they have developed a relatively narrow set of activities to which they assign value. This could be viewed as a form of perseveration, which may involve executive dysfunction, semantic memory loss or other deficits that deserve further investigation but should not be viewed as apathy. The currently available scales do not capture these subtleties that are frequently seen in FTD. Even more problematic is the potential confusion between concepts such as depression and apathy.[17] For example, a careful assessment for depression has been shown to markedly reduce the identified prevalence of apathy in PD.[71] Confusing depression and apathy also has therapeutic consequences if patients do not receive adequate treatment for their mood disorders. Given the subtleties of teasing out apathy from depressive and cognitive factors, apathy in FTD should be assessed with information provided by caregivers[23] but rated by an experienced clinician. Non-professional caretakers do not have experience with a large number of patients; therefore, ratings can be influenced by recall bias, culture, beliefs, expectations and social desirability.[38]

From a methodological standpoint, we believe that it is important to control for disease severity in statistical analyses since apathy tends to increase as the disease progresses. In terms of imaging methodology, no published neuroimaging studies of the correlates of apathy have used surface-based cortical thickness analyses, which could provide better anatomical precision for the cortex. As the number of studies on this topic grows, meta-analytic approaches could be useful to clarify a specific circuitry for the different behavioural symptoms of FTD.[67] In addition, multimodal network approaches combining structural and functional connectivity could provide further insight into this behavioural problem.

In conclusion, the field should keep working toward more precise definitions of symptom domains such as apathy, and these constructs should be validated by multimodal methods of neuroscientific inquiry, across different diagnostic classes, factoring in the variation of traits within healthy individuals (eg, normal variations in motivation). This research should be integrated within the framework of the Research Domain Criteria (RDoC) to study neuropsychiatric symptoms in terms of neurocircuitry regardless of diagnostic category (eg, studying apathy as a combination of deficits in approach motivation and arousal systems).

We argue that bvFTD represents an excellent population for RDoC investigations because neuropsychiatric symptoms are central to the disease and arise from readily measurable neuronal atrophy. However, the generalisability of the neurocircuitry model of apathy in bvFTD proposed in this article should be tested in other psychiatric and neurological disorders to determine if the neurocircuitry is similar in all conditions. Finally, the hope is to reach the point where the diagnostic criteria for apathy could be revised to fit with our understanding of the underlying neurocircuitry abnormalities, providing a more robust foundation for the development of treatments including neuromodulation approaches such as rTMS and tDCS, in addition to pharmacological approaches.

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Box 1

Clinical diagnostic criteria for behavioural frontotemporal dementia[1]

1. Three of the following behavioural/cognitive symptoms (A–F) must be present to meet criteria:
2. Shows progressive deterioration of behaviour and/or cognition by observation or history (as provided by a knowledgeable informant).

   A. Early[1] behavioural disinhibition

   B. Early apathy or inertia

   C. Early loss of sympathy or empathy

   D. Early perseverative, stereotyped or compulsive/ritualistic behaviour

   E. Hyperorality and dietary changes

   F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions.

From Rascovsky *et al.*[1]

Box 2

Diagnostic criteria for apathy[11]

For a diagnosis of apathy, the patient should fulfil criteria A, B, C and D.

A. Loss of or diminished motivation in comparison to the patient's previous level of functioning and which is not consistent with his age or culture. These changes in motivation may be reported by the patient himself or by the observations of others.

B. Presence of at least one symptom in at least two of the three following domains for a period of at least 4 weeks and present most of the time.

B1: Loss of, or diminished, goal-directed behaviour as evidenced by at least one of the following:

- Loss of self-initiated behaviour (eg, starting conversation, doing basic tasks of day-to-day living, seeking social activities, communicating choices).
- Loss of environment-stimulated behaviour (eg, responding to conversation, participating in social activities).

B2: Loss of, or diminished, goal-directed cognitive activity as evidenced by at least one of the following:

- Loss of spontaneous ideas and curiosity for routine and new events (ie, challenging tasks, recent news, social opportunities, personal/family and social affairs).
- Loss of environment-stimulated ideas and curiosity for routine and new events (ie, in the person's residence, neighbourhood or community).

B3: Loss of, or diminished, emotion as evidenced by at least one of the following:

- Loss of spontaneous emotion, observed or self-reported (eg, subjective feeling of weak or absent emotions or observation by others of a blunted affect).
- Loss of emotional responsiveness to positive or negative stimuli or events (eg, observer reports of unchanging affect or of little emotional reaction to exciting events, personal loss, serious illness, emotional-laden news).

C. These symptoms (A–B) cause clinically significant impairment in personal, social, occupational or other important areas of functioning.

D. The symptoms (A–B) are not exclusively explained or due to physical disabilities (eg, blindness and loss of hearing), to motor disabilities, to

diminished level of consciousness or to the direct physiological effects of a substance (eg, drug of abuse, a medication).

From Robert *et al.*[11]

Box 3

Recommended modifications to bvFTD diagnostic criteria B

B. Early apathy (one of the following symptoms (B.1–B.2) must be present):

- **B.1.** Loss of motivation.
- **B.2.** Diminished initiation and/or performance to completion of goal-directed behaviour.

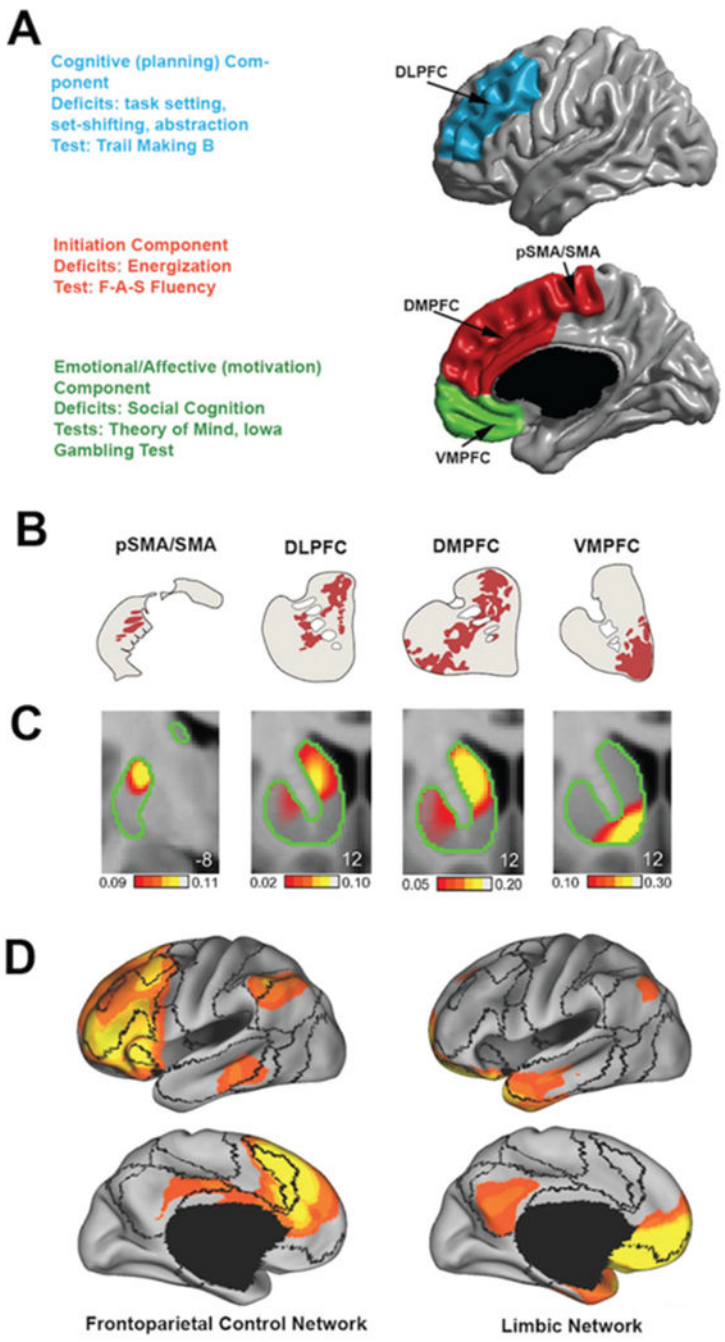

Figure 1.

Neurocircuitry model of the three components of apathy and associated cognitive deficits. (A) Hypothesised main neuroanatomical areas related to three subcomponents of apathy and associated cognitive deficits. (B) Striatal connections of key cortical nodes based on monkey tract tracing. pSMA/SMA has main connections with the medial putamen, DLPFC and DMPFC to dorsal caudate and VMPFC to ventral caudate (nucleus accumbens). (C) Resting state fMRI intrinsic connectivity of key cortical nodes with the striatum in humans corroborating anatomical findings in monkeys. (D) Main resting state intrinsic connectivity

networks associated with cortical nodes and related striatal connections. DLPFC, DMPFC and pSMA/SMA are mainly integrated as part of the frontoparietal control network. The VMPFC is integrated within the limbic network. (B–D) Adapted with permission from Choi *et al*.[63] Organisation of the human striatum estimated by intrinsic functional connectivity. DLPFC, dorsolateral prefrontal cortex; pSMA/SMA, presupplementary motor area/ supplementary motor area; DMPFC, dorsal medial prefrontal cortex; fMRI, functional MRI; pSMA, presupplementary motor area; VMPFC, ventromedial prefrontal cortex.

Table 1

Structural neuroimaging studies of apathy in FTD

Authors	Year	Sample	Apathy scale	Method	Main findings
Rosen *et al*[47]	2005	n=148 (AD, bvFTD, PNFA and SD)	NPI (continuous variable)	MRI–VBM	(1) Apathy in FTD/SD specifically associated with atrophy of right ventromedial superior frontal gyrus (2) Apathy and other neuropsychiatric symptoms associated with atrophy of right-sided frontotemporal areas, including the lateral OFC, MCC, vmSFG (mPFC), caudate head and ventral striatum
Zamboni *et al*[42]	2008	n=62 (bvFTD and PPA)	FrSBe (continuous variable)	MRI–VBM	(1) Apathy associated with increased atrophy in right DLPFC (2) Trends of association with left DLPFC, right ACC, right LOFC, right temporoparietal junction, right putamen
Massimo *et al*[44]	2009	n=40 (bvFTD=26, PPA=14)	NPI (continuous variable)	MRI–VBM	Apathy correlated with atrophy in bilateral mPFC, OFC, IFC, DLPFC, right middle temporal and right caudate
Links *et al*[45]	2009	n=21 (FTD)	Group contrast based on NPI	MRI–Semiautomated volume extraction	No association with basal ganglia
Eslinger *et al*[23]	2012	n=26 (bvFTD, SD, PNFA)	AES (continuous variable)	MRI–VBM	Apathy associated with higher atrophy in right caudate (ventral striatum), right temporoparietal junction, right posteroinferior and middle temporal gyri and the left anterior insula
Powers *et al*[46]	2014	n=11 (bvFTD)	NPI (continuous variable)	DTI-FA	Apathy severity associated with reduced FA in the temporal portion of the left uncinate faciculus
Massimo *et al*[42]	2015	n=18 (bvFTD)	Philadelphia Apathy Computerised Test	MRI-VBM DTI-FA	(1) Initiation deficits associated with decreased GM density in the ACC and reduced FA in the cingulum, inferior longitudinal fasciculus, unicinate fasciculus, corpus callosum (2) Planning deficits associated with decreased GM density in the DLPFC and decreased FA in the superior longitudinal fasciculus (3) Motivation deficits associated with decreased GM in the OFC and ACC and reduced FA in the uncinated fasciculus

AD, Alzheimer s disease; ACC, anterior cingulate cortex; AES, Apathy Evaluation Scale; bvFTD, behavioural variant frontotemporal dementia; DTI, diffusion tensor imaging; DLPFC, dorsolateral prefrontal cortex; FA, fractional anisotropy; FrSBe, Frontal Systems Behaviour Scale; FTD, frontotemporal dementia; GM, grey matter; IFC, inferior frontal cortex; LOFC, lateral orbitofrontal cortex; mPFC, medial prefrontal cortex; MCC, middle cingulate cortex; NPI, Neuropsychiatric Inventory; OFC, orbitofrontal cortex; PPA, primary progressive aphasia; PNFA, primary non-fluent aphasia; SD, semantic dementia; vmSFG, ventromedial superior frontal gyrus; VBM, voxel-based morphometry.

Table 2

Functional neuroimaging studies of apathy in FTD

Authors	Year	Sample	Apathy scale	Method	Main findings
Franceschi *et al*[51]	2005	n=18 (bvFTD)	Group contrast based on NPI	FDG-PET	(1) Apathy associated with hypometabolism of bilateral DLPFC, mPFC (MCC, SMA), frontal pole/anterior OFC, insula (2) Apathy and disinhibition associated with hypometabolism of bilateral insula and thalamus
Peters *et al*[50]	2006	n=41 (bvFTD)	NPI (continuous variable and group contrast)	FDG-PET	(1) No association with NPI apathy as a continuous variable (2) Subjects with predominant apathy (n=13) had hypometabolism in posterior mOFC (gyrus rectus) compared with controls
Le Ber *et al*[49]	2006	n=17 (bvFTD) vs 28 age-matched controls	Group contrast based on clinical assessment	SPECT	Apathy associated with predominant hypoperfusion in vmSFG, ACC, MCC, pre-SMA/SMA and DLPFC
McMurtray *et al*[48]	2006	n=74 (bvFTD)	Single item 5-point Likert scale (continuous variable)	SPECT	Apathy associated with frontal hypoperfusion
Schroeter *et al*[52]	2011	n=54 (AD, FTD, MCI, SCI, others)	NPI (continuous variable)	FDG-PET	(1) Apathy specifically associated to hypometabolism of VTA and left inferior and middle temporal gyri (2) Apathy, disinhibition and eating disorders associated with mPFC/ACC/MCC (BA 9, 10, 24, 32, 33) and left anterior SFG (BA 9, 10)
Farb *et al*[53]	2012	n=16 (bvFTD, SD) vs 16 age-matched controls	FBI	fMRI intrinsic connectivity	(1) Apathy associated with PFC hyperconnectivity (2) Apathy associated with increased angular gyrus connectivity in bvFTD only
Day *et al*[54]	2013	n=15 (bvFTD, SD)	FBI	fMRI	(1) No correlation between severity of apathy and resting state activity (2) Left insula integrity could predict short-term worsening of apathy

AD, Alzheimer's disease; ACC, anterior cingulate cortex; bvFID, behavioural variant frontotemporal dementia; BA, Brodmann area; DLPFC, dorsolateral prefrontal cortex; FDG-PET, fluorodeoxy glucose positron emission tomography; FBI, Frontal Behaviour Inventory; FTD, frontotemporal dementia; fMRI, functional MRI; mPFC, medial prefrontal cortex; MCC, middle cingulate cortex; MCI, mild cognitive impairment; NPI, Neuropsychiatric Inventory; OFC, orbitofrontal cortex; PFC, prefrontal cortex; SD, semantic dementia; SPECT, single-photon emission CT; SCI, subjective cognitive impairment; SMA, supplementary motor area; vmSFG, ventromedial superior frontal gyrus; VTA, ventral tegmental area.