https://doi.org/10.1093/brain/awac494

BRAIN
SCIENTIFIC COMMENTARY

Mechanisms underlying apathy in frontotemporal dementia

This scientific commentary refers to 'Effort avoidance as a core mechanism of apathy in frontotemporal dementia' by Le Bouc *et al.* (https://doi.org/10.1093/brain/awac427).

One of the defining features of behavioural variant frontotemporal dementia (bvFTD) can be the presence of apathy, a syndrome that is reported to occur in almost all patients with this diagnosis.[1] Often defined as a disorder of motivation, either in the behavioural, cognitive, emotional or social domain,[2] apathy is now known to be a common neuropsychiatric condition present across a range of brain diseases.[3] Although there has been some recent progress in treatment of apathy, particularly in Parkinson's disease (PD) and Alzheimer's disease, little is understood about the mechanisms underlying the syndrome.

One approach to study the cognitive and neural basis of apathy has been to consider it within the framework of effort-based decision making for reward.[3] In this conceptualization, individuals vary with respect to their subjective evaluation of whether a particular rewarding outcome is worth the physical or cognitive effort required to obtain it. Behavioural paradigms designed to probe how much effort a person is willing to invest to obtain different levels of reward have led to a neuroeconomic description of how motivated someone is. The effort that healthy people are willing to expend for a range of rewards varies considerably between individuals, but such tasks have revealed that patients with apathy show distinct differences from the norm.

In principle, individuals with pathological apathy might not be incentivized by reward or they might instead be hypersensitive to effort, or both. For physical effort, across three different conditions—PD,[4] cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)[5] and spontaneous, late-onset small vessel cerebrovascular disease (SVD)[6]—a common signature of apathy has been insensitivity to low rewards. Patients were unwilling to invest effort for low incentives but did so for higher ones. In SVD there was in addition hypersensitivity to high physical effort. For cognitive effort, in PD there is evidence of both aversion to effort and reduced incentivization by reward.[7]

In this issue of *Brain,* Le Bouc and colleagues[8] consider effort-based decision making for reward in bvFTD. They deployed a suite of tasks in 21 patients who were significantly more apathetic than the 40 healthy controls they also tested. In their motor performance task, participants were shown different monetary incentives on each trial and asked to squeeze a handgrip. They were told that the amount they could win was a fraction of the reward on offer calculated as a proportion of the force they exerted. Real-time feedback of the force applied meant that participants could view the effort they were exerting.

The raw data showed that, overall, individuals with bvFTD exerted far less force than controls over the range of incentives on offer, with the separation in physical effort between the two groups increasing with greater rewards. In fact, even on the calibration of maximum force prior to the main experiment, bvFTD patients produced significantly less force than controls, despite not having significantly different forearm muscle bulk. Computational modelling revealed that individuals with bvFTD had both significantly reduced reward sensitivity as well as increased sensitivity to effort compared to healthy people.

In addition to this force study, the authors also assessed participants' preferences for a range of items of different potential value (e.g. a bottle of champagne, stamp, apple, etc.) and a series of tasks with different potential effort costs, both physical and cognitive (e.g. climbing a flight of steps, beating eggs, filling in a tax form). Then they displayed pairs of items and tasks to ascertain whether, in the subjective evaluation of a participant, a particular reward was worth the effort shown (e.g. Would they climb a flight of steps for a stamp?). Cleverly, for each individual, they selected rewards and efforts depending on the choices made in the previous assessments of how much they preferred a reward and how much they disliked an effort. They also evaluated intertemporal choice by asking whether participants were willing to wait a variable length of time for an item they prized compared to receiving immediately an item they considered to be of low value.

Although bvFTD patients did not differ from controls on their subjective ratings (how much they valued) a rewarding item, they were significantly more likely to consider the tasks as more unpleasant, both for physical and cognitive effort. Overall, patients also showed a trend to accept fewer offers in the item–effort pairing task. Computational modelling revealed that the mean subjective value of rewarded items did not differ significantly between groups but the mean subjective value of effort was significantly higher in bvFTD cases. Further, the delay discounting parameter was also greater in patients compared to controls. When behavioural and modelling parameters were compared to apathy scores from a clinical questionnaire, there was a significant relationship between effort ratings in the preference task as well as modelled subjective effort value and sensitivity parameters.

The authors conclude overall that aversion to effort is the crucial factor associated with behavioural apathy in this group. While there is no doubt that hypersensitivity to effort is the common finding across the performance and preference tasks, it is also the case that there was evidence of blunted sensitivity to reward on the motor performance task in which participants actually had to make a physical effort. The authors argue that preference

Received December 22, 2022. Accepted December 22, 2022. Advance access publication December 26, 2022

tasks have the benefit of probing an individual's subjective assessment of how aversive a particular physical or cognitive effort task is. Moreover, they might be considered to provide a more ecologically valid means of probing more real-world decision making than evaluating whether or not to grip hard for a monetary reward. Although preference tasks do have the advantage of being easily administered, perhaps even in clinical settings, without the need for elaborate equipment, there are some important issues in this particular patient group.

Individuals with bvFTD often lack insight. For example, in the study by Le Bouc *et al*.,[8] self-reported apathy scores were not only lower than caregiver ratings but also did not correlate with them. In addition, people with bvFTD can make impulsive choices, as attested to by the reaction time data in this investigation. Thus, although preference tasks do have potential benefits, they might not be ideal measures in this group of patients. Nevertheless, this approach offers promise as a useful tool to recover subjective evaluation of how rewarding and how effortful a particular goal-directed behaviour might be for different individuals.

Le Bouc and colleagues[8] also investigated the brain correlates of behaviour and found that greater disliking of effort was associated with more atrophy in a region of the dorsal medial frontal cortex, which includes dorsal anterior cingulate cortex (dACC). This brain region has been implicated in some studies as a crucial node where effort costs are integrated with potential benefits in decision making.[9] The findings align well with recent conceptualisations of the key role of ventral striatal–medial frontal cortex connections in clinical apathy.[5,6]

At least two important questions about apathy in bvFTD remain unanswered though. First, the approach used by Le Bouc *et al*.[8] was specifically designed to investigate the behavioural or cognitive domains of apathy. Their paradigms did not address emotional or social apathy. A recent study combining several different patient groups, in which over half the patients had bvFTD, reported that higher emotional apathy is associated with poorer learning of socially rewarding as well as monetary outcomes.[10] Furthermore, initiation (behavioural) apathy did not correlate with the social reward learning impairment. It might be possible to use the preference techniques of Le Bouc and colleagues[8] also to address costs as well as benefits in emotional and social aspects of apathy in future studies.

Second, do findings on effort-based decision making tasks for reward have any implications for treatment? In PD, comparing patients ON and OFF their dopaminergic medication has revealed significant shifts in motivated behaviour, with greater willingness to expend both physical[4] and cognitive[7] effort when ON dopamine. The effects OFF medication were observed simply by asking patients to miss their morning dose of drugs (overnight withdrawal). Thus this approach provides a potentially cost effective means to assay whether a drug might alter apathy, although the pharmacokinetics of dopaminergic drugs and the pathology of PD might be a special case. Nonetheless, the value of experimental methods and computational modelling combined with brain imaging and pharmacological intervention to dissect out the mechanisms underlying apathy represents evidence of clear and significant progress being made across brain diseases to understand this important debilitating syndrome.

Masud Husain[1,2]

1 *Department of Experimental Psychology, University of Oxford, Oxford, UK*

2 *Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK*

E-mail: masud.husain@ndcn.ox.ac.uk

Competing interests

The author reports no competing interests.

References

1. Johnson E, Kumfor F. Overcoming apathy in frontotemporal dementia: Challenges and future directions. *Curr Opin Behav Sci*. 2018;22:82-89.
2. Dickson SS, Husain M. Are there distinct dimensions of apathy? The argument for reappraisal. *Cortex*. 2022;149:246-256.
3. Husain M, Roiser JP. Neuroscience of apathy and anhedonia: A transdiagnostic approach. *Nat Rev Neurosci*. 2018;19:470-484.
4. Le Heron C, Plant O, Manohar S, *et al*. Distinct effects of apathy and dopamine on effort-based decision-making in Parkinson's disease. *Brain*. 2018;141:1455-1469.
5. Le Heron C, Manohar S, Plant O, *et al*. Dysfunctional effort-based decision-making underlies apathy in genetic cerebral small vessel disease. *Brain*. 2018;141:3193-3210.
6. Saleh Y, Le Heron C, Petitet P, *et al*. Apathy in small vessel cerebrovascular disease is associated with deficits in effort-based decision making. *Brain*. 2021;144:1247-1262.
7. McGuigan S, Zhou SH, Brosnan MB, Thyagarajan D, Bellgrove MA, Chong TTJ. Dopamine restores cognitive motivation in Parkinson's disease. *Brain*. 2019;142:719-732.
8. Le Bouc R, Borderies N, Carle G, *et al*. Effort avoidance as a core mechanism of apathy in frontotemporal dementia. *Brain*. 2023; 146:712-726.
9. Pessiglione M, Vinckier F, Bouret S, Daunizeau J, Le Bouc R. Why not try harder? Computational approach to motivation deficits in neuro-psychiatric diseases. *Brain*. 2018;141:629-650.
10. Wong S, Wei G, Husain M, *et al*. Altered reward processing underpins emotional apathy in dementia. *Cogn Affect Behav Neurosci*. Published online 23 November 2022. doi:10.3758/s13415-022-01048-2