Findings that shed new light on the possible pathogenesis of a disease
or an adverse effect

Apathy and executive functions: insights from brain damage involving the anterior cingulate cortex

Progress Njomboro,¹ Shoumitro Deb,² Glyn W Humphreys³

¹Department of Psychology, University of Cape Town, Cape Town, South Africa

²Department of Psychiatry, School of Psychology, University of Birmingham, Queen Elizabeth Psychiatric Hospital, Birmingham, UK

³Department of Experimental Psychology, Oxford University, Oxford, UK

Correspondence to Dr Progress Njomboro, Progress.Njomboro@uct.ac.za

Summary

Patients with anterior cingulate cortex (ACC) lesions present an opportunity for understanding apathy's disputed neuropsychiatric features, as well as its associated neurocognitive phenotype. In this case report, two male patients (patient A and patient B) with lesions involving the ACC bilaterally were assessed for apathy, depressive symptoms, executive functioning, and also tested on the Iowa Gambling Task (IGT). Twenty neurologically intact controls also provided normative scores on the IGT. Patient A and patient B had high scores for apathy and low depressive symptoms scores. Patient A had relatively intact performance on standard executive function tests, but patient B had significant impairments. Both patients were significantly impaired on the IGT. Our findings suggest that executive function deficits are not crucial for the presence of apathy symptoms. These findings not only shed light on the relationship between apathy and executive function deficits, but also have important implications for patient care and rehabilitation.

BACKGROUND

Apathy is often seen as one of two common but distinguishable dysexecutive syndromes: one which is associated with poor motivation, reduced activity and emotion, against another characterised by excessive but maladaptive behaviour.¹ The clinical relevance of apathy is now widely appreciated in clinical practice and research, although questions around its syndromic position (especially in relation to depression) and its neurocognitive correlates remain largely unanswered.² For instance, it is now generally agreed that apathy and depression are separate neuropsychiatric conditions,³ but evidence shows that the two are often confused in clinical practice.⁴ Research on the neurocognitive correlates of apathy has also yielded mixed results (for a review see ref.⁵). This underscores the need for more research into this area.

Neurological models of apathy associate the syndrome with anterior cingulate cortex (ACC) dysfunction, with large or bilateral ACC lesions known to produce more severe apathy.⁶ The ACC is thought to motivate goal-directed behaviour by modulating cognitive, motor and affective processes related to drive.⁷ Apathetic patients with ACC lesions then present an opportunity to investigate questions around the syndrome.

We examine the relationship between apathy symptoms and executive functions (EFs) involved in the cognitive control of behaviour in two apathetic male patients with lesion involving the ACC bilaterally. On the basis of available literature, we hypothesised that the two patients would show deficits on standard EF tests and also show concurrent deficits on the Iowa Gambling Task (IGT⁸) test of socio-executive processing. We also evaluated the patients for depressive symptoms.

CASE PRESENTATION

We present evidence from two brain-damaged patients (patient A and patient B, aged 52 and 50 years, respectively, at the time of testing), whose damage includes the ACC bilaterally. Lesions were reconstructed using the software package patient AM5 ([http://www.fil.ion.ucl.ac.uk/spm/software/patient AM5](http://www.fil.ion.ucl.ac.uk/spm/software/patient%20AM5)) from the MRI scans for each patient. (see figure 1 for the lesion transcriptions).

Twenty neurologically intact controls (mean age=44.4; SD=19.4) provided norms on the IGT. The Intramural Ethics Committee approved the procedures and all participants gave informed written consent.

CLINICAL ASSESSMENTS

A basic neuropsychological screen was conducted. Apathy was assessed using the Informant-rated Version of the Apathy Evaluation Scale (AES-I⁹). Depressive symptoms were evaluated on the Hospital Anxiety and Depression Scale (HADS¹⁰) and the Beck Depression Inventory (BDI¹¹).

EF and socio-executive assessments

The Hayling and Brixton Tests,¹² the Stroop Colour-Word Test¹³ and the Wisconsin Card Sorting Test (WCST¹⁴) provided EF measures, and the IGT⁸ evaluated socio-executive processing.

RESULTS

Clinical assessments

Both patient B and patient A had a category-specific deficit for living things and marked retrograde and anterograde amnesia. Each patient completed neuropsychological

Figure 1 Transcriptions of the lesions in patients A and B. Patient B=red; patient A=blue; overlap=purple. The common areas included: anterior and middle cingulate (bilateral), superior medial frontal (left), middle frontal orbital cortex (right), rolandic operculum (bilateral), putamen (right), amygdala (bilateral), insula (bilateral), parahippocampal region and hippocampus (bilateral), superior temporal (bilateral), temporal pole (right), fusiform gyrus (right). The right hemisphere is on the right.

testing, which confirmed his selective impairment in long-term memory. Both patients had significant apathy symptoms and were not depressed.

Executive functions

Stroop

Patient A's colour-word score was normal (percentile score=100%; probability of brain damage=0.01), whereas patient B's was impaired (percentile score=2%; probability of brain damage=0.99).

Brixton tests

Patient B obtained a raw score of 20, which was within the moderate average score range on the test's norms. Patient A's raw score of 23 fell within the lower average performance range.

Hayling test

In Section 1 of the Hayling test, patient B's scaled score of 4 and patient A's score of 6 were within the average range. Response times on Section 2 of the Hayling test (unconnected words) were within the average range for both patients: 4 for patient B and 6 for patient A. patient B's Section B error score (1) was impaired and patient A's score (4) was within the low average range. Patient B's overall score (1) was impaired but patient A's (5) was within the low average range.

Wisconsin card sorting test

Patient A's WCST performance was normal. He completed all six categories within a total of 105 responses. He made 6 (6%) perseverative responses, which is an above average performance. Patient B only managed to complete one of the possible six categories, failed to maintain set six times (<1 percentile on the normative data), and produced a total of 75 correct responses and made 53 (41%) error responses, 34 of which were perseverative (27%) and ranged within the mild impairment category on the test's norms.

The IGT

We analysed card selections up to the 60th round because one of the patients' performance was so poor that he ran out of play money shortly after this. The rounds were divided into three blocks (Block 1=selections 1–20; Block 2=selections 21–40 and Block 3=selections 41–60). For each block, we then calculated the Gambling Index Score, which is the total number of cards selected from the less risky decks (decks C and D), minus the total number of cards selected from the risky decks (decks A and B).

Control participants picked more risky cards in block 1 (mean index=−4.63; SD=6.08) and then got positive indexes of 9.79 (SD=7.66) and 13.30 (SD=4.95) for Block 2 and Block 3, respectively (global index score=18.46). Patient B obtained an index score of −1 in Block 1 and an index of 0 for Blocks 2 and 3 (global index=−1). Patient A obtained an index score of 4 on the first block, and −6 and −4 for Blocks 2 and 3, respectively (global index=−6). In Block 3 IGT index scores for both patient B and patient A were below 2 standard deviations of the control participants' mean of 3.4 ($p<0.05$). Table 1 gives an overview of the results.

DISCUSSION

This study offers further evidence on the association between ACC lesions and apathy symptoms. The high levels of apathy found in both patient A and patient B are

Table 1 Clinical and neuropsychological data

	Patient B	Patient A
Gender, age	Male, 50	Male, 52
Aetiology, years post onset, clinical symptoms	Herpes simplex encephalitis, 14, amnesia, category-specific recognition deficit	Herpes simplex encephalitis, 6, amnesia, category-specific recognition deficit
Visual short-term memory		
Corsi block	5	7
Digits forwards	7	7
Digits backwards	4	6
Long-term memory		
WRM word	24/50	31/50
WRM faces	31/50	33/50
WMS verbal	<50	52
WMS visual	<50	54
AES-I	54	61
BDI	3	5
HADS	6	1
Stroop 1, colour-word, error	112, 13, 32	112, 112, 0
Brixton score	20	23
Hayling A, B, error	20, 78, 33	2, 13, 13
WCST errors	41	21
IGT index	−1	−6

Bold scores=impaired performance as compared against the normative values/control group.

AES-I, Apathy Evaluation Scale-Informant; BDI, Beck Depression Inventory; HADS, Hospital Anxiety and Depression Scale; IGT, Iowa Gambling Task; WCST, Wisconsin Card Sorting Test; WMS, Wechsler Memory Scale; WRM, Warrington Recognition Memory.

consistent with other reports on ACC patients. The low levels of depression for both patients reinforce the position that apathy is dissociable from depression. We found no significant association between apathy and impaired performance on standard EF tests. For instance, patient A's performance was within the tests' normal ranges on these measures. This diverges from studies that have associated executive deficits with apathy and also diverges from brain activation studies that have shown increases in ACC regional blood flow during performance on the EF tests.¹⁵ These relatively normal EF results in the presence of significant apathy symptoms suggest that EF deficits are not crucial for apathy symptoms. This study illustrates that apathy can occur in cases where executive functions are relatively intact.

Our two cases suggest that apathy modulate socio-executive decision-making. Both patients were impaired on this IGT. We have also reproduced this result on a larger sample of brain-damaged apathetic patients (Njomboro, Deb and Humphreys, unpublished material). Bechara *et al*⁸ have proposed a crucial role of emotional biasing signals (somatic markers) in guiding performance on the IGT, and proposed that the same emotional processes are crucial for motivated goal-directed activity, reasoning and decision-making in real-life social contexts. It is possible that patients with apathy do not generate these emotional inputs, a position made even more appealing when taken in the context of apathetic patients' attenuated emotionality. Future studies may follow up on our results by carrying out tests for autonomic processing in patients with apathy.

It is also possible that patients perform relatively normally on EF tests due to the structured nature of these tests. Instructions and intratest feedback can help structure, reactivate and cue test goals. Executive deficits can be under such tests because real-life behaviour occurs under more complex social environments than provided by the EF tests. Open-ended tasks like the IGT present a more ecologically valid measure of real-life goal-directed behaviour. Future neuropsychological batteries may benefit from including these open-ended tests. Our findings suggest that apathetic patients may possess the cognitive competence for effective task performance, and can perform at near-normal levels under structured environments where prompts, feedback and cues help guide goal-directed behaviour. This may significantly reduce the huge caregiver burden and distress associated with apathetic patients.

One possibility is that memory impairments negatively impacted on IGT performance since patient B and patient A both presented with significant anterograde and retrograde amnesia. However, research on the IGT suggests that decision-making processes recruited on the IGT are dissociable from memory processes.⁸ Furthermore, both patients' basic digit span and Corsi block performance indicated relatively intact working memory and the patients also did relatively well on the WCST and Brixton tests, which rely on working memory. Performance on the IGT can also be impaired in cases where participants have difficulties in utilising feedback, suppressing or inhibiting a previously

rewarded response and shifting mental set towards good decks. However, patient A was not significantly impaired on the EF tests that specifically measure these capacities.

Learning points

- ▶ Anterior cingulate cortex lesions associated with apathy symptoms.
- ▶ Apathy symptoms are separable from depressive symptoms and executive function deficits.
- ▶ Apathy symptoms may reflect underlying socio-executive deficits related to motivational decision-making.

Acknowledgements The research was supported by grants from The University of Cape Town, The University of Birmingham, Birmingham and Solihull Mental Health NHS Trust, the MRC, the Stroke Association and The Canon Collins Educational Trust for Southern Africa. We thank all the participants who took part in this study.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. Mesulam M. The human frontal lobes: transcending the default mode through contingent encoding. In: Stuss D, Knight R, eds. *Principles of frontal function*. New York: Oxford University Press, 2002:8–30.
2. Hama S, Yamashita H, Yamawaki S, *et al*. Post-stroke depression and apathy: Interactions between functional recovery, lesion location, and emotional response. *Psychogeriatrics* 2011;**1**:68–76.
3. Oguru M, Tachibana H, Toda K, *et al*. Apathy and depression in Parkinson disease. *J Geriatr Psychiatry Neurol* 2010;**23**:35–41.
4. Leentjens AFG, Dujardin K, Marsh L, *et al*. Apathy and anhedonia rating scales in Parkinson's disease: critique and recommendations. *Mov Disord* 2008;**23**:2004–14.
5. Van Reekum R, Stuss DT, Ostrander L. Apathy: why care. *J Neuropsychiatry Clin Neurosci* 2005;**17**:7–19.
6. Medford N, Critchley HD. Conjoint activity of anterior insular and anterior cingulate cortex: awareness and response. *Brain Struct Funct* 2010;**214**:535–49.
7. Holroyd CB, Yeun N. Motivation of extended behaviors by anterior cingulate cortex. *Trends Cogn Sci* 2012;**16**:122–28.
8. Bechara A, Damasio H, Tranel D, *et al*. Dissociation of working memory from decision-making within the human prefrontal cortex. *J Neurosci* 1998;**18**:428–37.
9. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the Apathy Evaluation Scale. *Psychiatry Res* 1991;**38**:143–62.
10. Snaith RP, Zigmond AS. *HADS*. Berkshire: The NFER-NELSON Publishing Company Ltd, 1994.
11. Beck AT. *Beck depression inventory*. San Antonio, TX: The Psychological Corporation, 1978.
12. Burgess PW, Shallice T. *The Hayling and Brixton tests*. Thurston, Suffolk: Thames Valley Test Company, 1997.
13. Heaton RK, Chelune GJ, Talley JL, *et al*. *Wisconsin card sorting manual: revised and expanded*. Odessa, FL: Psychological Assessment Resources, Inc., 1993.
14. Trener MR, Crosson B, DeBoe J, *et al*. *Stroop neuropsychological screening test (SNST)*. Odessa, FL: Psychological Assessment Resources, 1989.
15. Nieuwenhuis S, Yeung N, Wildenberg W, *et al*. Electrophysiological correlates of anterior cingulate function in a go/no-go task: Effects of response conflict and trial type frequency. *Cogn Affect Behav Neurosci* 2003;**3**:17–26.

This pdf has been created automatically from the final edited text and images.

Copyright 2012 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Njomboro P, Deb S, Humphreys GW. Apathy and executive functions: insights from brain damage involving the anterior cingulate cortex. *BMJ Case Reports* 2012;10.1136/bcr-02-2012-5934, Published XXX

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow