

Fourth Neuroscience Spring Conference

Translating neuroscience knowledge to clinical practice

London, March 13, 2020

Cutting Edge lecture

'Translational research in movement disorders'

Dr David Okai

South London and The Maudsley/King's College, London



Supported by the Gatsby Charitable Foundation and the Wellcome Trust





Fourth Neuroscience Spring Conference

Translating neuroscience knowledge to clinical practice

London, March 13, 2020

Introduction

Impulse control behaviours [or impulsive-compulsive behaviours](ICBs) in Parkinson's disease (PD) are common, heterogeneous and pleasurable **actions performed repetitively, excessively, and compulsively**.

Common key symptom: failure to resist an impulse or temptation to an act or specific behaviour, which is ultimately harmful to oneself or others and interferes in major areas of life functioning.

Impulse control disorders (ICDs) are behaviours with a significant impact on social or occupational function. In some cases, they have serious financial, legal and psychosocially devastating consequences (Gatto and Aldinio, 2019).

Baig, F. et al. (2019) Impulse control disorders in Parkinson disease and RBD: A longitudinal study of severity. *Neurology* 93(7), e675–e687.

Gatto, E.M. and Aldinio, V. (2019) Impulse Control Disorders in Parkinson's Disease. A brief and comprehensive review. *Front. Neurol.* 10: 351.



Fourth Neuroscience Spring Conference

Translating neuroscience knowledge to clinical practice

London, March 13, 2020

Introduction

Prevalence estimates vary from 14% to 40%. Part of this is due to the relative lack of gold-standard, semi-structured interviews that conform to DSM-5 (or DSM-5 aligned) diagnostic criteria. Also, insufficient prospective studies limits understanding of the course and prognosis of ICBs in PD (Baig et al., 2019).

ICBs are **common in the early stages of PD** (19.1% prevalence). Most patients with ICBs remain symptomatic a year later, with a proportion of those with subsyndromal ICD going on to develop the more severe disorder (Baig et al., 2019).



Fourth Neuroscience Spring Conference

Translating neuroscience knowledge to clinical practice

London, March 13, 2020

Introduction

Identified (Baig et al., 2019) **risk factors** include:

- Dopaminergic medication, predominantly dopamine agonists (DAs)
- Demographic factors
- Disease-specific factors, such as the presence and severity of motor complications
- External factors, such as major life events and social support networks

Anatomical regions thought to be involved include:

- Planning and judgment areas: *caudal orbitofrontal cortex, ventromedial prefrontal cortex (PFC)*
- Reward system: *ventral striatum (VS-nucleus accumbens [NA])*
- Conditioned responses and emotional processing: *amygdala*
- Medial dorsal and anterior nucleus of the thalamus

Recent work suggests a more complex mechanism **beyond dopaminergic corticostriatal networks**, including **serotonergic/ noradrenergic interactions** (Bhattacharjee, 2017).



Fourth Neuroscience Spring Conference

Translating neuroscience knowledge to clinical practice

London, March 13, 2020

Intended Learning Outcomes

By completing this module, you will:

- ✓ **Review** different definitions of Impulse Control Behaviours (ICBs) in Parkinson's Disease (PD)
- ✓ **Understand** the social impact of ICBs in PD
- ✓ **Identify** the proposed mechanisms underlying ICBs in PD
- ✓ **Recognise** the importance of assessing the severity of ICBs in PD, as well as their presence/absence
- ✓ **Evaluate** evidence for the effectiveness of Cognitive Behavioural Therapy (CBT) as a therapeutic approach to ICBs in PD

Fourth Neuroscience Spring Conference

Translating neuroscience
knowledge to clinical practice

London, March 13, 2020

South London and Maudsley **NHS**
NHS Foundation Trust

Translational Research in Movement Disorders

13th March 2020

Dr David Okai MD(Res) MRCPsych DipCBT

Clinical Lead in Neuropsychiatry | Consultant Neuropsychiatrist

South London and Maudsley NHS FT | Kings Health Partnership

Honorary Senior Clinical Lecturer, University of Oxford

www.slam.nhs.uk

(Neurosciences)

KING'S HEALTH PARTNERS

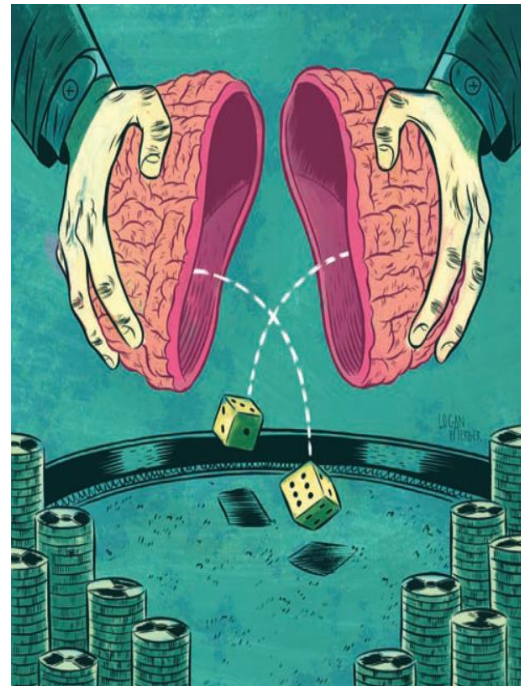


Impulse Control Disorders (ICDs)

- DSM-IV Definition:
 - ICDs constitute a group of psychiatric disorders, their essential feature being a failure to resist an impulse or temptation to perform an act that is harmful.
- DSM-5:
 - PG - Substance related and addictive disorders
 - ? “compulsive spectrum”
 - Insufficient evidence to identify sex, exercise and shopping as behavioural addictions.

Parkinson's disease (PD-ICBs)

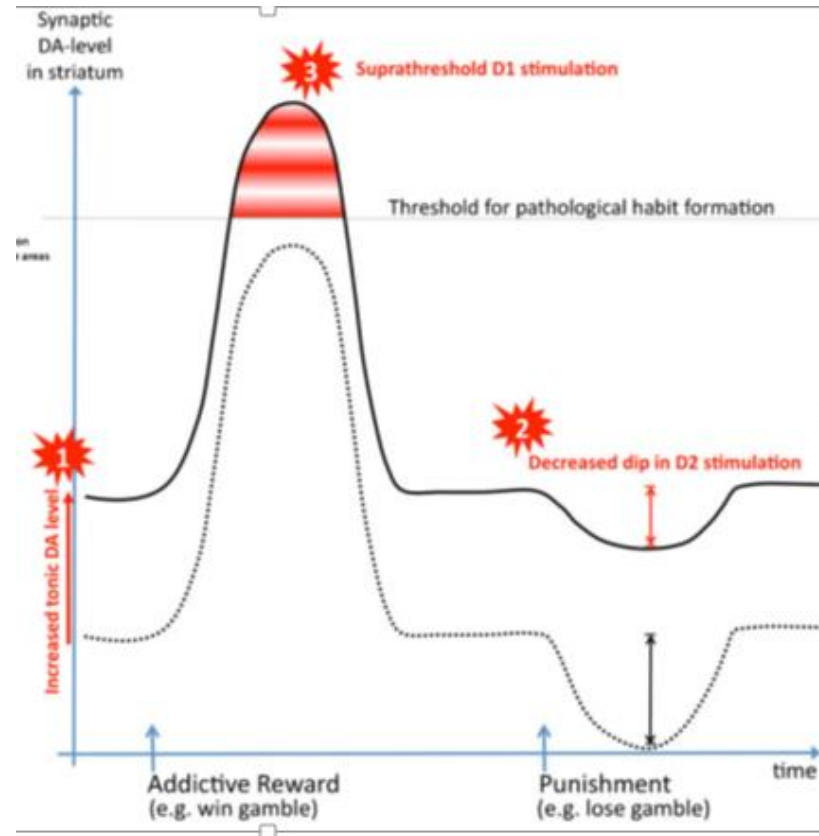
- **Gambling**
 - Slot machine gambling most common
 - Cue driven, Chasing losses
- **Shopping**
 - Impulsive buying, shopping around for a 'bargain'.
 - May lead to excessive clutter
- **Sex**
 - Hypersexuality (normative and less common behaviours).
 - Assaultiveness and paedophilia rarely
- **Eating**
 - Change in preference for sweet things
 - No disturbance of body image



Social - impact

- Those with multiple PD-ICB (+) worse quality of life compared to PD-ICB (-) on the PDQ-39 (Rohde, Riedel et al., 2013).
- PD-ICBs (n=35), with PD patients with predominant apathy symptoms, against the findings of healthy controls (n=38). ICB patients were associated with greater social burden on their families (Leroi et al, 2012)
- Carers rate Marital Satisfaction to PD-ICB patients as 'poor-to-bad' (Okai et al., 2013)
- Rating did not significantly improve after a patient-carer psychosocial intervention (Okai., 2013)

Mechanism



? D3 Receptor Stimulation

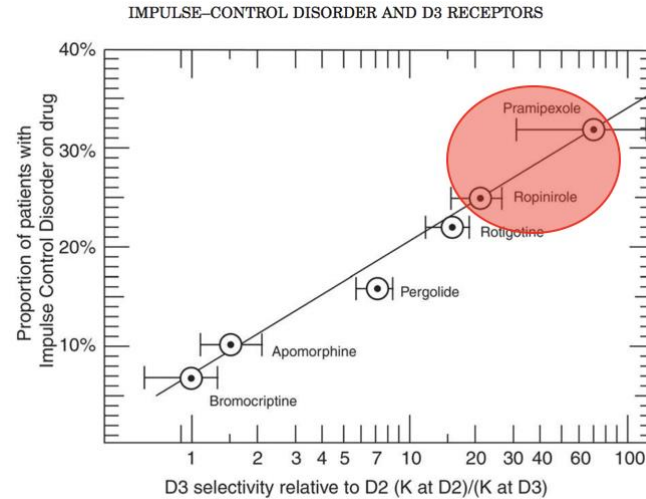


Table 3. Dopamine Receptor Agonist Drugs Associated With Impulse Control Disorder Events

Drug	ICD Events, No.	All Events, No.	D ₃ Selective	PRR ^a
Pramipexole	410	2095	Yes	455.9
Ropinirole	188	2414	Yes	152.5
Cabergoline	56	1592	No	62.9
Bromocriptine	30	613	No	86.1
Rotigotine	14	677	No	36.0
Apomorphine	12	605	No	34.5

Reflections: Legal

- 2015 Federal Court approved settlement against Pfizer Inc. (Australia)
 - N=150
 - Cabergoline
 - PD or restless leg
- 2013 Eli Lilly similar settlement
- 2012 French man settlement
- 2008 Mirapex \$8Million (Canada)

Parkinson's sufferer wins six figure payout from GlaxoSmithKline over drug that turned him into a 'gay sex and gambling addict'

Father-of-two says he developed an uncontrollable passion for gay sex and gambling - at one point even selling his children's toys to fund his addiction




The INDEPENDENT

Rationale for CBT for ICB in Parkinson's Disease

1. Medical management not always possible or effective
 - Stop or reduce DA (agonists) – may lead to poor control of PD symptoms
 - ICBs may persist despite conservative Rx
2. ICBs are often complex
 - Biological (disease, treatment, genetics)
 - Personal (history, personal circumstances)
 - Social (other people)
3. CBT effective in modifying maladaptive cognitions and behaviour in wide range of conditions
4. CBT can 'change the brain' - Neuroplasticity
 - Patterns of activation to stimuli, cues, threats, etc.
 - Altered connectivity



Cognitive Behavioral Therapy

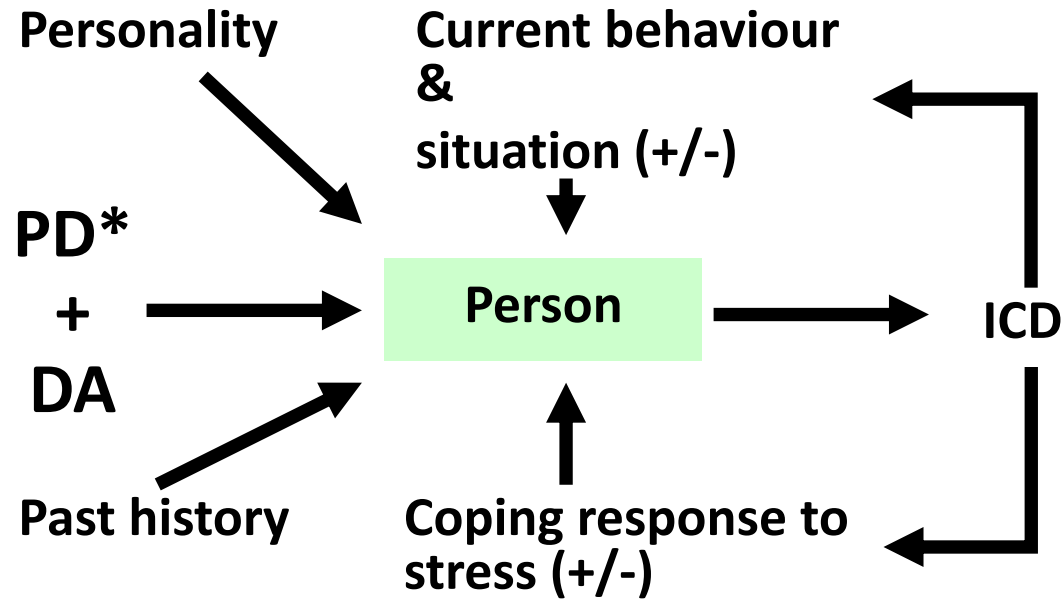
- Psychotherapeutic approach – addressed **dysfunctional emotions, maladaptive behaviours** and **cognitive processes & content**
 - Beliefs, attitudes, interpretations, perceptions
 - Coping behaviours, safety behaviours
- ‘Here and now’, goal/problem orientated
- Dynamic relationships maintain and exacerbate problem – ‘vicious cycles’



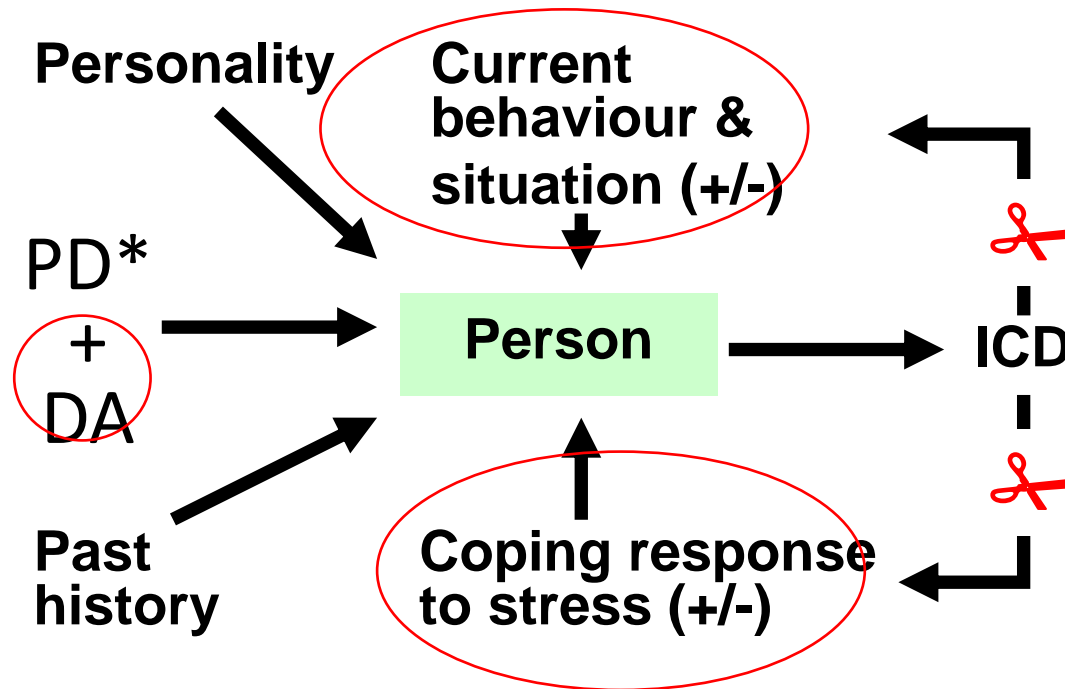
- **Therapy included**

- Reformulation of patient's personal model (problem and solution) – chosen behaviours might be maintaining problem – trapped in vicious cycle
- Psychoeducation on probability, chasing losses, and skill component to gambling
- Experiments to test/challenge beliefs and model (e.g. spending time with kids rather than buying things, small treats; pizza night rather than family holiday)
- Saving money for delayed rewards

ICDs: Psychosocial approach



ICDs: Psychosocial approach



Results (Patients)

	Baseline		Adjusted mean change		Group Difference (95% CI)	P-value	Effect Size* (partial eta-sq)
	CBT	Waitlist	CBT	Waitlist			
Primary	N=28	N=17	N=23-25	N=13-17			
CGI	4.0 (0.6)	3.7 (0.61)	-1.4	-0.3	-0.8 (-1.2 to -0.5)	0.004	0.21
NPI	26.0 (18.3)	22.0 (13.9)	-9.5	0.2	-4.7 (-9.1 to -0.3)	0.033	0.12
Secondary	N=12*-27	N=9*-17	N=10*-22	N=8*-14			
ICBSS	8.9 (6.2)	9.2 (4.8)	-6.1	-2.2	-4.17 (-5.8 to -2.5)	0.020	0.18
WSAS	27.1 (8.7)	26.9 (11.7)	-8.2	0.90	-3.6 (-6.0 to -1.3)	0.001	0.32
GRIMS *	33.2 (8.7)	34.0 (11.5)	-2.7	3.0	0.05 (-4.0 to 4.1)	0.158	
GHQ-28	10.5 (5.7)	10.5 (6.5)	-7.8	0.2	-3.8 (-5.6 to -2.0)	<0.001	0.38
BDI	19.5 (9.6)	17.9 (9.2)	-9.2	2.3	-3.5 (-6.6 to -0.4)	0.001	0.31
BAI	19.3 (13.3)	21.5 (13.6)	-6.5	2.9	-1.8 (-5.4 to 1.8)	0.013	0.18

Okai et al. (2013) Trial of CBT for impulse control behaviors affecting Parkinson patients and their caregivers. *Neurology*. 80:792-9.

* 0.1 'small', 0.25 'medium', 0.4 'large'

Results RCT:

Clinical Global Impression Scale

Treatment	Waitlist
78% Improved	14% Improved
13% No Change	57% No Change
9% Worse	29%Worse

There was a significant difference in those who improved after 6 months, between the two groups

Reflections: Impulse Control Disorders

The association of such behaviours with dopaminergic medication = underlying biological process to the behavioural addictions.



- Little focus on the severity of behaviours or recognition of subsyndromal behaviours
- Even less know about De-Novo vs Exacerbation



Severity scales

MDS COMMISSIONED REVIEW

Scales to Assess Impulsive and Compulsive Behaviors in Parkinson's Disease: Critique and Recommendations

Andrew H. Evans, FRACP, MD ^{1*} David Okai, MRCPsych, MB, BS,² Daniel Weintraub, MD,^{3,4} Shen-Yang Lim, FRACP, MD,⁵ Sean S. O'Sullivan, FRCP, PhD,^{5,6} Valerie Voon, MD, PhD,⁷ Paul Krack, MD, PhD,⁸ Cristina Sampaio, MD,⁹ Bart Post, MD, PhD,¹⁰ Albert F.G. Leentjens, PhD,¹¹ Pablo Martinez-Martin, MD, PhD,¹² Glenn T. Stebbins, PhD,¹³ Christopher G. Goetz, MD,¹³ Anette Schrag, MD, PhD ¹⁴ and the Members of the International Parkinson and Movement Disorder Society (IPMDS) Rating Scales Review Committee

¹Department of Neurology, the Royal Melbourne Hospital, Parkville, Australia

²Kings College London, Institute of Psychiatry, Section of Cognitive Neuropsychiatry, London, UK

³Department of Psychiatry, University of Pennsylvania, Philadelphia, Pennsylvania, USA

⁴Parkinson's Disease and Mental Illness Research, Education and Clinical Centers (Philadelphia Parkinson's Disease Research, Education and Clinical Center (PADRECC) and Mental Illness Research Education Clinical, Centers of Excellence (MIRECC)), Philadelphia Veterans Affairs Medical Center, Philadelphia, Pennsylvania, USA

⁵Division of Neurology, Department of Medicine, University of Malaya, Kuala Lumpur, Malaysia

⁶Department of Neurology, Bon Secours Hospital, Cork, Ireland

⁷Department of Psychiatry, University of Cambridge, Cambridge, UK

⁸Movement Disorders Center, Department of Neurology, University Hospital (Inselspital) and University of Bern, Bern Switzerland

⁹Cure Huntington's Disease Initiative/El (CHDI) Management/CHDI Foundation, Princeton, New Jersey, USA

¹⁰Department of Neurology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

¹¹Department of Psychiatry, Maastricht University Medical Center, Maastricht, The Netherlands

¹²National Center of Epidemiology and Centro de Investigacion Biomedica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Carlos III Institute of Health, Madrid, Spain

¹³Department of Neurological Sciences, Rush University Medical Center, Chicago, Illinois, USA

¹⁴Department of Clinical Neurosciences, Institute of Neurology, University College London, London, UK

'Ecologically Valid' Scales

Requirements

- Reliable and valid
 - Reliable – precise questions, operationalised ratings
 - Valid – measures key aspects of problems
- Consistent format that takes into account individual circumstances and different problem areas
- Uses clinician ratings based on interview and additional evidence
- Self report unreliable – denial, lack of insight
- Clinical judgement needed to rate intensity and/or impact of problem behaviour relative to individual circumstances
- Sufficient range of scores to be sensitive to change
- Incorporates aspects of intensity of problem and impact

Issues

- Not a diagnostic interview but may capture information relevant for diagnosis
- Time frame of Ax (long enough to catch infrequent but severe problems but not too long to impact on sensitivity to change)
- Ask about upper and lower levels of problem – not just 'average' or 'typical'. Upper level admitted to may be better reflection of problem in making ratings.
- Estimate scale of problem from extremes (e.g. largest win/loss, rather than attempting to estimate total winnings/losses over period).
- Impact needs to take into account individual circumstances. High stake betting, frequent pornography use, etc. is not in itself sufficient to indicate negative impact. Riskiness of behaviour to personal finances, social relationships, health, etc. a better basis for rating.

Parkinson's Impulse-Control Scale for the Severity Rating of Impulse-Control Behaviors in Parkinson's Disease: A Semistructured Clinical Assessment Tool

David Okai, MRCPsych, M DSc, FRCP, MD,⁵ Michael

Abstract: Backg (PD) as drug-rela authors describe syndromal and si (hobbyism) repet Methods: The Pa cover the full ran including interratt patients with ICB Results: The scal patients with syn 92%–95%). Cutof

Intensity of gambling

1. How often would you gamble in an average month? (e.g. over the past 6 months). What is the average number of times you would gamble? What would be the most? [NB: Include all forms of gambling behaviour]

	Average	Max
Less than once a month	1	1
Once a month	2	2
1 to 3 times a month	3	3
1 to 3 times a week	4	4
4 to 6 times a week	5	5
Once a day	6	6
1 to 3 times a day	7	7
More than 3 times a day	8	8

2. How often have you gambled in the past month? (rate 1-8)

3. How long do you spend gambling on each session in the past month? What is the average? What is the longest?

	Average	Max
Less than 5 minutes	1	1
5-10 minutes	2	2
10-20 minutes	3	3
20-30 minutes	4	4
30-60 minutes	5	5
1-2 hours	6	6
2-4 hours	7	7
More than 4 hours	8	8

4. In the past month, what is the typical size of your bet? What is the average? What is the largest?

	Average	Max
≤10p	1	1
10p-19p	2	2
20p-49p	3	3
50p-99p	4	4
£1-£4.99	5	5
£5-£9.99	6	6
£10-£20	7	7
>£20	8	8

Impact of gambling

9. When you have lost money in the past month, has it affected your ability to do other things that you would like to do, or to pay for essential items? Have you had to cut back your spending on treats? Have you had problems paying for bills or having enough money for food or other essentials?

- 0 No impact
- 1 Slight impact on other discretionary activities
- 2 Moderate impact on discretionary activities and/or some impact on non-discretionary expenditure.
- 3 Marked impact on other discretionary activities and/or definite impact on non-discretionary expenditure

10. In the past month have you borrowed money from a family member or friend in order to gamble? How often? Do they know what the money is for? Have you ever taken money from them without telling, intending to replace it afterwards?

- 0 Has not borrowed/taken money
- 1 Has borrowed occasionally (1-2 times)
- 2 Borrows money regularly (>2 times in past month) with their knowledge.
- 3 Has taken money from another person without asking permission, and/or borrows with deception

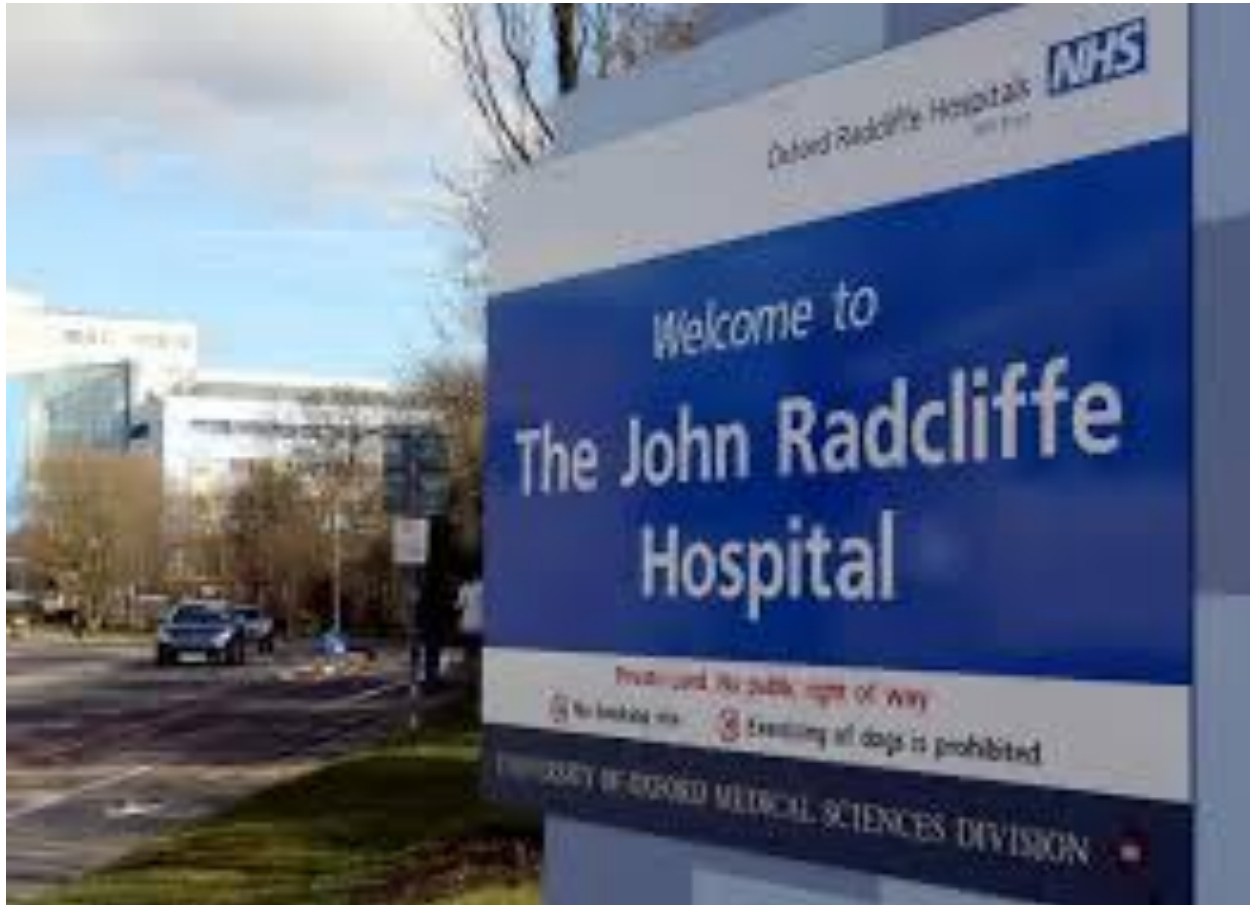
11. Are you concerned about your gambling? Do you think it is a problem? Are you always open about any losses?

- 0 No worry or does not admit to worry. Does not consider it a problem.
- 1 Slight worry reported or apparent from interview. Does not consider it a problem No debt.
- 2 Moderate worry and/or considers gambling a problem. May be some debt. May hide some losses.
- 3 Marked concern. Considers gambling a serious problem. Significant debt. Hides/lies about losses.

12. Is your gambling a concern for your family or friends? Do they think it is a problem?

- 0 Others do not express any concern. Do not think it is a problem.
- 1 Others express slight concern. Do not think it is a real problem
- 2 Others express moderate concern and/or consider gambling a problem
- 3 Others express marked concern. Consider gambling a serious problem.

Oxford



Our study objectives (Oxford)

1. Assess the severity of PD-ICB symptoms using the Semi-structures interview (Parkinson's Impulse Control scale - PICS)
2. Follow-up participants with ICB 1-2 years later to assess progression over time.
3. Identify factors associated with PD-ICB

Gambling Intensity in past month (* High/Low stake value needs to take into account individual circumstances)

- 1 Infrequent low stake* betting. No High stake* betting. Minimal loss risk.
- 2 More frequent low stake betting, and/or occasional high stake betting. Moderate loss risk.
- 3 Very frequent low stake betting and/or frequent high stake betting. High loss risk.
- 4 Very frequent high stake betting. Very high loss risk.

Gambling Impact in past month

- 1 No or minimal impact on other activities, or non-discretionary expenditure. No worry or concern expressed by self or others. Gambling within financial means. No debt. No borrowing.
- 2 Moderate social/financial impact on other areas of expenditure. Some/occasional debt. Has borrowed to fund gambling. Some concern expressed by self and/or others. Not fully open about losses.
- 3 Significant social/financial impact. Significant debt problem. Has stolen or used deception to fund gambling. Hides losses. Marked concern expressed by self and/or others.

Gambling Intensity x Impact Score _____ [NB Score 0, if no gambling behaviour]

Interviewer confidence in ratings

- 1 Low confidence in accuracy of ratings. Likely to underestimate scale of true problem.
- 2 Acceptable confidence in accuracy of ratings. Probably reflects approximate nature and scale of problem.
- 3 Good confidence in accuracy of ratings. Likely to reflect true nature and scale of problem.



Study question

What are the prevalence and risk factors for ICBs among healthy participants and patients with PD and RBD respectively?

Study cohort:



Patients with PD (early diagnosis ≤ 3.5 year)



Patients with RBD



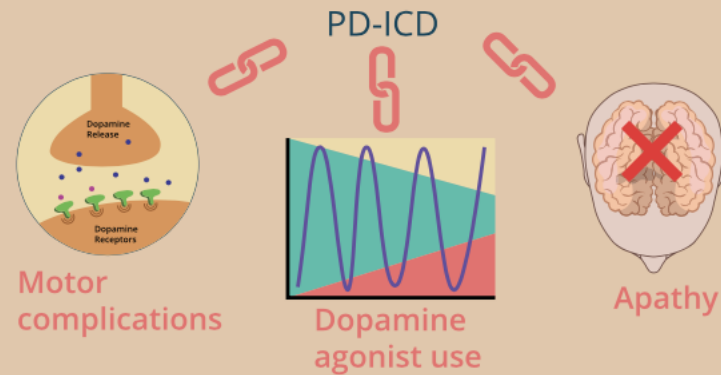
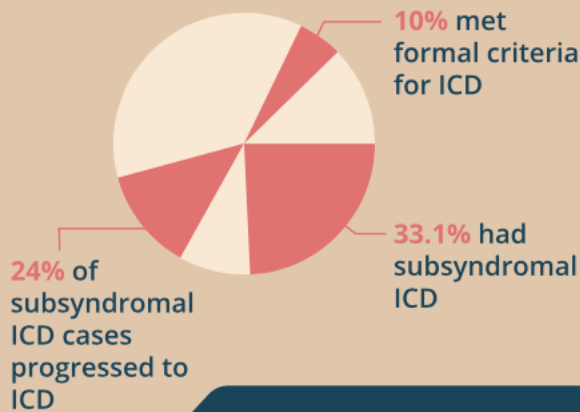
Control subjects

ICB screened-positive patients were stable over 3 years (21-25%)

ICB screening: Questionnaire for Impulse Control disorders in PD (QUIP-S)

Prevalence of PD-ICB was **19.1%**

Of the ICB screened-positive patients...



But not associated with PD-RBD

ICB occurring in early PD stages may persist or worsen overtime, influenced by both biological and nonpharmacologic factors.

Executive ('Frontal lobe') Function - ICD-10 Organic personality change (F07)

- Predominantly Neurobehavioral

'Pseudo-depressive' (Dorsolateral PFC)

- Apathy with lack of initiative
- Slowing of thought and motor activity

'Pseudo-psychopathic' (Ventromedial PFC)

- Disinhibition, Euphoria
- Irritability
- Impulsivity
- Antisocial behaviour

Impulsivity

Cognition, 50 (1994) 7-15
 0010-0277/94/\$07.00 © 1994 - Elsevier Science B.V.

Insensitivity to future consequences following damage to human orbitofrontal cortex

Antoine Bechara, Antonio R. Damasio
 Steven W. Anderson

Department of Neurology, Division of Behavioral Neurosciences
 University of Iowa College of Medicine, Iowa City, IA

Abstract

Following damage to the ventromedial prefrontal cortex, patients exhibit a severe impairment in real-life decision-making, which contrasts with their intact intellectual functions. Currently, there is no neurophysiological explanation. Here, using a laboratory task that simulates decision-making in the way it factors uncertainty as reward and punishment, we find that patients are almost completely oblivious to the future consequences of their choices, focusing only on immediate prospects. This finding offers a new perspective on the nature of the impairment and suggests directions for investigating its possible causes.

Introduction

Patients with damage to the ventromedial prefrontal cortex exhibit a severe impairment in real-life decision-making, but with intact intellectual functions. The impairments are especially marked in situations where the future consequences of actions are uncertain (Damasio, Tranel, & Damasio, 1991). Patients with this condition often decide against his



'Pseudo-depressed'

Journal of Neurology, Neurosurgery, and Psychiatry 1985;48:97-100

Occasional review

The pre-morbid personality of patients with Parkinson's disease

CJ TODDES, AJ LEES*

From the Paddington Centre for Psychotherapy, Department of Children and Parents, and the Department of Neurology, University College Hospital, and The National Hospital for Nervous Diseases, Queen Square, London, UK*

SUMMARY A review of the extensive descriptive literature suggests that many Parkinsonian patients exhibit an emotional and attitudinal inflexibility, a lack of affect and a predisposition to depressive illness, which may antecede the development of motor abnormalities by several decades. Introspective, over-controlled, anhedonic personality traits together with suppressed aggressivity are frequently found. It is unclear whether these behavioural patterns are relevant aetiological factors or prodromal symptoms of the disease.

Parkinsonism and Related Disorders 37 (2017) 72–78



Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis



Personality and addictive behaviours in early Parkinson's disease and REM sleep behaviour disorder



Fahd Baig^{a,b}, Michael A. Lawton^c, Michal Rolinski^{a,b}, Claudio Ruffmann^{a,b}, Johannes C. Klein^{a,b}, Kannan Nithi^{a,d}, David Okai^e, Yoav Ben-Shlomo^{a,c}, Michele T.M. Hu^{a,b,*}

^a Oxford Parkinson's Disease Centre, University of Oxford, Oxford, UK

^b Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK

^c School of Social and Community Medicine, University of Bristol, Bristol, UK

^d Department of Neurology, Northampton General Hospital NHS Trust, Northampton, UK

^e Psychological Medicine Service, Oxford University Hospitals NHS Trust, Oxford, UK

A B S T R A C T

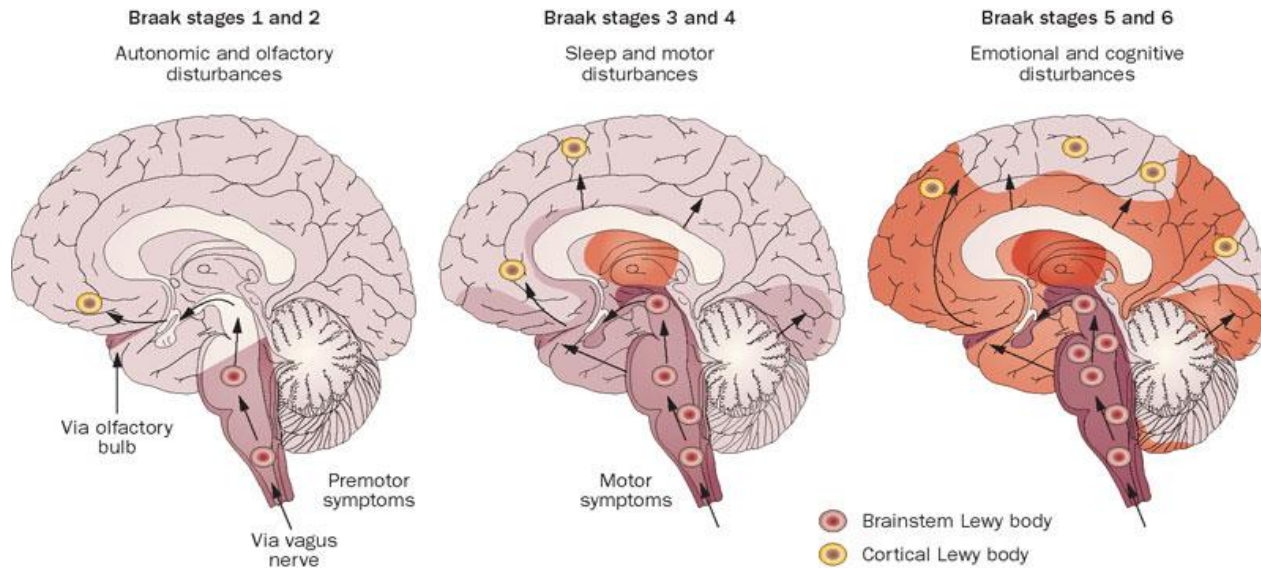
Introduction: Changes in personality have been described in Parkinson's disease (PD), with suggestion that those with established disease tend to be risk averse with a disinclination for addictive behaviour. However, little is known about the earliest and prodromal stages. Personality and its relationship with addictive behaviours can help answer important questions about the mechanisms underlying PD and addiction.

Methods: 941 population-ascertained PD subjects within 3.5 years of diagnosis, 128 patients with rapid eye movement sleep behaviour disorder (RBD) and 292 control subjects were fully characterised for motor symptoms, non-motor symptoms and across the following 5 personality domains: 1) neuroticism 2) extraversion 3) conscientiousness 4) agreeableness 5) openness using the Big Five Inventory.

Results: Patients with early PD were more neurotic ($p < 0.001$), less extraverted ($p < 0.001$) and less open than controls ($p < 0.001$). RBD subjects showed the same pattern of being more neurotic ($p < 0.001$), less extraverted ($p = 0.03$) and less open ($p < 0.001$). PD patients had smoked less ($p = 0.02$) and drunk less alcohol ($p = 0.03$) than controls, but caffeine beverage consumption was similar. Being more extraverted ($p < 0.001$), more open ($p < 0.001$), and less neurotic ($p < 0.001$) predicted higher alcohol use, while being more extravert ($p = 0.007$) and less agreeable ($p < 0.001$) was associated with smoking more.


Conclusions: A similar pattern of personality changes is seen in PD and RBD compared to a control population. Personality characteristics were associated with addictive behaviours, suggestive of a common link, but the lower rates of addictive behaviours before and after the onset of motor symptoms in PD persisted after accounting for personality.

Braak Staging



Doty, R. L. (2012) Olfactory dysfunction in Parkinson disease
Nat. Rev. Neurol. doi:10.1038/nrneurol.2012.80

Position Paper

A clinical approach to diagnosis of autoimmune encephalitis 

Francis Graus, Maarten J Titulaer, Ramani Balu, Susanne Benseler, Christian G Bien, Tania Cellucci, Irene Cortese, Russell C Dale, Jeffrey M Gelfand, Michael Geschwind, Carol A Glaser, Jerome Honnorat, Romana Höftberger, Takahiro Itouka, Suresh R Itani, Eric Lancaster, Frank Leypoldt, Harald Prüss, Alexander Rae-Grant, Markus Rando, Myma R Rosenfeld, Kevin Rostasy, Albert Saiz, Anun Venkatesan, Angela Vincent, Klaus-Peter Wandinger, Patrick Waters, Josep Dalmau

Encephalitis is a severe inflammatory disorder of the brain with many possible causes and a complex differential diagnosis. Advances in autoimmune encephalitis research in the past 10 years have led to the identification of new syndromes and biomarkers that have transformed the diagnostic approach to these disorders. However, existing criteria for autoimmune encephalitis are too reliant on antibody testing and response to immunotherapy, which might delay the diagnosis. We reviewed the literature and gathered the experience of a team of experts with the aims of developing a practical, syndrome-based diagnostic approach to autoimmune encephalitis and providing guidelines to navigate through the differential diagnosis. Because autoantibody test results and response to therapy are not available at disease onset, we based the initial diagnostic approach on neurological assessment and conventional tests that are accessible to most clinicians. Through logical differential diagnosis, levels of evidence for autoimmune encephalitis (possible, probable, or definite) are achieved, which can lead to prompt immunotherapy.

Lancet Neurol 2016
 Published Online
 February 13, 2016
[http://dx.doi.org/10.1016/S1473-0422\(15\)00401-9](http://dx.doi.org/10.1016/S1473-0422(15)00401-9)
 See Online/Correspondence
[http://dx.doi.org/10.1016/S1473-0422\(16\)00205-9](http://dx.doi.org/10.1016/S1473-0422(16)00205-9)
 Neuroimmunology Program,
 Institut d'Investigacions
 Biomèdiques August Pi i
 Sunyer, Barcelona, Spain

Clinical need for accurate clinical identification and prompt treatment

Panel 4: Diagnostic criteria for anti-NMDA receptor encephalitis

Probable anti-NMDA receptor encephalitis*

Diagnosis can be made when all three of the following criteria have been met:

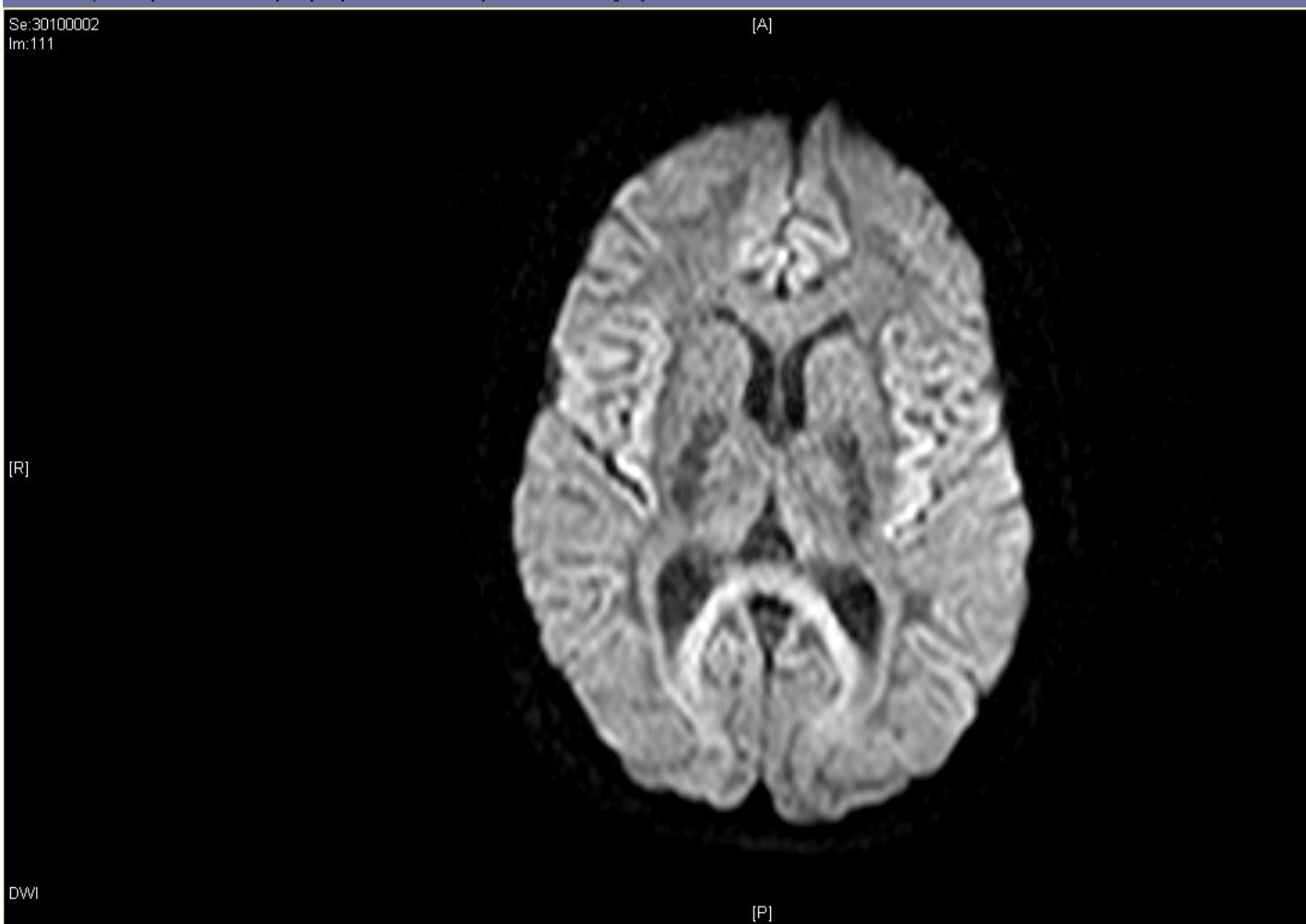
- 1 Rapid onset (less than 3 months) of at least four of the six following major groups of symptoms:
 - Abnormal (psychiatric) behaviour or cognitive dysfunction
 - Speech dysfunction (pressured speech, verbal reduction, mutism)
 - Seizures
 - Movement disorder, dyskinesias, or rigidity/abnormal postures
 - Decreased level of consciousness
 - Autonomic dysfunction or central hypoventilation
- 2 At least one of the following laboratory study results:
 - Abnormal EEG (focal or diffuse slow or disorganised activity, epileptic activity, or extreme delta brush)
 - CSF with pleocytosis or oligoclonal bands
- 3 Reasonable exclusion of other disorders (appendix)

Diagnosis can also be made in the presence of three of the above groups of symptoms accompanied by a systemic teratoma

Definite anti-NMDA receptor encephalitis*

Diagnosis can be made in the presence of one or more of the six major groups of symptoms and IgG anti-GluN1 antibodies,† after reasonable exclusion of other disorders (appendix)

*Patients with a history of herpes simplex virus encephalitis in the previous weeks might have relapsing immune-mediated neurological symptoms (post-herpes simplex virus encephalitis). †Antibody testing should include testing of CSF. If only serum is available, confirmatory tests should be included (eg, live neurons or tissue immunohistochemistry, in addition to cell-based assay).



Taskforce diagnostic criteria for NMDARE

4 or more***	Abnormal (psychiatric) behaviour or cognitive dysfunction	✓	✓	✓	✓	✓
	Speech dysfunction (pressured speech, verbal reduction, mutism)	✓	✓	✓	✓	✓
	Seizures	×	✓	✓	✓	✓
	Movement disorder, dyskinesias, or rigidity/abnormal postures	✓	✓	✓	✓	✓
	Decreased level of consciousness	✓	✓	✓	✓	✓
	Autonomic dysfunction or central hypoventilation	×	✓	✓	✓	✓
and 1 or more	Abnormal EEG (focal or diffuse slow or disorganised activity, epileptic activity, or (extreme delta brush)	✓	✓	✓	✓	✓
	CSF with pleocytosis or oligoclonal bands	×	×	✓	×	✓
OR	Presence of IgG anti-GluN1 antibodies in CSF	✓	✓	✓	✓	✓
Teratoma		×	×	×	✓	×

The psychopathology of NMDAR-antibody encephalitis in adults: a systematic review and phenotypic analysis of individual patient data

Adam Al-Diwani, Adam Handel, Leigh Townsend, Thomas Pollak, Misabel Lata, Paul J Harrison, Belinda R Lennox, David Okai, Sanjay G Manohar, Saresh R Irani

Summary

Background Early immunotherapy administration improves outcomes in patients with N-methyl-D-aspartate receptor (NMDAR)-antibody encephalitis. As most patients with NMDAR-antibody encephalitis present to psychiatrists, the psychopathology of NMDAR-antibody encephalitis needs to be clearly defined to encourage accurate clinical identification and prompt treatment.

Methods For this systematic review, we searched PubMed for all studies published in English between Jan 1, 2005, and Oct 7, 2017, to identify individually reported adult patients (≥18 years) who satisfied consensus criteria for definite NMDAR-antibody encephalitis. After generating a list of 50 fine-grained, lower-level features, we extracted psychopathological data in addition to demographic and aetiological data. The lower-level features were later organised within higher-level categories. As a means of quality control, we filtered the data according to proxy markers of psychiatric involvement in their description. Subsequently, we compared lower-level features from individual patient data with operationalised psychiatric syndromes using a constrained combination approach and principal component analysis, and did a network analysis to explore the inter-relationships between multiple lower-level features. This review protocol was prospectively registered with PROSPERO, number CRD42017068981.



Lancet Psychiatry 2019

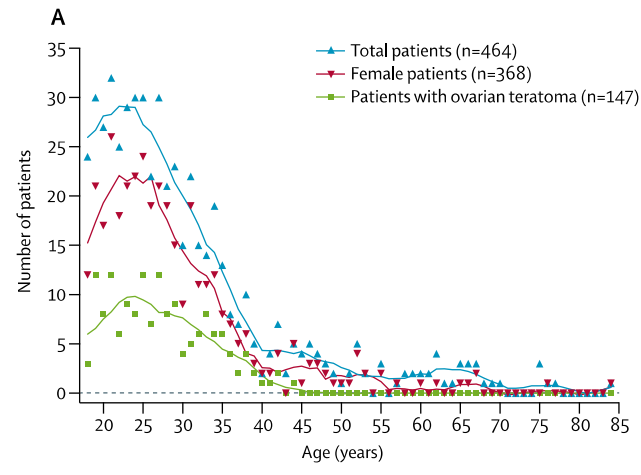
Published Online

February 11, 2019

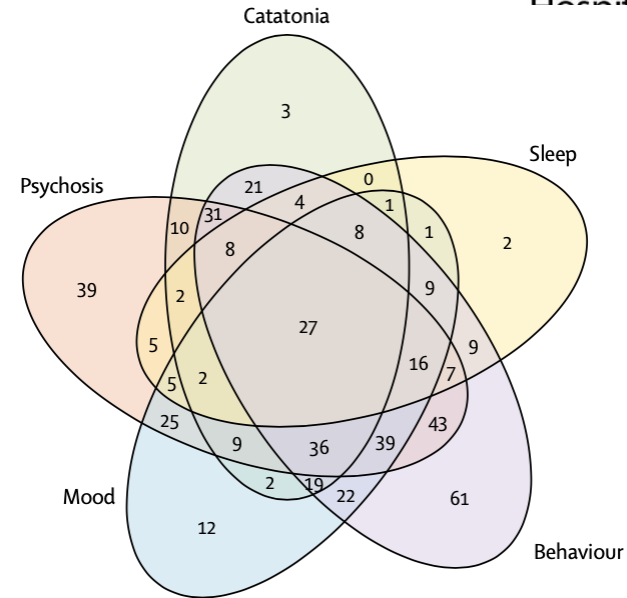
[http://dx.doi.org/10.1016/S2215-0366\(19\)30001-X](http://dx.doi.org/10.1016/S2215-0366(19)30001-X)

See Online for Comments!

[http://dx.doi.org/10.1016/S2215-0366\(19\)30001-X](http://dx.doi.org/10.1016/S2215-0366(19)30001-X)



encephalitis. We analysed a large cohort of individual patient data, and found a complex pattern that crossed multiple domains of psychopathology. With computational modelling, we observed that mixed mood-psychosis syndromes fit each patient better than any single diagnosis alone. The frequency of psychopathological features was stable across demographic and aetiological variables, and its network features were highly coherent, particularly after enrichment for reports reflecting greater expertise in descriptive psychopathology.



Interpretation

- The distinctive aspect of NMDAR-antibody encephalitis psychopathology is complexity
- Core aspects of mood and psychotic disorders consistently coexist within individual patients.
- Alongside the predominant young female demographic, these psychopathological features could help psychiatrists identify patients who would benefit from cerebrospinal fluid testing and immunotherapies.

Postencephalitic Parkinsonism

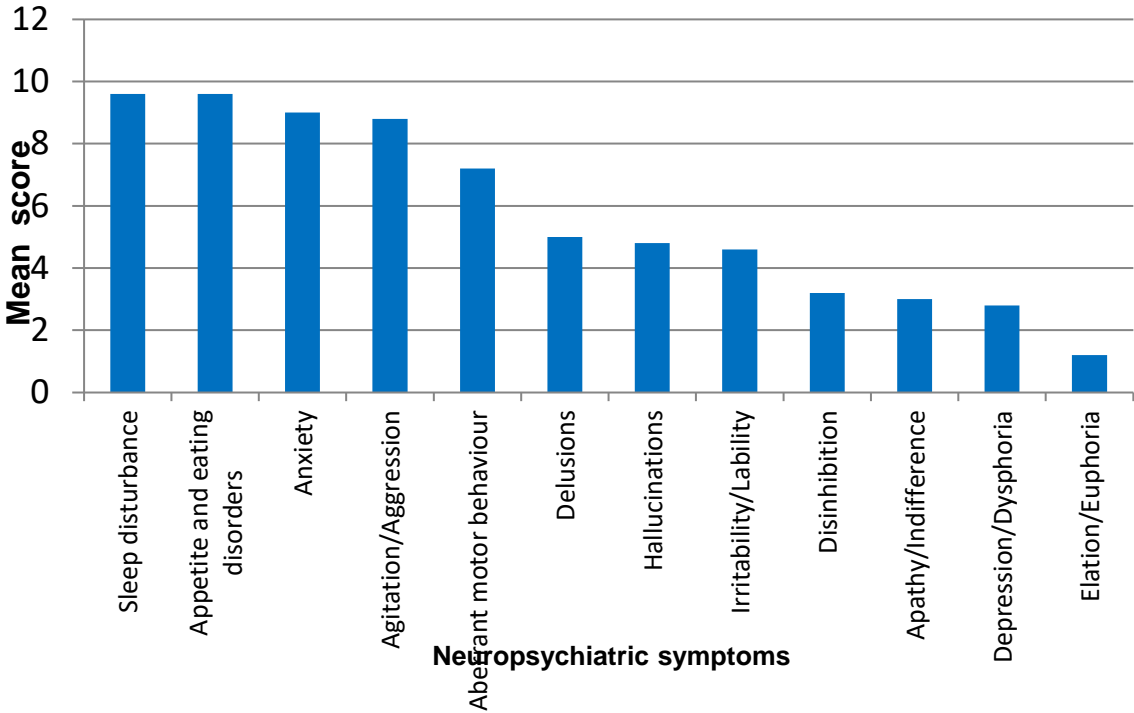


Young woman with EL showing an oculogyric crisis. Notable is the classic combination of torticollis, forced lateral and upward eye movements and flexed arm positioning.

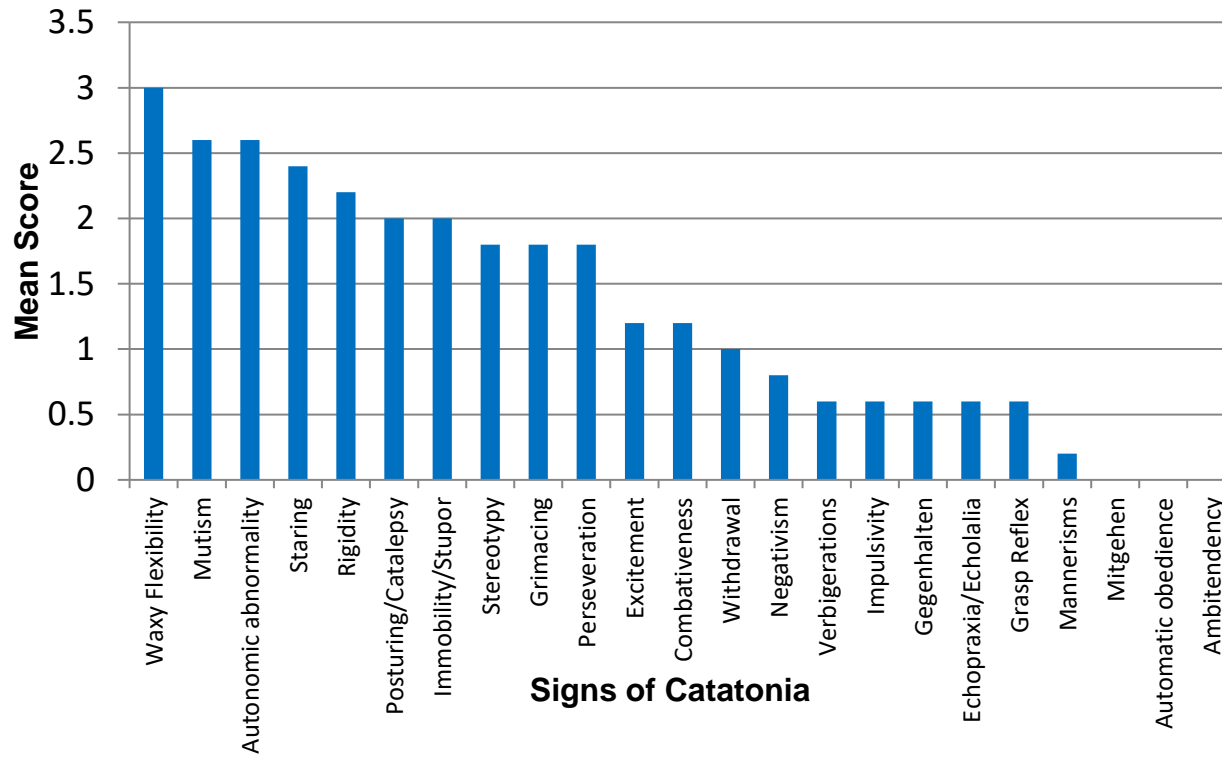


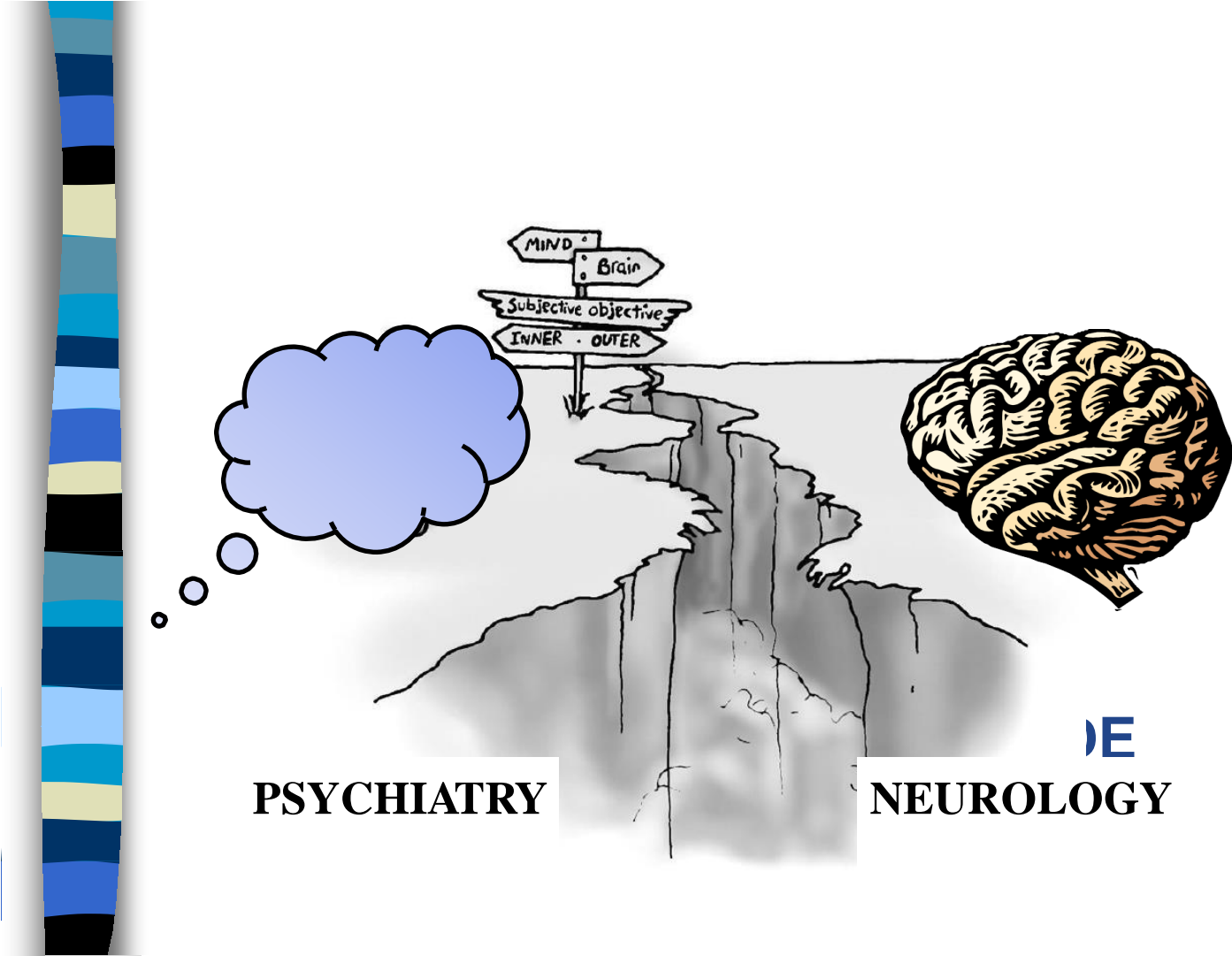
“They would be conscious and aware - yet not fully awake; they would sit motionless and speechless all day in their chairs...they registered what went on about them without active attention, and with profound indifference. They neither conveyed nor felt the feeling of life; they were as insubstantial as ghosts, and as passive as zombies” –Oliver Sacks

Neuropsychiatric Inventory



Bush-Francis Catatonia scale





What next?!

- Antidepressants in PD (NIHR)
- Antidepressants in TBI (NIHR)
- Neuropsychiatry of LGI-1 encephalitis (Wellcome/BRC)
- ICDs in Deep Brain Stimulations (Local network)

Acknowledgements and Thanks

Funded by
Parkinson's UK
National
Institute of
Health


*National Institute for
Health Research*

Investigators

David Okai ***

Sally Askey-Jones ***

Richard Brown

K Ray Chaudhuri

Tony David

Joel Mack

Ann Martin

Sean O'Sullivan

Mike Samuel


Funded by

PARKINSON'S^{UK}
CHANGE ATTITUDES.
FIND A CURE.
JOIN US.



- Dr Fahd Baig
 - Dr David Okai
 - Mr Michael Lawton
 - Prof Michele Hu
 - Prof Ben-Shlomo
 - Dendron team
- ALL THE PARTICIPANTS WITHOUT WHOM THIS IS NOT POSSIBLE





Fourth Neuroscience Spring Conference

Translating neuroscience knowledge to clinical practice

London, March 13, 2020

Summary (1)

The **underlying neuropathology** of Parkinson's disease (PD) is summarised by **Braak staging**. This is based on the development and progression of pathological changes to α -synuclein (a protein in the presynaptic terminal of neurons) in the brain.

Stages 1–2:

Changes limited to brain stem and olfactory nerve, causing **loss of atonia in REM sleep, detectable anosmia**

Stages 3–4:


Involvement of frontal lobe (dlPFC and vmPFC) leading to behavioural disinhibition, apathy, 'Lilliputian' hallucinations. Marked appearance of motor symptoms.

Stages 5–6:

Widespread pathological changes: **neurocognitive deficits become dominant feature**

dlPFC, dorsolateral prefrontal cortex

vmPFC, ventromedial prefrontal cortex



Fourth Neuroscience Spring Conference

Translating neuroscience knowledge to clinical practice

London, March 13, 2020


Summary (2)

Impulse control behaviours [or impulsive-compulsive behaviours](ICBs) are common in PD. The marked social impact of ICBs, including significant carer burden and marital breakdown, has brought them into the domain of neuropsychiatry.

The underlying mechanism of ICBs is believed to be related to the use of dopamine agonists to relieve the motor symptoms in PD.

Historically, research focused on the presence or absence of ICBs in PD. Recently developed **severity scales** are a welcome tool to measure the **extent to which ICBs are a problem for individual patients**. These are useful for identifying a **maximum as well as an average** ('typical') **for addictive behaviours**, such as alcohol consumption. Systematic use of these scales reveals that when sub-syndromal cases are included the incidence of ICBs in patients with PD may reach 30—40%.

Psychological therapies, such as CBT, form the mainstay of treatment for pathological gambling and **are effective in many patients** with PD-associated ICDs. Nevertheless, the **association of such behaviours with dopaminergic medication strongly indicates an underlying biological process** to these ICDs.



Fourth Neuroscience Spring Conference

Translating neuroscience knowledge to clinical practice

London, March 13, 2020

Self-assessment of learning

For each of the following questions, choose the best answer from the options given.

Answers on the next slide.

1. The 'ICBs' seen in some patients with PD are:

- A) Impulse control blocks
- B) Internet compulsive behaviours
- C) Impulsive compulsive behaviours
- D) Impulse control buying

2. A 2013 trial of CBT for ICBs in patients with PD by Okai et al. found the intervention lead to clinical improvement in what percentage of patients?

- A) 78%
- B) 56%
- C) 13%
- D) 29%

3. In the Braak Staging of Parkinson's Disease, how many stages are there?

- A) 3
- B) 6
- C) 8
- D) 4

4. Which of these is NOT one of the four major ICBs seen in patients with PD:

- A) Binge eating
- B) Compulsive buying/shopping
- C) Extraversion
- D) Hypersexuality

Fourth Neuroscience Spring Conference

Translating neuroscience knowledge to clinical practice

London, March 13, 2020

Self-assessment of learning

Answers.

1. The 'ICBs' seen in some patients with PD are:

- A) Impulse control blocks
- B) Internet compulsive behaviours
- C) Impulsive compulsive behaviours**
- D) Impulse control buying

2. A 2013 trial of CBT for ICBs in patients with PD by Okai et al. found the intervention lead to clinical improvement in what percentage of patients?


- A) 78%**
- B) 56%
- C) 13%
- D) 29%

3. In the Braak Staging of Parkinson's Disease, how many stages are there?

- A) 3
- B) 6**
- C) 8
- D) 4

4. Which of these is NOT one of the four major ICBs seen in patients with PD:

- A) Binge eating
- B) Compulsive buying/shopping
- C) Extraversion**
- D) Hypersexuality



Fourth Neuroscience Spring Conference

Translating neuroscience knowledge to clinical practice

London, March 13, 2020

Extension activities

Extend your learning by following one of these suggestions:

WATCH A useful [patient-friendly explanation of ICBs](#) from Parkinson's UK and look at [three stories of lived experience](#).

READ The 2019 Special Issue of the journal *Parkinson's Disease* on [Behavioral and Emotional Dysfunction in Parkinson's Disease](#), or the 2019 Special Issue of *Frontiers in Neurology* on [Impulse Control Disorders, Impulsivity and Related Behaviors in Parkinson's Disease](#) (free ebook download)

WRITE a 750-word article on 'Psychiatric aspects of Parkinson's Disease' and submit it to '*Psynapse*', the RCPsych's Neuroscience eNewsletter (visit rcpsych.ac.uk/training/neuroscience-in-training/neuroscience-resources for inspiration). Published articles will earn you a [£50 discount on registration](#) for the RCPsych 2021 Neuroscience Spring Conference, London, 26 March 2021. *Submit your article [here](#).*