

Computer-based diagnosis of illness in historical persons

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ABSTRACT Retrospective diagnosis of illness in historical figures is a popular but somewhat unreliable pastime due to the lack of detailed information and reliable reports about clinical features and disease progression. Modern computer-based diagnostic programmes have been used to supplement historical documents and accounts, offering new and more objective approaches to the retrospective investigations of the medical conditions of historical persons. In the case of King George III, modern technology has been used to strengthen the findings of previous reports rejecting the popular diagnosis of variegate porphyria in the King, his grandson Augustus d'Esté and his antecedent King James VI and I. Alternative diagnoses based on these programmes are indicated. The Operational Criteria in Studies of Psychotic Illness (OPCRIT) programme and the Young mania scale have been applied to the features described for George III and suggest a diagnosis of bipolar disorder. The neuro-diagnostic programme SimulConsult was applied to Augustus d'Esté and suggests a diagnosis of neuromyelitis optica rather than acute porphyria with secondarily multiple sclerosis, as proposed by others. James VI and I's complex medical history and the clinical features of his behavioural traits were also subjected to SimulConsult analysis; acute porphyria was rejected and the unexpected diagnosis of attenuated (mild) Lesch-Nyhan disease offered. A brief review of these approaches along with full reference listings to the methodology including validation are provided. Textual analysis of the written and verbal outputs of historical figures indicate possible future developments in the diagnosis of medical disorders in historical figures.

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KEYWORDS King George III, King James VI/I, Augustus d'Esté, computer diagnostics, acute porphyria, neuropsychiatric disorders

DECLARATIONS OF INTERESTS No conflicts of interest declared.

INTRODUCTION

The results of our research^{1–8} have challenged the claims that George III and many of his relatives suffered from variegate porphyria.^{9–13} We believe that the exponents of the porphyria diagnoses have been misled, a fact that raises further important questions. In the first place, why were medical historians misled, and what was the reason for the incorrect diagnosis? Secondly, what differential diagnosis was considered? Thirdly, what lessons can be learned from other reports of diagnoses of historical figures? Finally, has the incorrect diagnosis inhibited other studies of the King's behaviour and actions during his reign? The answers to some of these questions raise issues that are important, particularly with the growing contemporary interest in diagnostic errors.¹⁴

KING GEORGE III (1738–1820)

In 1965 Ida Macalpine and her son Richard Hunter, both general psychiatrists and amateur historians, claimed that King George III had not suffered from the primary

psychiatric disorder manic-depressive psychosis which had been proposed by psychiatrists in the USA.^{15–18} They claimed instead that he suffered from the rare inherited metabolic disorder acute intermittent porphyria,¹⁹ though this diagnosis was later changed to the even rarer and milder condition, variegate porphyria.²⁰ The errors in Macalpine and Hunter's diagnostic reasoning have recently been investigated in detail² and some of the causes and consequences of their misdiagnosis have been discussed.⁵

Macalpine and Hunter discounted many signs, symptoms and features of the King's recurrent illness that were incompatible with their diagnosis. More significantly, they did not discuss their diagnostic process, formulate any differential diagnoses, or attempt to show how their proposal met objective criteria such as that available in the *International Classification of Disease* (ICD) and the *Diagnostic and Statistical Manual of Mental Disorders* (DSM). They rejected the accepted diagnosis of manic-depressive psychosis because mania was '...no more specific a description of an abnormal mental state than

“fever” was of an abnormal physical one’.⁹ In spite of these failures of process, the diagnosis of porphyria gained widespread support, even though the diagnostic processes followed would not be acceptable under today’s standards.

The OPCRIT system

George III clearly met the diagnosis of recurrent mania as determined by the DSM-III and DSM-IV-TR and ICD-10 criteria.^{3,4} The operational criteria in studies of psychiatric illnesses (OPCRIT) system developed by Peter McGuffin and colleagues is used for the diagnosis of the major psychiatric disorders from patient case notes and was developed as part of a programme for investigating genetic components of bipolar disorder and schizophrenia.^{21,22} It is well-validated and widely used for research purposes. It has a 90-item input checklist and provides an output of 12 classification systems. A recent study has successfully applied the OPCRIT system to a selection of authors and poets from the fourteenth to the twentieth centuries, some with indications of mental disorders,²³ and more recently to members of a consanguineous eighteenth-century Portuguese Royal family with severe psychiatric disease.²⁴

The results of the OPCRIT studies of King George’s recurrent episodes of mental illness are shown in Table 1. It was claimed that he had four significant episodes of mental illness: in 1788–9, 1801, 1804 and 1810–11. There are contemporary letters and diaries but no detailed medical records for the 1804 episode.^{9,10} There were thus insufficient data from the 1804 episode for an OPCRIT-based diagnosis, illustrating an important constraint in the use of this programme. In contrast, the data available for the 1788–9, 1801 and 1810–11 episodes are sufficient to give clear diagnoses under the principal diagnostic categories available. The diagnoses for 1788–9 and 1801 include mania and mania with psychosis; the 1810–11 episode appears less severe with hypomania the predominant diagnosis. This episode was followed by a decade of chronic mental ill health. It has been suggested that from 1810 until his death on 29 January 1820, the King suffered from chronic mania with accompanying dementia.^{3,4}

The Young mania scale

The Young mania rating scale is a well-validated questionnaire widely used for clinical and research purposes.²⁵ Unfortunately a detailed assessment of the King by a single observer during this episode is not available. He was initially under the care of Sir George Baker and a group of Royal physicians, but no details of their observations remain. However he was also attended by an equerry, Robert Greville, who kept a detailed diary.²⁶ Highly detailed assessments become available following the King’s removal to Kew Palace and the summons of Rev Dr Francis Willis and his two medically qualified sons, and are available in the British Library.²⁷ A comparison of Greville’s records of the King’s symptoms, including sleep patterns, with those documented in Willis’s reports show general agreement³ and this is summarised in an aggregate sequential score in Table 2. This score indicates that during his most disturbed phase he would be classified as severity rating IV (Table 3). This is the most severe category reported by Young and his colleagues.

The OPCRIT and Young scores were the result of joint observations by TJP (who has a detailed knowledge of the King’s illness) and an experienced psychiatrist with an interest in the history of his specialty (Dr Allan Beveridge).

The Charleson index

A further example of the use of modern indices to assess the King’s health and prognosis during the 1810–20 episode can be obtained using the Charleson index.²⁸ This well-validated and useful clinical index^{29,30} takes into consideration patient age and co-morbid factors in predicting survival over the subsequent decade. At the age of 70, and with evidence of early cognitive impairment, George III has a score of four with a predicted ten-year survival of 50%. His actual survival for ten years in the early nineteenth century reflects well on the level of care provided but also indicates the absence of any underlying serious medical condition.

TABLE 1 Operational criteria in studies of psychotic illness (OPCRIT) analysis of King George III’s mental health disorders in 1788–9, 1801 and 1810–11

Criteria	1788–9	1801	1810–11
DSM III	Mania with psychosis	Mania with psychosis	Mania with psychosis
DSM IIIR	Manic episode with psychosis	Manic episode with psychosis	Hypomanic episode
DSM IV	Manic episode with psychosis	Manic episode with psychosis	Hypomanic episode
Taylor and Abrams	Mania	Mania	Mania
ICD-10	Mania with psychosis	Mania with psychosis	Hypomania
RDC	Mania	Mania	Hypomania

DSM= Diagnostic and Statistical Manual of Mental Disorders; **ICD**= International Classification of Disease; **RDC**= Research Diagnostic Criteria.

TABLE 2 Serial Young mania scores for George III's 1788–9 episode of acute mania

Date	Sir George Baker, MD	Col Robert Greville	Willis family doctors	Aggregate (±5)
24–30 October 1788	24			25
19–24 November 1788		37		35
23–8 December 1788		39	36	40
23–7 January 1789		15	16	15
23–8 February 1789		5	7	5
17–26 March 1789			5	5

TABLE 3 Median rating scales of patients with acute mania²⁶

Severity	I	II	III	IV
Global rating	0–1.5	2.0–2.5	3.0–4.0	>4.0
No.	11	7	11	6
Mean rating scale	12.5	19.3	25.5	37.9

AUGUSTUS D'ESTE (1794–1848)

D'Esté was the son of George III's sixth son, Augustus Fredrick, Duke of Sussex (1773–1843), and his morganatic wife, Lady Augusta Murray. At the age of 28 d'Esté developed a chronic but remitting and relapsing neurological condition that has been claimed to be the first recorded case of multiple sclerosis (MS).^{31–5} D'Esté wrote a detailed diary of the signs and symptoms of his illness and the medical interventions. Some of the clinical features were atypical for MS, particularly the apparent absence of nystagmus, intention tremor, scanning speech or cognitive impairment. On this basis Macalpine and Hunter⁹ suggested that he (and therefore his father and grandfather) all suffered from acute porphyria. A detailed re-assessment of his neurological condition has therefore been undertaken using the computer-based diagnostic programme SimulConsult Neurological Syndromes.

The SimulConsult Neurological Syndromes programme

This programme provides a weighted differential diagnosis from a database of 2,500 diseases, and the demographic, clinical and laboratory information associated with each. The database includes all the acute porphyrias and a range of demyelinating disorders.^{36–9} Figure 1 shows the results of inputting the principal features of d'Esté's condition as reported in the patient's diary. The resulting principal diagnosis was neuromyelitis optica (Devic's syndrome), with MS as a less likely alternative; variegate porphyria does not appear in the differential diagnosis. Interestingly the reports supporting the claim that d'Esté was the first recorded case of MS do not include neuromyelitis as a potential alternative, even though the condition was recorded in 1894 by Devic and Gault⁴⁰ and is listed as the principal differential diagnosis in suspected MS in standard neurological

textbooks.⁴¹ A possible reason for this omission is that until relatively recently a diagnosis could only be made on clinical grounds, which emphasised the myelitic and optic components. Modern criteria, however, are based on the condition's autoimmune aetiology, allowing its clinical spectrum to be broadened.⁴²

Diseases	Incidence used	Relative Probability
Devic neuromyelitis optica (NMO)		High
Multiple sclerosis		Low
Acute transverse myelitis		Low
Vitamin B12 (cobalamin) deficiency (pernicious anemia)		Low
Vitamin B1 (thiamine) deficiency (beriberi), dietary		Low
Amyotrophy, hereditary neuralgic, with predilection for		Low
Porphyria, acute intermittent		Low
Leber hereditary optic neuropathy (LHON)		Low
Strachan amblyopia, painful neuropathy, orogenital d		Low
Cerebrotendinous xanthomatosis (CTX, cerebral cho		Low
Adrenomyeloneuropathy (AMN)		Low
CMTX5: Charcot-Marie-Tooth disease (PRPS1-relat		Low
Leprosy (Hansen's disease)		Low
Herpes simplex (HSV) meningoencephalitis (herpetic		Low
SPG15: Kjellin spastic paraplegia and retinal degene		Low

FIGURE 1 Results of inputting principle features of d'Esté's condition as reported in the patient's diary, into SimulConsult®.

SimulConsult offers the option of adjusting the case differential diagnosis with respect to the relative incidence of the diseases. If this is done for d'Esté, MS (with an incidence 17 times that of neuromyelitis optica) becomes the principal diagnosis, with neuromyelitis the second most likely.⁶ We believe that this approach should be used with caution, especially with historical persons and those of non-European ethnicity, in whom disease risk and clinical features may differ significantly from those observed in the present.^{43,44}

KING JAMES VI AND I (1566–1625)

The absence of a diagnosis of porphyria in George III makes it very unlikely that any of his relatives, antecedents and descendants, suffered from the condition, so a detailed re-assessment of the claimed cases would be unnecessary as well as impractical.^{9–13, 45–7} A single case study of the medical condition(s) of James VI and I is, however, of value given the quality of the medical information available about him and the interest in his unusual behaviour. A detailed medical report on King James, prepared by Theodore de Mayerne (an early seventeenth-century physician in England and a long-standing physician to the Royal family) has been preserved in full. In 1623, de Mayerne had to return to Switzerland to attend to some family business and left a detailed medical history and report with diagnoses and treatment protocols for the local physicians who would be looking after James during his absence. A full translation of this report is now available, providing detailed information on his health and the diagnostic process undertaken.^{7,8} Until recently only a partial translation was available to medical historians for use in their research.⁴⁸

The SimulConsult Neurological Syndromes programme

King James had a complex medical history with problems originating in his childhood and persisting throughout his life, suggestive of a multi-system disorder with movement, behavioural, renal, locomotor and endocrine features.⁸ The following principal clinical features were selected for input into SimulConsult: 59-year-old male with motor development delay from the age of around one year old, renal calculi onset aged 40 years, and abnormal speech of unknown onset. As with Augustus d'Este, SimulConsult was employed in this case to objectively verify or disprove the claimed diagnosis of variegate porphyria. The most unexpected results are shown in Figure 2. None of the acute porphyrias (particularly variegate porphyria) were among the first 15 differential diagnoses. The mild neurological form of Lesch-Nyhan disease followed by the more classical forms of the condition were the only significant diagnoses offered. Rickets, poliomyelitis, Charcot-Marie-Tooth disease or cerebral palsy with athetoid features, all conditions that have also been suggested,^{49,50} did not feature in the list of possible diagnoses.

Lesch-Nyhan as originally described is an X-linked disorder with marked neurological features and mental retardation.⁵¹ Subsequent studies have identified a defect in purine metabolism with reduced activity of the purine salvage pathway enzyme, hypoxanthine phosphoribosyl transferase.⁵² More recent studies have identified attenuated (milder) variants with significant residual enzyme activity.⁵³ A key feature of the mild

Diseases	Incidence used	Relative Probability
Lesch-Nyhan disease, mild neurological (Group 2 HPR)		High
Lesch-Nyhan disease, classical (Group 4 HPRT1 deficiency)		High
Lesch-Nyhan disease, severe neurological (Group 3 HPR)		High
Alkaptonuria (alcaptonuria)		Medium
Wilson disease (hepatolenticular degeneration)		Medium
Mucopolipidosis III γ (atypical, variant pseudo-Hurler polydystrophy)		Low
Leg length disparity		Low
Rheumatoid arthritis, juvenile		Low
Mucopolipidosis III α/β (pseudo-Hurler polydystrophy)		Low
Alström Syndrome (Alström-Hallgren)		Low
Systemic lupus erythematosus (SLE)		Low
Multiple epiphyseal dysplasia, dominant (EDM1, EDM2)		Low
Fibromyalgia		Low
PRS superactivity, infantile (phosphoribosylpyrophosphatase)		Low
Stickler syndrome (arthroophthalmopathy)		Low
Marfan syndrome, infantile		Low
Marfan syndrome, classical		Low

FIGURE 2 Results of inputting principle features of King James' condition into SimulConsult®.

variants is that sufferers may lack cognitive dysfunction, particularly those with only mild neurological symptoms. A key feature of untreated Lesch-Nyhan disease is hyperuricaemia with renal calculi characteristic of uric acid crystals (cloudy red urine with sandy-coloured grains), as observed in James,^{54,55} a feature that has been unaccountably overlooked in previous attempts to reach a diagnosis.

The adult Asperger assessment diagnostic criteria

Maladaptive behaviour is a frequent feature of attenuated Lesch-Nyhan and this would be consistent with some of James's characteristic conduct. The descriptions of him as 'the wisest fool in Christendom'⁵⁶ and 'one of the most complicated neurotics to sit on either the English or the Scottish throne'⁵⁷ aphoristically describe this condition. James's behaviour and his apparently high intelligence are consistent with a diagnosis of Asperger's syndrome, which may also occur in attenuated Lesch-Nyhan disease, and he meets the DSM-IV and ICD-10 criteria for the condition.⁸ Asperger's syndrome is a component of the autistic spectrum disorders, characterised with little or no evidence of cognitive impairment. The use of the adult Asperger assessment diagnostic criteria developed by Baron-Cohen and colleagues gives a quantitative and objective measure.⁵⁸ It assesses the individual's social skills, obsessions, communication and imagination domains on an 18-point scale; James scores 12, above the threshold of ten for a diagnosis of Asperger's syndrome.⁸ A detailed review^{59,60} of his psychological traits under these domains is necessary for a definitive diagnosis, but his lack of empathy towards his mother's plight, his alcohol misuse, the failures in his interpersonal relationships and 'the fatal consequences of the first acts of the [English] reign', highlighted by Trevelyan,⁶¹ are key indicators.

In an attempt to determine the nature of his cognitive decline in the last five years of James's life, Williams and colleagues used a computer-based linguistics programme to analyse his surviving letters. The programme suggested that his writing might have been influenced by the effects of vascular cognitive impairment, a focal cerebral infarct, or the normal aging processes.⁶²

DISCUSSION

Retrospective diagnosis of historical figures is complicated and problematic, as evidenced by the various theories about Jane Austen's cause of death. Sir Zachary Cope claimed that Austen died of Addison's disease.⁶³ He based his theory on a diary entry on 23 March 1817, some four months before she died: 'I am... recovering my looks a little, which have been bad enough, black and white and every wrong colour...'. This is insufficient evidence to diagnose Addison's disease, particularly as there are no extant medical records. We only have the author's own surviving letters, though this did not deter other claims as to the cause of her early death including typhus, tuberculosis, Hodgkin's disease, gastric carcinoma and, recently, arsenic poisoning. The evidence that she was anaemic is convincing but the cause must remain speculative.⁶⁴

In the case of George III, Macalpine and Hunter might have had ulterior motives for suggesting a diagnosis of porphyria and these have been discussed elsewhere.^{2,5} They believed that psychiatric practice should be within the province of neurologists; they opposed the establishment of the Royal College of Psychiatrists and had academic ambitions and specific views on the care and treatment of psychiatric patients. There was also a desire to remove the 'taint of madness from the House of Windsor', and the possibility of success being rewarded with an invitation to Buckingham Palace. The recent finding that they donated several Georgian medals to the Royal Collection may relate to the latter aim.⁶⁵

Computer-based diagnostic instruments have been available for more than 50 years, most notably the Bayesian-based approach developed by de Dombal and colleagues at Leeds.⁶⁶ Their original computer-aided diagnosis of acute abdominal pain programme reliably distinguished six causes of abdominal pain in surgical admissions. It did not include 'medical' causes of pain, including the porphyrias.⁶⁷ The SimulConsult diagnostic decision support system uses an iterative approach to distinguish 2,500 neurological conditions, including the four acute neuro-visceral porphyrias and is now used by the US Library of Medicine. The developer, Dr M Segal, is preparing a detailed review of the basis, applications, benefits and recent and proposed developments of the programme.

The computer-based diagnostic instruments we have described only process the data that are provided, in an objective and reproducible fashion. The conclusions can easily be updated or even overturned by the discovery of new evidence or the re-evaluation of known information, whether about a historical figure's medical history (as in the case of King George III) or a disease process (as with Augustus d'Este and King James). These methods are increasingly being used in clinical practice and we cautiously suggest that this may be extended to retrospective studies.

Caution is however required because of the current limitations of this approach. Firstly, the range of information that can be used with diagnostic databases, particularly those of cardiac, endocrine and metabolic disorders, include laboratory and radiological findings, which would obviously not be available for nineteenth-century figures. Programmes for aiding the diagnosis of psychiatric, psychological and neurological disorders on the other hand, are often particularly applicable. The interest in programmes for dermatological disorders may also be relevant.⁶⁸⁻⁷⁰ Google diagnoses were correct in 15 of 26 patients in a recent *New England Journal of Medicine* report, a further example of the use of this facility, albeit not specifically designed for this purpose.⁷¹ Secondly, it is important to use programmes that indicate when there is insufficient data to provide a reliable diagnosis. Systems such as the OPCRIT programme are specifically designed for use with patient case notes and would seem to be particularly appropriate for assessing more recent historical individuals from the twentieth century, where data and information are more readily available.⁷²⁻⁴ Use of computer-assisted diagnosis will minimise observer bias; input should therefore be done by relevant specialists. This is an early use of this diagnostic approach to historical figures and more detailed protocols still need to be developed. In addition, independent evaluation, perhaps using contemporary figures where there is an accurate diagnosis, will provide additional support for this approach.

TEXTUAL ANALYSIS

Future developments include the insights that are emerging from 'cognitive archaeology', a term coined by Garrard⁷⁵ to describe systematic retrospective textual analysis as a tool for understanding the earliest stages of slowly progressive neurodegenerative dementias. It was argued that examining samples of language predating the earliest symptoms of cognitive inefficiency may help us to understand the elusive, pre-symptomatic phases of dementia. Unlike memory, attention, or problem-solving, linguistic activity can be, and often is, recorded, surviving in written or spoken format for many years with minimal information decay. One of the best-known studies of retrospective language use involved an extensive archive

of writings produced by members of a religious community. One of the most remarkable findings of the Nun Study⁷⁶ was that language characteristics of early adulthood impact on the likelihood of developing late life dementia. Later studies have used computer algorithms to characterise large volumes of text and explore how aspects of written language change through the lifetime of a prolific author. When such cases have involved the language of people who are known to have developed Alzheimer's disease, the results are particularly intriguing.^{77,78} In selected cases, similar methods can be applied to archived transcripts of language use – an approach that was used in an attempt to identify early cognitive change in former British Prime Minister, Harold Wilson.⁷⁵

Latent semantic analysis (LSA) is an algorithmic approach to capturing and quantifying the similarity of meaning between two pieces of text. It has been used extensively in the analysis of connected speech in those with schizophrenia and affective illness, indicating that thematic incoherence may be a diagnostically useful marker. Similar methods could be used to assess the changes observed in the correspondence of King George III, and chronologically date both onset and recovery, or even to discover previously unidentified symptomatic periods.

Finally, large volume computerised language analysis that identifies temporal trends in the use of particular words or word types could prove important in recognising and measuring the changes associated with

'hubris syndrome'. This term was recently introduced by David Owen, a medically qualified former British Foreign Secretary, to describe an acquired, stereotypical personality disorder, to which powerful leaders are peculiarly liable to succumb, often with devastating consequences.⁷⁹ Such leaders, particularly those within the political arena, cannot but leave a constantly updating record of written and spoken linguistic data from which future historians with more advanced analytical tools will have much to learn.

CONCLUSION

Computer-based diagnostic techniques have lent further weight to the case against a diagnosis of porphyria in George III, his grandson August D'Este and James VI and I and alternative diagnoses have been postulated. Computer-assisted diagnosis may prove to be a valuable additional tool in the diagnosis of illness in historical figures despite the fact that their disease risk may differ from that of a modern population and clinical features may have been interpreted and recorded differently. The use of computers to analyse text offers the intriguing prospect of diagnosing cognitive impairment and affective disorders in historical leaders and assessing their development over time.

Acknowledgements

We are grateful to Allan Beveridge and John Stephenson for advice and assistance in the selection and inputting of the clinical data.

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