Eur. J. Psychiat. Vol. 21, N.° 2, (99-116)
2007

Keywords: Cotard syndrome, Neuroimaging neurophysiology, Neuropsychology.

An overview of the neurological correlates of Cotard syndrome

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ABSTRACT – *Background and objectives:* Considerable etiologic ambiguity surrounds Cotard syndrome and a range of psychodynamic, existential and biological theories have been proposed to explain its etiopathogenesis. Despite the often-noted neurological abnormalities on examination and assessment in Cotard syndrome, an in-depth evaluation is lacking. In this paper, we provide an overview of the neurological (neurostructural, neurophysiological and neuropsychological) correlates of Cotard syndrome and discuss the implications of our findings from an etiological and clinical perspective.

Methods: We searched electronic databases and key journals using the appropriate search terms. All reported cases of Cotard syndrome with neurological investigations published in English were included in the review. The two authors independently reviewed the full text of over 100 papers and selected the papers for inclusion in the final review.

Results: Various organic conditions such as typhoid fever, temporal lobe epilepsy, brain tumours and brain injuries have been reported in association with Cotard syndrome. The most commonly reported neurological abnormalities in these patients include structural brain changes (bilateral cerebral atrophy, dilated lateral ventricles), functional brain changes (hypoperfusion in the frontal and parietal cortices) and neuropsychological abnormalities (impaired face recognition).

Conclusions: In summary, although not all, some cases of Cotard syndrome are associated with structural and functional brain dysfunction. From a clinical perspective, it is crucial to maintain a low threshold for suspicion of organicity in cases of this uncommon psychiatric syndrome, and thereafter to consider appropriate neurological investigations.

Received 17 January 2006
Accepted 19 June 2006

Jules Cotard, a French physician, in 1880, described the case of a 43-year-old woman who reported that she had 'no brain, nerves, chest, or entrails and was just skin and bone –neither God nor the Devil existed– she was eternal and would live forever'[1]. He called it '*delire de negation'*, and this was to posthumously bear his name and later be popularised as 'Cotard syndrome'. Although, the central symptom of Cotard syndrome is the nihilistic delusion, it can present with varying degrees of severity, ranging from mild forms where patients express feelings of despair, through to more severe forms where patients deny their own existence and or the existence of the world itself.

Considerable nosological ambiguity surrounds Cotard syndrome. Berrios & Luque, in an extensive review of the conceptual history of Cotard syndrome, concluded that Jules Cotard probably viewed it as a subtype of melancholia (anxious melancholia)[2]. However, others view it as a syndrome (associated with a range of conditions such as depression, psychosis, organic conditions and so on), while some others consider it a distinct entity. In an attempt to further understand the phenomenology of Cotard syndrome, Berrios & Luque, using an exploratory factor analysis of 100 cases of Cotard syndrome reported in literature, extracted three factors: psychotic depression, Cotard type I and Cotard type II[3]. The psychotic depression patients mostly had depression and few nihilistic delusions. Cotard type I patients on the other hand, had only the nihilistic delusions (pure Cotard syndrome) and few depressive symptoms, whereas Cotard type II patients were a mixed group with depression, anxiety and auditory hallucinations.

It is worth emphasizing that Cotard Syndrome is best conceptualised as being on a spectrum (complete / incomplete): the complete form in which nihilistic delusions are clearly present and the incomplete forms which are often combinations of depressed mood, delusions of guilt and hypochondriasis, and hallucinations. Also the nihilistic delusion itself could vary in its degree of severity - from severe (patient denies his own and the world's existence) to mild (patient feels that he is loosing his reasoning and feelings). Yamada *et al*.[4] attempted to trace the onset and longitudinal progression of Cotard syndrome from a phenomenological perspective and identified 3 distinct stages: the germination stage (prodromal period associated with depression and hypochondriacal symptoms), the blooming stage (full blown development of the syndrome with delusions of negation) and the chronic stage (chronic depressive type or chronic delusional type). They equated the above 3 stages to the earlier classification of Cotard Syndrome by Berrios & Luque as follows: the germination stage corresponds to psychotic depression, the blooming stage to Cotard type 2 and the chronic stage to Cotard type 1.

Nosological ambiguity often does not lend itself well to etiological clarity. So much so that, a range of diverse etiological explanations has been proposed to explain the genesis of Cotard syndrome: psychodynamic, existential, sociological and biological[1]. Notwithstanding the isolated case reports/case series describing some of the neurological abnormalities in Cotard syndrome, a detailed evaluation of the neurological aspects of the syndrome is lacking. In this paper, we attempt to provide an overview of the neurological (neurostructural, neurophysiological and neuropsychological) correlates of Cotard syndrome and discuss the implications of our findings.

Methodology

We conducted an extensive literature review and searched the following electronic, bibliographic databases: Medline (1951 to date), Embase (1974 to date) and Psychinfo (1887 to date). Our search used the terms Cotard, Cotard syndrome, severe depression, Cotard delusion and nihilistic delusion. References of studies thus identified were searched for further studies and we also hand searched key journals and books. Our exclusion criteria included studies published in non-English languages, cases of Cotard syndrome with no reported neurological investigations and cases of Cotard syndrome coexisting with delusional misidentification syndromes. In the first phase, the two authors (S.K & S.G) independently reviewed the full text of over 100 papers reporting cases of Cotard syndrome, and excluded those papers that did not meet the inclusion criteria. In phase II, all included papers were analysed by the first author (S.K) and the relevant information was extracted, based on a pre-designed proforma. See Table I for organic conditions associated with Cotard syndrome and Table II for the detailed neurodiagnostic findings identified in literature.

In Table II (in the 3rd column) we give a brief description of the psychopathology/phenomenology of each case included in this paper (where the information was available). As is evident from the findings presented here, there is no universally accepted definition of Cotard syndrome and hence it is best viewed as a 'spectrum of completeness/incompleteness of the syndrome'. For the purposes of this paper, we adopted a broad definition of Cotard syndrome and were guided by Berrios and Luque's conceptualisation – 'there is little support for the view that delire des negations should refer only to the delusion of being dead. Such a view is likely to waste information and hamper any possibility of finding out whether the symptom-cluster involved has any stable brain representation.

Results

Structural neuroimaging (CT/MRI) studies

Thirty-five cases of Cotard syndrome with structural neuroimaging findings were identified in the literature (see Table II for details).

Table I
Organic conditions associated with Cotard syndrome.

Condition	Cited description
Typhoid fever	Campbell, Volow & Cavenar (20)
Cerebral infarction	Drake (6)
Brain tumours (Astrocytoma)	Drake (6) Bhatia (8)
Temporal lobe epilepsy	Drake (6) Young, Leafhead (22)
Traumatic brain injury	Drake (6) Young *et al.* (10)
Migraine	Bhatia (14)
Laurence-Moon-Bardet-Biedl syndrome	Lerner *et al.* (33)
A-V malformations	Gardner-Thorpe (9)
Multiple sclerosis	Gardner-Thorpe (9)
Parkinson's disease	Factor, Molho (34)

Table II
Neurodiagnostic findings in Cotard syndrome.

CS-Cotard Syndrome, m-male, f-female,NR-not reported, N-normal, R-right, L-left, BL-bilateral, TIA-Transient Ischemic Attack, NART-National Adult Reading Test, BVRT-Benton Visual Retention Test, WRMT-Warrington Recognition Memory Test, BLOT-Benton Line Orientation Test, BTFR-Benton Test of Facial Recognition, KDAM-Kapur's Dead or Alive Memory test, MMPI-Minnesota Multiphasic Personality Inventory, BWF-Benton Word Fluency, MEAMS-Middlesex Elderly Assessment of Mental State, BDHI-Buss Durkee Hostility Inventory, WAIS-Wechsler Adult Intelligence Scale, MMSE-Mini Mental State Examination, WISC-Wechsler Intelligence Scale for Children, EEG-Electroencephalography, CT-Computed Tomography, MRI-Magnetic Resonance Imaging, SPECT-Single Photon Emission Computerised Tomography

No. & Cited description.	Age & Sex.	Phenomenological description.	Diagnosis / Neurological examination.	EEG.	Neuro-psychological testing.	CT.	MRI.	SPECT.
1. Campbell S (20)	27 m	Delusions of being dead, disorganised behaviour.	CS, Typhoid fever / N	Mild generalised slowing, might be due to typhoid encephalopathy.	NR	N	NR	NR
2. Joseph AB (5)	34 f	Depressed mood, suicidal, depersonlisation, delusion of being deak and immortal.	CS / N	N Brain electrical activity mapping – generalized electrophysiologic abnormalities with R temporal predominance.	N	BL Atrophy at frontal, temporal, parietal lobes and vermis. Abnormal enlargement at sylvian fissures and inter-hemispheric fissures.	NR	NR
3. Joseph AB (5)	37 f	Bipolar disorder.	CS / NR	NR	NR	BL Atrophy at frontal and temporal lobes and vermis. Abnormal enlargement at sylvian and interhemi-spheric fissures.	NR	NR
4. Joseph AB (5)	26 f	Depression.	CS / NR	NR	NR	N	NR	NR
5. Joseph BA (5)	47 f	Bipolar disorder.	CS / NR	NR	NR	BL Atrophy at temporal lobes and basal ganglia. Calcification at BL basal ganglia. Abnormal enlarge-ment at sylvian fissure.	NR	NR
6. Joseph AB (5)	30 m	Schizophrenia.	CS / NR	NR	NR	BL atrophy at frontal and temporal lobes. Abnormal enlargement at sylvian and interhemispheric fissures.	NR	NR

Table II (continue)

No. & Cited description.	Age & Sex.	Phenomenological description.	Diagnosis / Neurological examination.	EEG.	Neuro-psycho-logical testing.	CT.	MRI.	SPECT.
7. Joseph AB (5)	37 f	Schizophrenia.	CS / NR	NR	NR	BL atrophy at frontal temporal lobes and vermis. Abnormal enlargement at sylvian and interhemispheric fissures.	NR	NR
8. Joseph AB (5)	64 f	Bipolar disorder.	CS / NR	NR	NR	BL atrophy at frontal, temporal, parietal and occipital lobes. Abnormal enlargement at sylvian and interhemispheric fissures.	NR	NR
9. Joseph AB (5)	51 f	Depression.	CS / NR	NR	NR	BL atrophy at frontal lobes. Abnormal enlargement at interhemispheric fissures.	NR	NR
10. Drake ME (6)	22 f	Depressed mood, de lusion that she was dead and her body was putrefying, denied exis-tence of her body parts.	CS, Chronic Seizure Disor-der / Mild left hemiparesis	Sleep deprived EEG-polymorphic delta slowing and epiliptiform discharges in the R temporal region, and a partial & secondary generalized seizure originated in the R anterior temporal area.	NR	Irregular rounded hypo-dense area with enhance-ment, surrounded by edema and with mass efect. Biopsy- astrocytoma	2*4cm round high signal intensity focus in the R pos-teroinferior frontal lobe, with some mass effect of adja-cent temporal lobe.	NR
11. Drake ME (6)	33 m	Delusion that he was dead, agitation, belief that internal organs were liquefied, mute at times, disorganised behaviour.	CS, Closed Head injury / NR	Prolonged sleep deprived video EEG-plymorphic R frontotemporal delta slowing with R frontal & anterior temporal sharp waves and spike-wave activity.	NR	R temporal lobe atrophy, sylvian fissure enlarge-ment with extensive encephalomalacia of R frontal lobe	NR	NR
12. Drake ME (6)	56 m	Delusion of being dead, depressed affect.	CS, Seizure disorder / NR	Prolonged sleep deprived video EEG – normal background activity and R anteromesial temporal sharp waves.	Average intellectual function but mild deficits consistent with anterior right cerebral hemisphere dysfunction. MMPI suggested depression, anxiety, somatic preoccupation	Irregular ovoid 2*3 cm hypodensity in the inferior frontal region, without enhancement.	Similarly shaped high signal intenstiy focus in the R frontal lobe consistent with infarction Cerebral angiog-raphy – N.	NR

Table II (continue)

No. & Cited description.	Age & Sex.	Phenomenological description.	Diagnosis / Neurological examination.	EEG.	Neuro-psycho-logical testing.	CT.	MRI.	SPECT.
13. Young AW (10)	28 m	Delusions of being dead being taken to hell, loss of familiarity of builidings and people's faces, feelings of unreality.	CS, Head injury / L hemipaersiis	NR	Pre Morbid IQ 120 using NART. BVRT - normal; Severe impairment on the Faces part of the WRMT. BLOT - normal, no sign of visuo spatial neglect. Recognition of emotional facial expression - impaired Recognition of familiar faces - impaired Recognition of unfamiliar faces - normal BTFR - borderline impairment These findings suggest a fairly general impairment of all aspects of face processing, but not as dramatic as that revealed in Faces part of the WRMT. KDAM - normal, thus no evidence that face recognition impairment could be attributed to loss of knowledge of familiar people. Recognition of famous buildings - normal.	Multiple haemorrhagic contusions of the R temporal cortex with some pressure on the occipital horn of the R lateral ventricle. Repeat scan - low attenuation areas corresponding to these areas of contusion in the R temporal region extending through the region of the R internal capsule. On both scans low attenuation on surfaces of both frontal lobes suggesting a degree of frontal atrophy. Dilatation of the ventricular system.	Dilatation of the ventricular system.	Reduced tracer uptake in R temporal lobe and adjacent parietal regions.
14. Terato T (15)	62 m	Depression, feelings of guilt, suicidal ideation, anxiety, delusions of guilt and poverty, delusions of immortality.	CS / N	N	NR	NR	N, slight cortical atrophy probably due to ageing.	NR
15. Bhatia MS (14)	32 f	Delusion of being dead.	CS, Migraine / N	N	NR	N	NR	NR

Table II (continue)

No. & Cited description.	Age & Sex.	Phenomenological description.	Diagnosis / Neurological examination.	EEG.	Neuro-psycho-logical testing.	CT.	MRI.	SPECT.
16. Bhatia MS (8)	12 m	Normal affect, delusion of being dead and visual hallucinations.	CS, Parietal Lobe tumor (Astrocytoma) / N	N	NR	Dense shadow in the L parietal area displacing midline towards R side.	NR	NR
17. Young AW, Leafhead KM (22)	29 f	Depressed mood, delusions of guilt, delusions of being dead, denied existence of others, suicidal ideation, derealisation.	CS, Bipolar Affective Disorder / NR	N	General face processing difficulties, impaired recognition of familiar faces and facial expressions, Poor ability to match or remember unfamiliar faces. Normal recognition memory for words High score on magical ideation scale-17/30.	Prominent cortical sulci.	NR	NR
18. Young AW, Leafhead KM (22)	35 m	Depressed mood, persecutory delusions, delusions of being dead, olfactory hallucinations, denied existence of his internal organs.	CS / N	Maximal sharp activity over anterior temporal and frontal regions supporting of Complex partial seizure of temporal lobe origin.	Able to recognise familiar faces Match pictures of unfamiliar faces Recognised facial expressions of emotion although slow Normal recognition memory for words Impaired recognition mem-ory for faces using WRMT.	N	NR	NR
19. Petracca G (11)	56 m	Depressed mood, nihilistic ideas, denied existence of hand and blood, delusions being dead.	CS / N	N	NR	N	N	Hypoperfusion at BL dorosolateral frontal lobes, frontoparietal medial cortex, the basal ganglia and the thalamus. Second study immediately

Table II (continue)

No. & Cited description.	Age & Sex.	Phenomenological description.	Diagnosis / Neurological examination.	EEG.	Neuro-psycho-logical testing.	CT.	MRI.	SPECT.
								after ECT showed increased perfu-sion and third study after 1 month after ECT showed greater perfusion.
20. Lerner V (33)	20 f	Depressed mood, suici-dal ideas, paranoid delu-sions, AH, delusions of immortality, denied exis-tence of internal organs.	CS, Schizophrenia Laurence-Moon-Bardet-Biedl syndrome / NR.	Diffuse abnormalities	WAIS – 77	N	NR	NR
21. Leafhead KM (23)	29 f	Delusions of being dead, suicidal ideas, depressed mood.	CS, Bipolar Affective Disor-der / NR.	N	Poor recognition of familiar faces, poor at identifying facial expressions, poor at matching and remembering unfamiliar faces. Recognition memory for unfamiliar buildings was impaired. After, a variant of Stroop paradigm was used to investigate attention bias, patient was shown sets of words printed in different colours and was asked to name the colour of each word. There were 3 separate testing sessions which took place over a 2 yr period. Patient was significantly slower to colour name test lists containing words related to her delusional beliefs. When patient improved following treatment, not slower to colour name any of the test word lists.	Prominent cortical sulci.	NR	NR

Table II (continue)

No. & Cited description.	Age & Sex.	Phenomenological description.	Diagnosis / Neurological examination.	EEG.	Neuro-psycho-logical testing.	CT.	MRI.	SPECT.
22. Leafhead KM (24)	61 m	Depressed mood, suicidal ideas, delusions of being dead, feelings of unreality.	CS / NR	NR	NART - 87 however as pt. was semi-literate little weight can be given to these scores. BWF – poor worse than patients with severe dementia MEAMS – failed in name-learning, naming 3 objects and arithmatic Contrast Sensitivity – using Vistech 6000, normal WRMT – there was discrepancy between faces and words subtests. But the test inconclusive considering his literacy problems Facial identification – normal with unfamiliar faces Facial Disguise Test – normal, Labelling of Emotional Facial Expressions – slightly low Gaze Direction – slightly lower, Recognition Memory for Buildings – lower score Identification of Famous Buildings – normal This suggests his memory for faces was impaired, his ability to process faces in tasks requiring little or no memory function was unimpaired. Suggestion that memory component of visual processing may be differentially affected in the Cotard delusion.	NR	NR	NR

Table II (continue)

No. & Cited description.	Age & Sex.	Phenomenological description.	Diagnosis / Neurological examination.	EEG.	Neuro-psycho-logical testing.	CT.	MRI.	SPECT.
23. Silva JA (25)	62 f	Depressed mood, ideas of hopelessness, denied existence of the world and other people, derealisation.	CS / N	NR	BFRT – Normal WRMT - face processing component impaired but normal word recognition.	N	NR	NR
24. Cohen D (16)	15 f	Depressed mood, catatonia, delusions of being dead and denied existence of body organs.	CS, Neuroleptic Malignant Syndrome for antipsychotic treatment / Muscular rigidity, trismus, hyperthermia (38C).	N	NR	N	NR	NR
25. Hansen ES (17)	54 m	Suicidal ideas, paranoid, denied existence of internal organs, hypochondriacal ideas.	CS / N	N	NR	NR	NR	NR
26. Hansen ES (17)	74 m	Suicidal ideas, delusion of being dead, hypochondriacal ideas.	CS / NR	N	NR	NR	Moderate cortical atrophy	NR
27. Hansen ES (17)	54 m	Depressed mood, delusion of being dead.	CS / N	N	NR	NR	NR	NR
28. Silva JA (35)	46 m	Delusion of being dead, delusions of guilt, depressed mood, paranoid ideas.	CS / NR	NR	BFRT – normal WMRT for words normal WMRT for faces low score BDHI below average score	N	NR	NR
29. Allen JR (19)	10 m	Suicidal ideas, delusion of being dead.	CS / NR	Diffuse nonspecific abnormalities.	WISC IQ – 77, performance IQ 78, Verbal 81 2 yrs before IQ 90, performance 90, verbal 92 Visual motor Index significant decline Projective testing – greater need for nurturance and	NR	NR	NR

Table II (continue)

No. & Cited description.	Age & Sex.	Phenomenological description.	Diagnosis / Neurological examination.	EEG.	Neuro-psycho-logical testing.	CT.	MRI.	SPECT.
					determination to take care of himself but no depression, thought disorder, or poor reality testing.			
30. Baeza (36)	20 m	Flat affect, nihilistic delusions about his body and his existence, depersonalisation, derealisation.	CS, Bipolar Affective Disorder / N	NR	NR	N	NR	NR
31. Duggal HS (18)	32 m		CS / N	Nonspecific background abnormalities	Elevated Benders visuomotor gestalt test scores, Strub and Black battery – frontal and parietal lobe dysfunction (constructional apraxia).	N	NR	NR
32. Hashioka S (12)	57 f	Delusions of negation concerning concepts and existence, hypochondriacal delusions.	CS, Presenile Dementia / N	8-9Hz dominant rythms with a few slow waves	WAIS – 72, verbal-82, performance-66 MMSE-15.	N	N	Significant hypoperfusion in BL frontal lobes. After 6 months treatment with antidepressant imipramine and amisulpeiride, clinical improvement but No improvement in perfusion. Remission maintained and after 15 months

Table II (continue)

No. & Cited description.	Age & Sex.	Phenomenological description.	Diagnosis / Neurological examination.	EEG.	Neuro-psycho-logical testing.	CT.	MRI.	SPECT.
								improvement in bifrontal hypoperfusion.
33. Caliyurt O (17)	27 m	Nihilistic delusions, depressed mood.	CS, at age 6 years Mumps and Meningitis with full recovery / N.	N	NR	Dilatation of lateral and third ventricles.	Central atrophy and BL atrophic dilatation at temporal horns of the lateral ventricle.	Hypo perfu-sion at L tem-poral , L infe-rior frontal and L Parietal lobe. Post ECT total improvement of L inferior frontal and L parietal hypop-erfusion. Mini-mal hypoperfu-sion at L temporal lobe.
34. De Risio S (13)	43 m	Depressed mood, delusion of being dead, denied existence of internal organs.	CS / N	NR	NR	N	NR	No perfusion deficits. But D2 receptor binding with 123 I-IBZM-SPECT reduced striatal D2 receptor Binding.(R-1.281, L-1.344) After 3 mnths of treatment further BL decrease in D2 Receptor bind-ing with R vs

Table II (continue)

No. & Cited description.	Age & Sex.	Phenomenological description.	Diagnosis / Neurological examination.	EEG.	Neuro-psycho-logical testing.	CT.	MRI.	SPECT.
								L decrement less than in Previous (R-1.264, L-1.282)
35. Gardner-Thorpe C (9)	46 m	Visual and olfactory hallucinations, delusions of negation.	CS, TIA, Marfans syndrome, Mitral value prolapse Aortic valve replacement / N.	NR	NR	L posterior pareital haemorrhagic infarct.	Cryptic vascular malformation in the medial part of the R cerebral hemisphere and in several other sites, and an arteriovenous malformation in the L cerebral hemisphere.	NR
36. Gardner-Thorpe C (9)	38 f	Delusions of negation.	CS, Demyelinating disorder / Minimal ataxia, nystagmus on gaze to the left that raised the possibility of demyelinating disese.	Brainstem auditory evoked responses were abnormal suggestive of demyelinating disease.	NR	N	NR	NR
37. Factor SA (34)	51 f	AH, delusion of being dead.	CS, Parkinson disease.	NR	NR	NR	NR	NR

Joseph compared the CT scans of eight patients who had Cotard syndrome with eight controls (without Cotard syndrome but matched for the psychiatric diagnosis) and noted significant differences between the two groups[5]. The most common abnormalities in patients with Cotard syndrome were bilateral cerebral atrophy, sylvian and interhemispheric fissure enlargement, and dilatation of lateral ventricles. There were no differences in basal ganglia abnormalities and frontal, temporal or parietal atrophy. Drake described three patients with right fronto-temporal structural lesions and temporal lobe epilepsy, who all also had Cotard syndrome[6]. MRI scan in his first patient revealed a 2 x 4 cm round high signal intensity focus in the right postero inferior frontal lobe. In his second patient, with post head injury seizures and Cotard syndrome, CT scan showed right temporal lobe atrophy and sylvian fissure enlargement, and in the third patient, CT revealed a 2 x 3 cm hypo density in the inferior frontal region. Other structural abnormalities found in association with Cotard syndrome include dilation of the third and lateral ventricles[7], left parietal lobe lesions[8,9] and haemorrhagic contusion of the right temporal cortex[10]. Notwithstanding the above listed structural abnormalities, it is important to note that many more cases of Cotard syndrome with normal CT/MRI findings have been reported (see Table I).

SPECT studies

Limited research in this area precludes valid inferences being drawn. Only five cases of Cotard syndrome with SPECT findings were identified. Two cases report blood flow abnormalities to the brain that resolved after treatment with ECT[7,11]. In the first patient (Cotard syndrome with depression), SPECT showed bilateral hypo-perfusion in the dorsolateral frontal lobes, fronto parietal medial cortex, basal ganglia and thalamus.

Subsequent SPECT scan studies immediately after and one month after a course of ECT demonstrated progressively greater perfusion in the above-mentioned region[11]. In the second patient (Cotard syndrome with schizophreniform disorder), hypo perfusion in the left temporal, left inferior frontal and left parietal lobe, improved completely, post-ECT, except for persisting minimal left temporal lobe hypo perfusion[7]. Hashioka noted no improvement in perfusion on SPECT, six months after pharmacological treatment, despite clinical remission. However, SPECT scan in the same patient done 15 months later revealed improvements in the bifrontal hypo perfusion[12]. In the only study that evaluated D2 receptor binding using SPECT, De Risio noted reduced striatal D2 receptor binding (right vs. left percentage decrement – 4.92%), with visual inspection confirming left > right uptake[13]. Three months after treatment with clozapine, further bilateral decrease in D2 receptor binding, with right vs. left decrement less than in the previous SPECT was noted.

Neurophysiological studies

Eighteen reports of neurophysiological investigations in cases of Cotard syndrome were noted (see Table II). Most revealed no EEG abnormalities[7,8,11,14-18] whereas others revealed diffuse non-specific abnormalities[19] and abnormalities suggestive of the underlying organic condition such as typhoid fever or multiple sclerosis[9,19,20], Drake studied three patients with TLE and Cotard syndrome and noted the following abnormalities on sleep-deprived EEG: poly-

morphic delta slowing and epileptiform discharges in the right temporal region (case 1), polymorphic right frontotemporal delta slowing with right frontal and anterior temporal sharp waves and spike wave activity (case 2) and right anteromesial temporal sharp waves (case 3)[6]. Joseph used BEAM (brain electrical activity mapping) in a 34-year-old woman with Cotard syndrome to find generalized electrophysiological abnormalities with a right temporal predominance[21].

Neuropsychological studies

These studies in Cotard syndrome have most commonly focussed on various tests of intelligence and tests of facial recognition and memory. In all, 12 case studies were identified but only 4 had mentioned the neuropsychological findings in detail[10,22-24].

Neuropsychological testing of a 28-year-old man with Cotard syndrome revealed severe impairment on the faces part of the Warrington Recognition Memory Test, impairment of recognition of emotional facial expression and recognition of familiar faces and borderline impairment on the Benton test of facial recognition. These findings suggest a fairly general impairment of all aspects of face processing, with no evidence that face recognition impairment could be attributed to loss of knowledge of familiar people. Leafhead studied a 61-year-old man with Cotard syndrome, using a neuropsychological test battery and found impaired recognition memory for words, faces, and buildings and for identification of faces[24]. She also demonstrated normal recognition of emotional facial expressions and facial disguise. Similar findings (impairments in recognition of familiar faces and facial expressions) have also been noted by others[22,23,25,26].

Discussion

This study had three important limitations: language bias, publication bias and the small sample size. First, language bias. Exclusion of papers published in non-English languages might have limited the total number of cases available for inclusion. Second, publication bias. It is to be noted that not all cases of Cotard syndrome seen by psychiatrists in their day-to-day practice are likely to be written up and published. It is more likely that cases of Cotard syndrome with positive neurological findings will be published. Hence, the inferences and generalizations that can be drawn from a largely skewed sample (only those cases with abnormal neurological findings) regarding the underlying neurological correlates of Cotard syndrome in general, are limited. Third, despite encouraging trends, research into the neuropsychological and neuroimaging aspects of Cotard syndrome is limited, as evidenced from the limited number of case reports eligible for inclusion in the study. A larger sample would have probably enhanced the validity of our conclusions.

Most of the above-discussed cases of Cotard syndrome had an associated, underlying organic condition such as TLE, head injury, or brain tumour (see Table I). So, it could be argued that the neurological abnormalities (neuropsychological or neurostructural) noted are a manifestation of the underlying organic condition and not of Cotard syndrome itself. Simply demonstrating an association/coexistence between Cotard syndrome and neurological abnormalities does not prove causality. Hence, it is not possible to draw valid inferences about the aetiology of Cotard syndrome from such studies. However, they still point to some possible underlying neurological

substrates that might play a role in the etiopathogenesis of Cotard syndrome. In summary, although not all, some cases of Cotard syndrome are associated with structural and functional brain dysfunctions. From a clinical perspective, it is crucial to maintain a low threshold for suspicion of organicity in cases of this uncommon psychiatric syndrome (Cotard syndrome), and thereafter to consider appropriate neurological investigations.

Although not consistent, most CT/MRI studies of Cotard syndrome noted abnormalities in the non-dominant frontal, temporal and occasionally the parietal lobes. Drake noted that Cotard syndrome is most probably due to an irritative focus in the right frontal and temporal lobes[6]. This is in keeping with previous research linking Cotard syndrome with non-dominant cerebral hemisphere abnormalities[21]. There is also considerable evidence linking the origins of content-specific delusions to the right hemisphere, especially the frontal lobe[27,28]. The importance of right temporal lobe dysfunction superimposed on widespread cerebral atrophy in the aetiology of Cotard syndrome was further highlighted by Joseph and O'Leary[5], who demonstrated overall brain atrophy in 8 patients as compared to controls. They also found interhemispheric fissure enlargement in 6 of their 8 cases and hypothesized that it might be secondary to medial frontal lobe atrophy.

SPECT scan studies too have identified abnormalities in the frontal region of the brain in Cotard syndrome, often reversible with treatment[11]. They noted decreased blood flow in the medial fronto parietal and frontal dorsolateral cortex. However, this study did not rule out whether these perfusion abnormalities were due to the underlying depression or the Cotard syndrome itself. Authors argue that the medial frontoparietal and thalamic perfusion abnormalities produce a degraded body schema, which in the context of depression, leads to the development of Cotard syndrome.

So far, most of the neuropsychological findings in Cotard syndrome point towards face processing impairments as the central mechanism in its aetiology. Young and Leafhead proposed a neuropsychological model of Cotard syndrome, incorporating components of face–processing impairments, abnormal feelings, derealization and depressed mood[22]. They viewed Cotard syndrome as 'a depressed person's attempt to account for abnormal perceptual experiences'. The overlap of Cotard syndrome with misidentification syndromes, and Capgras syndrome in particular, has been extensively studied[25,26,29]. As Cotard syndrome has been noted to coexist and even sequentially follow Capgras syndrome[5,30], and given the commonalities in the neuropsychological (face-processing impairments) and neurostructural (non-dominant cerebral hemisphere lesions) abnormalities, it has been suggested that they may share common pathophysiological mechanisms[21,30]. A detailed discussion of the neuropsychological models of Capgras syndrome is beyond the remit of this paper – see references[31,32].

In 1995, concluding a review of the conceptual history of Cotard syndrome, Berrios and Luque remarked 'we suggest that before speculation starts on any neurobiological basis for the delire des negations, efforts should be made to remap its clinical features and basic clinical correlations'[2]. Ten years on, our review has hopefully shed some light on the recent advances in the field of neurobiology of Cotard syndrome and will encourage enthusiastic clinicians and researchers to revisit this area. Much more research is needed before definitive

conclusions about the neurological substrates of Cotard syndrome can be drawn.

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(Although non-English articles were excluded from our review, here is a selection of some such papers for the interested reader).

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