



Mania caused by a diencephalic lesion

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Abstract

We describe the case of a young male patient, SN, who suffered a MR-documented ischaemic lesion of both dorsomedial thalami and presented with a transient maniform syndrome. SN's neuropsychological, structural and functional imaging findings are compared with similar reported cases and are discussed in the framework of fronto-subcortical circuits and their proposed behavioural disorders. SN's mania was characterized by restlessness, mood elevation, a tendency for pleasurable activities, inflated self-esteem and loss of disease awareness. Other symptoms were sexual disinhibition, tactlessness, abnormal discourse, and reduced need for food and sleep. His neuropsychological assessment revealed an anterograde amnesia, and an impairment of frontal-executive functions. A SPECT-study showed diaschisis-related areas of hypoperfusion in both prefrontal regions which were interpreted as equivalents of SN's frontal-dysexecutive syndrome. In addition, there was a perfusion deficit in the right orbitofrontal cortex, which was taken as the imaging correlate of SN's secondary mania and personality disorder. These findings suggest that SN's mania and his other symptoms result from the twofold disruption of fronto-subcortical connections, namely of the right orbitofrontal loop which is concerned with mood regulation and socially appropriate behaviour, and of the dorsolateral prefrontal loop which mediates executive cognitive functions. © 2001 Elsevier Science Ltd. All rights reserved.

Keywords: Mania; Thalamus; Fronto-subcortical circuits; Orbitofrontal area; Dorsolateral prefrontal region

1. Introduction

The core behavioural abnormalities of the acute bilateral paramedian thalamic infarct (BPTI) comprise a state of somnolence and abulia accompanied by amnesia and a 'frontal brain' syndrome [38]. The disorder of vigilance often starts with a transient coma, followed by a gradually remitting stupor or hypersomnia during which patients present slow, apathetic and emotionally impoverished. During this state of 'psychic akinesia' spontaneous activity is decreased and patients require repeated and vigorous external stimulation during conversation or psychometric testing. With recovery of consciousness, behavioural and neuropsychological abnormalities become evident, mostly encompassing diencephalic amnesia [7,27,29,39], and frontal-executive dysfunction [10,33]. In addition to these standard find-

ings, some case studies have described mood changes, such as cheerfulness, depression, lability with sudden switches from sadness to irritability, and outbursts of anger coupled with physical aggression [7,10,14,15,27]. Other forms of reported behavioural changes include sexual disinhibition and uncontrolled eating behaviour [8,15]. At present, no conclusive evidence exists as to exact origin of mood disorders following thalamic lesions. We report on a patient who suffered an acute manic episode due to a BPTI. The patient's findings are compared with similar, previously published cases in order to specify 'diencephalic mania' in greater detail, and an attempt is made to propose a neurological background hypothesis for the abnormalities of mood and cognitive behaviour following lesions of the diencephalon. Since it is known from experimental and clinical case studies that the frontal lobes are part of a complex neural network responsible for mood regulation and social behaviour [28], the approach adopted in this study will focus on the functional relationship

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between the diencephalon and frontal brain areas, and on the consequences of a focal diencephalic lesion on this network.

2. Case description

SN, a 38-year-old previously healthy male commercial artist, was found deeply unconscious during a summer holiday in Turkey. During the next 48 h the patient gradually regained consciousness and was flown to his home country where he arrived awake and in good somatic condition, but logorrheic and profoundly amnesic. Apart from a complete vertical gaze paralysis and a slight dysarthria there were no other focal deficits. His history was free of drug abuse, previous neurological diseases, vascular risk factors or a recent trauma. No psychotic episodes were known in his family, and he had never gone through a period of mania or depression. MR-imaging depicted a fresh ischaemic lesion of both mediodorsal thalami on day 9 (Fig. 1). There were no ischaemic lesions in the frontal lobe. Since an echocardiogram showed a patent foramen ovale, and a transcranial Doppler sonography revealed air bubbles after i.v.-ingestion, a paradoxical embolism causing a transient occlusion of the vertebral-basilar circulation was assumed, inducing the initial coma and an ischaemic BPTI, and the patient was put on i.v. heparin.

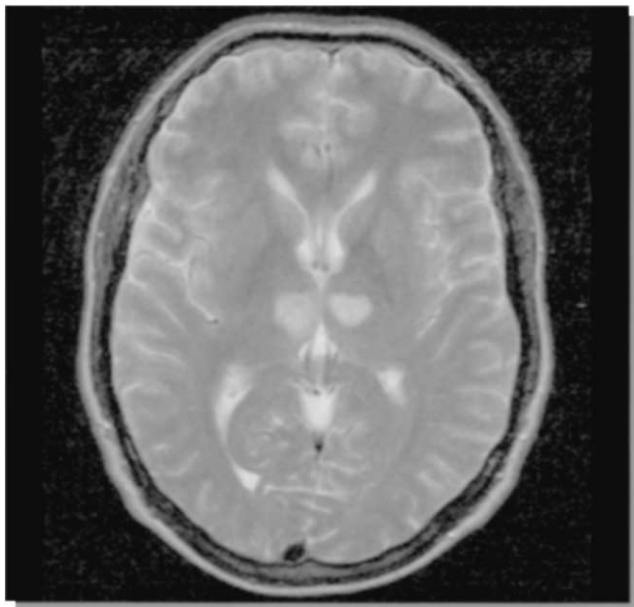


Fig. 1. MRT showing bilateral ischaemic lesion, including both dorsalmedial thalami; the lesion also includes parts of the intralaminar and anterior nuclei.

3. Behavioural findings

During the next 4 weeks SN's clinical picture was dominated by striking behavioural abnormalities. Different from other cases of the BPTI who present with hypersomnolence and apathy in the immediate period after their ictus, SN was continuously restless and agitated. He spent his time switching rapidly from one activity to another, writing letters, inventing and drawing new designs, portraying team members of the stroke unit, listing phone numbers from memory, or discussing plans for a wealth-growing future business. His mood was markedly elevated and his self-esteem inflated. He started long-winding discussions with every person he came across, producing tangential and often incoherent forms of speech. SN was easily distractable and had difficulties to stick to a topic, gave approximate answers (*vorbeireden*) and produced chains of 'klang-associations', puns and odd jokes. He also made many inappropriate or tactless comments and sexually suggestive remarks, behaved in a puerile and overfamiliar manner, had an exaggerated concept of his memory and cognitive abilities, and poor disease awareness. Though explicitly forbidden to him, he undertook spontaneous taxi excursions to the surroundings of the clinic. There were no signs of hallucinations or delusions, and he did not behave in an aggressive or irritated manner. His need for food and sleep was markedly decreased. It was soon noted that SN's memory was poor for the more recent time period, whereas he had no difficulties remembering distant, past events. His restlessness, agitation and extensive periods of wakefulness required low-dose treatment with a neuroleptic. Eight weeks after onset the majority of SN's manifold symptoms appeared markedly ameliorated and his medication could be discontinued. He had only limited memories of the manic episode.

4. Methods

Neuropsychological testing was performed on day 8 and during week 8 post disease onset. The assessment included standard tests such as the estimation of pre-morbid verbal intelligence [23], the MMSE [13], the Digit Span Test [43], the Trail Making Test [25], an oral test of mental arithmetics [20], and a test tapping visual organization [18]. Verbal and figural memory was assessed using an abbreviated version of the *Münchner Gedächtnistest* [19], a German equivalent of the California Verbal Learning Test [11], the Recognition Memory Test [42] and the Complex Figure Test [34]. SN's mnemonic abilities and his tendency to produce provoked confabulations was further tested on a confabulation battery designed after Dalla Barba [9] tapping his personal (names and date of birth of family

Table 1
Neuropsychological findings and mania rating

	Day 8		Day 80	
	Raw score	Percentage score	Raw score	Percentage score
Estimated premorbid verbal IQ	123	92–95	n.d.	
Mini Mental State Examination	27/30, (orientation 10/10)		n.d.	
Trail Making Test:				
Form A	53 s	PS <10	28 s	PS 50–75
Form B	73 s	PS 25–50	60 s	PS 50–75
Digit Span Test				
Digits forward/backward	5/4	18/30	n.d.	
Oral calculation	10		12	
Hooper Visual Organization Test	23	34	24.5	34
Complex Figure Test:				
Copy	32	40	31	30
Long term free recall	13	20–30	28	>90
Münchener Gedächtnistest:				
Learning trials 1–5	3-6-7-7-6		4-6-8-8-8	
Short delay free recall	2/16		5/16	
Long delay free recall	0/16		5/16	
Recognition	11/16		14/16	
False positives	4		4	
Confabulations and intrusions	15		21	
Recognition Memory Test:				
Words	32/50	5	33/50	
Faces	30/50	5	42/50	
Category word fluency (animals/min.)	11		22	
Wisconsin Card Sorting Test:				
Categories achieved			6	PS <16
Perseverative responses	n.d.		24	PS = 5
Nonperseverative errors			8	PS = 53
Mania Rating Scale	28/44		7/44	

PS = percentage score, n.d. = not done.

members etc.), episodic (facts regarding the patient's newer history, hospital stay etc.) and general semantic memory (historical dates, celebrities). Frontal-executive functions were assessed with the Wisconsin Card Sorting Test [17] and a category fluency test (animals). A common rating scale was used to diagnose and quantify mania [2]. A measurement of resting regional cerebral blood flow was performed using standard perfusion-SPECT with 555 MBq ^{99m}Tc -Bicisate (Neurolite®).

5. Results

5.1. Neuropsychology

Results of both formal neuropsychological testings and mania ratings are summarized in Table 1. SN's estimated premorbid verbal IQ was above average. His language, reading, writing and drawing performances were all undisturbed, and his visuomotor tracking, oral

calculation, figure copying and visual organization abilities were average. In the acute stage learning, immediate and long-term spontaneous recall of a word-list were all severely reduced. SN produced many confabulations and errors of intrusion during spontaneous recall, and false positives during recognition. Recall of figural information was defective and recognition memory for words and faces was subnormal. Despite his severe amnesic syndrome he was oriented to time and place, and his personal and general semantic memory were well preserved on the confabulation battery. Card sorting was normal except an above average number of perseverative responses; semantic word fluency was below average. A sum-score of 28 on the Bech et al. [2] rating scale confirmed the diagnosis of a maniform syndrome. Follow-up assessment after 2 months showed a substantial recovery of memory functions; however, SN's learning and recall abilities were still in the subnormal range and he continued to produce provoked confabulations during spontaneous recall and

errors of commission during recognition memory testing. Mania rating indicated that SN had recovered but still indicated mild hypomania.

5.2. SPECT findings

Visual inspection of transverse, coronal and sagittal slices and the three-dimensional-surface display of the standard perfusion-SPECT image data revealed markedly reduced perfusion in the right thalamus and both dorsolateral prefrontal regions (Fig. 2). Furthermore, a perfusion deficit was evident in both lateral frontobasal areas, again with a clear predominance on the right side (Fig. 3). The observed perfusion deficits were interpreted as indicating thalamocortical diaschisis.

6. Discussion

Mania is a rare consequence of neurological diseases,

and the pathomechanism of mania following focal brain lesions is poorly understood. Neurogenic mania has been described following different brain lesions, such as the right basotemporal region [21,37,38], the orbitofrontal area [36,38], the caudate [5,32], and the diencephalon (see Table 2). We describe the case of a previously healthy young patient who, after a short initial period of decreased vigilance developed an acute manic syndrome as a sequel of a bilateral, paramedian diencephalic lesion. In contrast to the majority of BPTI-cases who present with persistent hypersomnolence and abulia [39], SN's clinical picture was dominated by hyperactivity, euphoria, a tendency for pleasurable activities, verbal sexual disinhibition and rule-breaking behaviour. His mania became apparent immediately after regaining wakefulness, lasted over a period of 2 months and showed good recovery in response to mild neuroleptic treatment. With these symptoms and disease course, and lacking a previous psychiatric disorder, SN meets the clinical criteria for a non-psychotic, episodic, organic-aff-

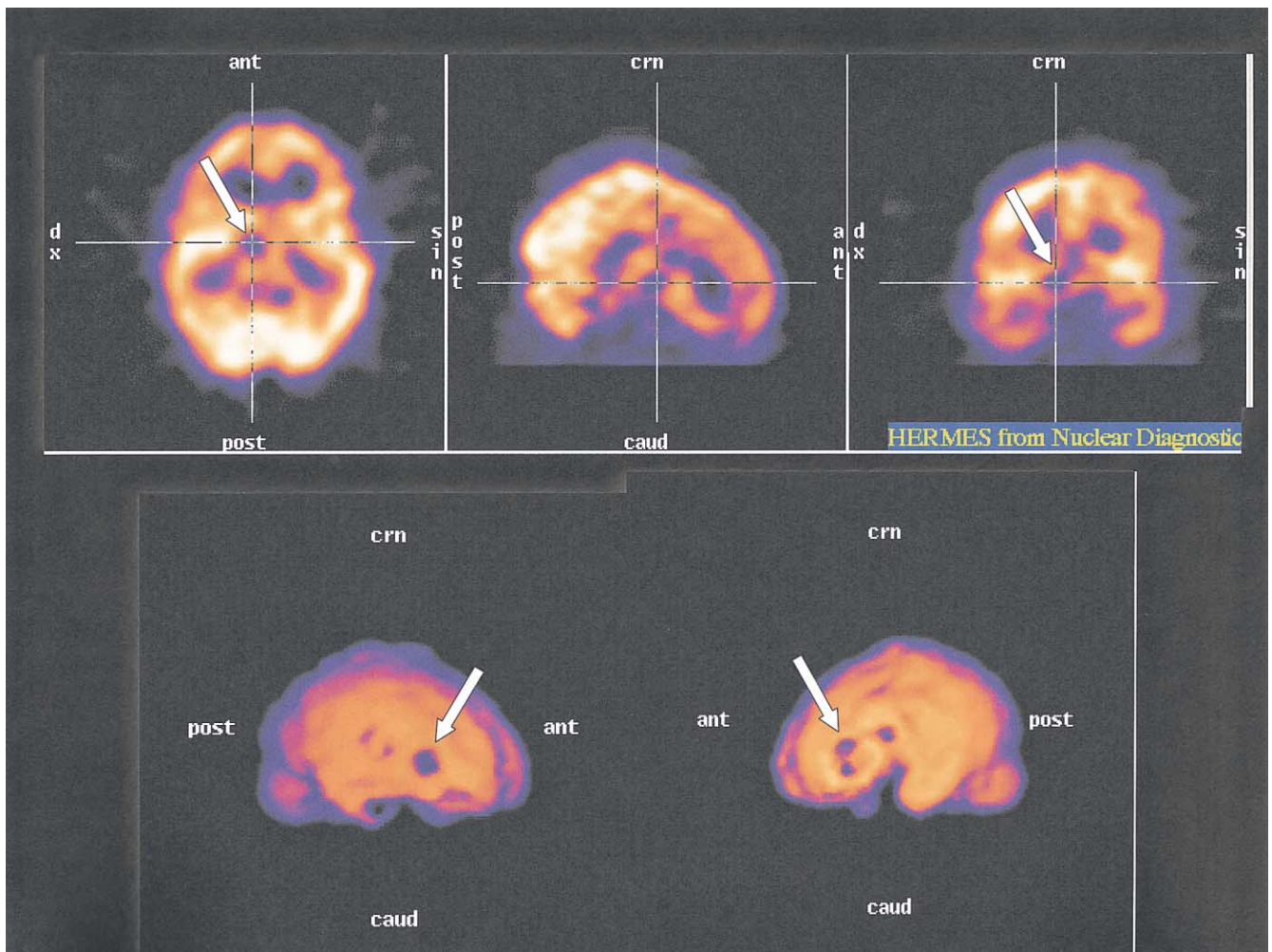


Fig. 2. Upper panels: transverse, sagittal and coronal slices showing a perfusion deficit in the right and slightly decreased perfusion in the left dorsomedial thalamus. Lower panels: three-dimensional-surface display, right and left oblique views. rCBF-SPECT shows scattered perfusion defects in the dorsolateral-prefrontal cortex bilaterally.

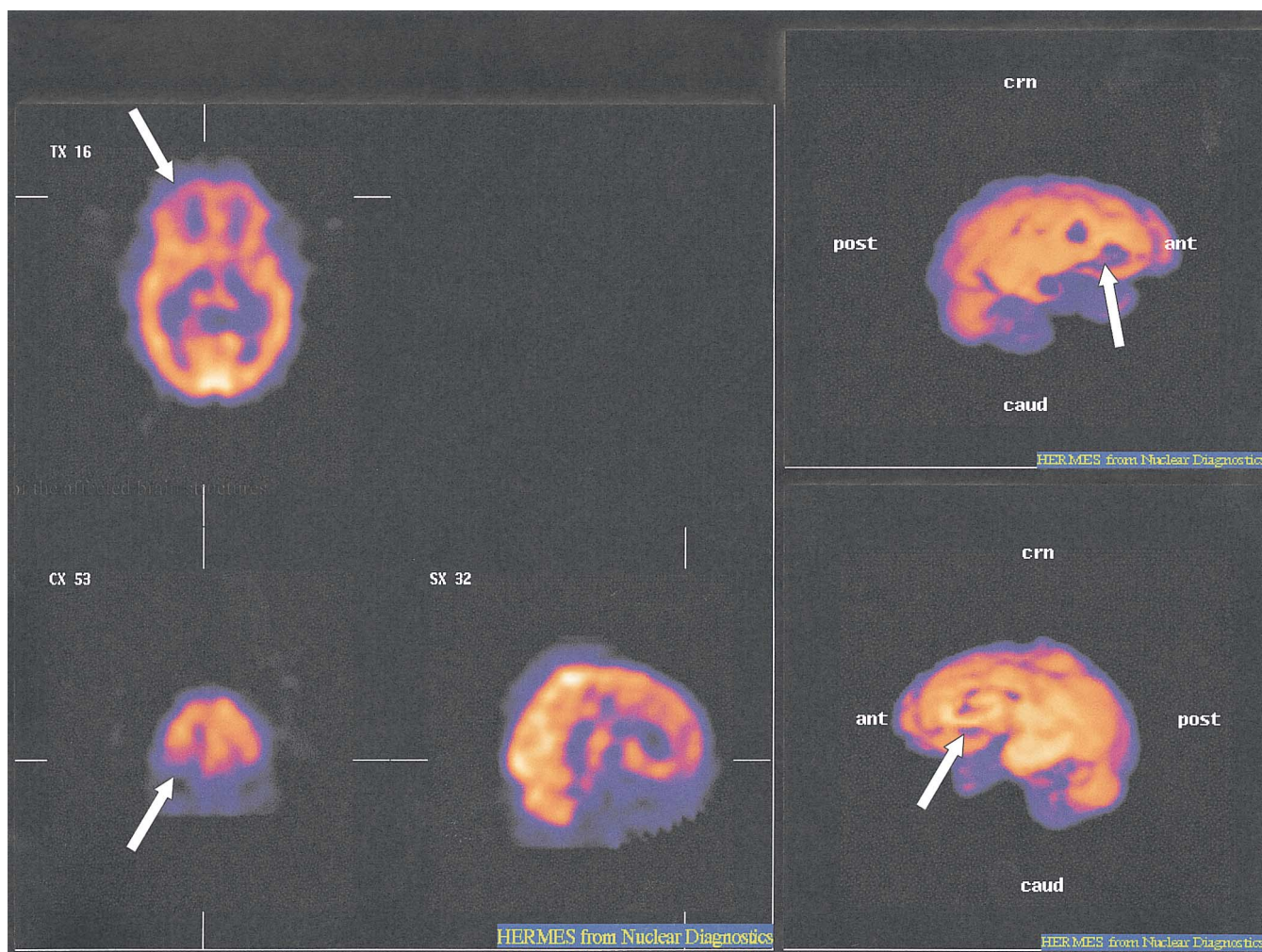


Fig. 3. Perfusion deficits at the level of the frontobasal cortex. Left panel: transverse, coronal and sagittal slices showing slightly reduced rCBF in the left and markedly reduced perfusion in the right frontobasal cortex. Right panel: three-dimensional-view of right and left frontobasal cortex. Arrows indicate areas of hypoperfusion. ant = anterior, post = posterior, crn = cranial, caud = caudal.

fective disorder of the manic type [12]. SN's case confirms that mania may also result from a diencephalic lesion as previously described in a small number of thalamic patients (Table 2).

According to SN's findings and earlier case descriptions (Table 2), 'diencephalic mania' presents with euphoric, logorrheic, restless and hyper-vigilant behaviour, often coupled with sexual disinhibition and sleep reduction, and sometimes with paranoia, irritability and aggression. Thus, 'diencephalic mania' appears to be behaviourally identical with common mania; however, its association with certain neuropsychological impairments, such as the combination of amnesia with frontal-executive dysfunction is unique and may help to differentiate thalamic mania from other manic syndromes. It emerges either as pure form [4,8,15], as recurrent, manic-depressive psychosis [30], or as short-lived, transient state in a series of rapidly chang-

ing mood swings [10,15,30]. Mania often diminishes under neuroleptic treatment within a few weeks to a state of slight mood elevation [4,8,22]; however, persistence of mania has also been reported [14,41], possibly due to predisposing factors such as a family history of psychiatric disorders [35,36]. Remarkably, the course and recovery of mania is not always paralleled by the course of associated cognitive impairments [14]. Diencephalic mania appears to follow either bilateral or unilateral right thalamic lesions, including its paramedian, dorsomedial, lateral and anterior regions (Table 2). Thus, the critical lesion site within the diencephalon is presently unrecognized, as is the precise pattern of metabolic changes in distant brain regions.

SN's MR-study showed a bilateral, dorsomedial thalamic lesion which possibly also included the intralaminar and anterior nuclei (Fig. 1). His SPECT-study displayed a predominantly right-sided local hypoperfu-

sion in the diencephalon (Fig. 2), corroborating the hypothesis that lesions of in the right brain have a predisposition for the occurrence of a maniform syndrome, as suggested before [3,8,37,38]. Further areas of hypometabolism were found in both dorsolateral-prefrontal regions and in the orbitofrontal cortex (Figs. 2 and 3). Dorsolateral-prefrontal hypoperfusion following a dorsomedial or anterior thalamic lesion is a well-known finding; clinically, this constellation is frequently associated with frontal lobe dysfunction [24,33]. SN's frontal-dysexecutive impairment was characterized by poor divergent thinking, a tendency to perseverate, rule breaking behaviour, and distractibility. His conversational discourse was abnormal, with increased distractibility, and an inability to maintain and appropriately shift themes. A similar disorder of conversation has been described by Chatterjee et al. [6] who interpreted the bizarre and incoherent speech of their paramedian thalamic patient LB as thalamic thought disorder caused by a disruption of behavioural, 'cortical' coherence due to thalamo-cortical disconnection. It seems likely that SN's impairment of executive control also weakened his ability to make use of strategic encoding, to employ semantic cues, suppress confabulatory responses, or monitor recognition processes, resulting in a further exacerbation of his verbal amnesia (Table 1). The dorsomedial and anterior thalamus has dense connections to the prefrontal cortex. Both structures are part of the dorsolateral-prefrontal loop, an

important basal ganglia-thalamo-cortical circuit [1] which subserves 'executive function' [31]. Thus, it is suggested that SN's dysexecutive syndrome was caused by a disconnection of the dorsolateral-prefrontal loop which happened at the diencephalic level.

SN's SPECT showed further areas of focal metabolic depression in both sides of the orbitofrontal cortex, again with a predominance on the right side (Fig. 3). It is well recognized that the frontobasal cortex is involved in the control and modulation of social and mood states [16,28]. SN's behaviour differed from the lack of spontaneity, irritability, loss of affective control, sudden aggression, or environmental dependency which is often found after orbitofrontal lesions [16]. However, his decreased social sensitivity, disinhibition, his tendency to confabulate, and also his maniform syndrome are well-known features found in a subgroup of patients with damage to the orbitofrontal brain [16,36,38]. The orbitofrontal area belongs to the paleocortical division of the limbic system, whereas the archicortical division is made up of the hippocampal formation, the Papez' circuit and the cingulate; both divisions are strongly interconnected [37]. Fibres from the orbitofrontal cortex are linked with the magnocellular division of the dorsomedial thalamus, and both structures are implemented in the orbitofrontal circuit which mediates emotionally tuned and socially adapted behaviour [31]. Based on SN's SPECT findings documenting focal perfusion deficits in the orbitofrontal area we

Table 2
Synopsis of cases with mania following vascular lesions of the diencephalon

Reference	Symptomatology	Lesion site
[40]	Cyclic manic psychosis (case 2)	Right thalamus (hemorrhage)
[8]	Talkative, sexual suggestive remarks, euphoric, irritable, lack of judgement (case 1); euphoric, sleep reduction, aggressive outbursts, preoccupied with religion, mania followed by depressive episode (case 2)	Right thalamus (no lesion study)
[15]	Cheerful, sexually disinhibited (case 1); voracious eating, restlessness, aggressiveness, paranoid, childish, euphoric (case 2); voracious eating and drinking, irritability (case 3)	Bilateral paramedian thalamus (ischaemic)
[4]	Inappropriate cheerfulness, logorrhea, rapid switching of ideas, fantastic stories, lack of spontaneity, disinhibition	Right dorsomedian thalamus (ischaemic) plus old lesion in left caudate
[36]	Elated, delusions, hyperactivity, diminished sleep (case C); elated, pressured speech, flight of ideas, grandiose delusions, hypersexuality (case D)	Right thalamo-capsular infarct (case C), right thalamocapsular haemorrhage (case D)
[30]	Apathy and depression altering with periods of elation, sexual disinhibition, bulimia, flight of ideas, lack of sleep; cyclic manic psychosis	Bilateral paramedian thalamus (ischaemic)
[22]	Euphoric, grandiose delusions, distractable, pressured speech, inappropriate jokes, decreased need for sleep, talkative	Right thalamus (ischaemic)
[10]	Talkativeness, sexual insinuations, disinhibition, mood switches from sadness to irritability and verbal aggression	Right anterior thalamus (ischaemic)
[14]	Euphoria, 'childish' behaviour, (Ganser-like approximate answers), mischievous, puerile, lack of insight	Bilateral paramedian thalamus (ischaemic)
[41]	Recurrent hypomania, prosopafective agnosia	Right lateral thalamus (ischaemic)
[26]	Agitated, talkative, flirtatious, cheerful, fluctuating awareness of hemiplegia	Right thalamus (haemorrhage)

conclude that SN's mania emerged from a disruption of the right orbitofrontal loop at the diencephalic level. Whereas dorsolateral-prefrontal diaschisis has previously been observed in BPTI [24,33], this is, to our knowledge, the first case where a correspondence between a diencephalic lesion, mania and a perfusion deficit in the orbitofrontal region has been documented. Although it is clear that these findings from a single case will need further confirmation by future studies, we conclude from SN's case that lesions in the diencephalon may produce a distant pattern of hypometabolism in the right frontobasal area which is causally related to the origin of a maniform syndrome. The available lesion and perfusion data suggest that the basotemporal region, the thalamus and the caudate nucleus, all structures functionally connected to the orbitofrontal cortex, are part of a functional network which is involved in the regulation of mood. Lesions in this limbic and limbic-related network seem to play a role in the production of neurogenic mania [3,36,37]. In terms of the fronto-subcortical circuit framework, this network is largely identical with the so-called orbitofrontal loop [3,31].

In summary, SN's case exemplifies that several, distinctive behavioural impairments such as mania and a frontal dysexecutive syndrome may result from a diencephalic lesion. The presumed pathomechanism is a disconnection of the thalamus from subcortico-cortical networks which subserve behavioural functions. The disruption of thalamo-fronto-limbic circuits is associated with metabolic depression in target areas of the thalamus, which, in our case is located in two crucial areas of the frontal brain. Fronto-subcortical loops appear to play an important role in the regulation of mood, social conduct, and personality, in addition to their role in human cognition.

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