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Apathy, cognitive dysfunction and impaired social cognition in a patient with bilateral thalamic infarction

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We describe the case of a patient with bilateral thalamic lesions due to brain infarcts in the paramedian thalamic artery territories. The patient demonstrated symptoms of apathy (e.g., loss of initiative and interest in others, poor motivation, flattened affect). Neuropsychological assessment 3 and 5 years post-infarct revealed severe deficits in verbal and non-verbal immediate and delayed memory, attention, and executive functioning, with minimal improvement over time. Also, he demonstrated difficulties in social cognition (i.e., perception of facial expressions of others and of sarcasm). These findings are discussed and interpreted in light of current theories regarding the neurobiological substrate of apathy.

Keywords: Personality changes; Emotion perception; Theory of mind; Sarcasm; Dorsomedial thalamic lesions.

Thalamic infarctions sometimes result in complex neuropsychological deficits including impaired motivation and goal-oriented behavior, as well as cognitive, and, in some cases, affective symptoms, such as apathy (Bogousslavsky et al., 1991; Levy et al., 1998; Starkstein & Leentjens, 2008). Apathy as a neurobehavioral symptom has been described in detail in a number of studies and associated with variable lesion topographies. It has been proposed that bilateral lesions of the globus pallidus, the striatum, and the white matter of the frontal lobes are responsible for apathy symptoms (Laplane, Baulac, Widlöcher, & Dubois, 1984). Other researchers have shown that prefrontal damage alone is associated with apathy (Shamay-Tsoory, Tomer, & Aharon-Peretz, 2002; Shamay-Tsoory, Tomer, & Aharon-Peretz, 2005) and they ascribe

it particularly to ventromedial prefrontal cortex (vmPFC) dysfunction (Eslinger, 1998; Shamay-Tsoory, Tomer, Berger, & Aharon-Peretz, 2003). Accordingly, it has been suggested that interruption of the striatal-ventral pallidal-thalamic-frontomesial limbic loop may result in the loss of self-activation that characterizes patients with apathy (Bogousslavsky et al., 1991; Engelborghs, Marien, Pickut, Verstraeten, & De Deyn, 2000; Haber, Goeneweger, Grove, & Nauta, 1985; Jorge, Starkstein, & Robinson, 2010).

Patients with thalamic infarctions also tend to present with various patterns of cognitive impairment, including memory deficits and executive dysfunction (Bogousslavsky, Regli, & Assal, 1986; Engelborghs et al., 2000; Kumral, Evyapan, Balkir, & Kutluhan, 2001; Neau & Bogousslavsky, 1996;

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Perren, Clarke, & Bogousslavsky, 2005; Stuss, Guberman, Nelson, & Larochelle, 1988; Winocur, Oxbury, Roberts, Agnetti, & Davis, 1984). The cognitive symptomatology usually resembles temporal lobe anterograde amnesia, subsequent to mammillo-thalamic tract (MTT) disconnection (Mennemeier, Fennell, Valenstein, & Heilmanvan, 1992; van der Werf, Witter, Uylings, & Jolles, 2000; van der Werf et al., 2003). For instance, damage to the MTT causes diencephalic amnesia, a syndrome that involves defective long-term episodic memory, but intact short-term memory (van der Werf et al., 2003). However, damage to the dorsomedial (DM) or other midline and intralaminar nuclei impact executive functions (van der Werf et al., 2000, 2003). These symptoms are presumed to be due to inattention; several studies have shown that thalamic infarctions are associated with “prefrontal” behavior including reduced initiative, as well as executive dysfunction and inattention (reviewed in van der Werf et al., 2000).

Apart from apathy and cognitive symptoms, thalamic infarctions may impact social cognition as well. This term refers to the ability to understand the social cues in a situation, such as beliefs, intentions, and emotions of others (Shamay-Tsoory et al., 2005). Interpreting others’ emotional responses requires the activation of internal affective representations related to empathy, which are mediated by thalamic circuits bilaterally (Hooker, Verosky, Miyakawa, Knight, & D’Esposito, 2008).

One aspect of social cognition is Theory of Mind. It includes the ability to infer other people’s mental states and thoughts, a process known as mentalizing (Uchiyama et al., 2006). Sarcasm is based on this process. It communicates implicit criticism and disapproval towards the listener or the situation (Shamay-Tsoory et al., 2005). The perception of sarcasm requires the awareness of another person’s beliefs and evaluative judgments regarding someone else or a situation, taking into account the social context (Uchiyama et al., 2006). There is ample evidence supporting prefrontal mediation of mentalizing and sarcasm, in particular. For instance, Shamay-Tsoory and colleagues reported that lesions to the right ventromedial PFC are associated with impairment in interpreting sarcasm (Shamay et al., 2002; Shamay-Tsoory et al., 2005). In addition, fMRI studies suggest the existence of a neural circuit, including the anterior rostral medial frontal cortex, subserving sarcasm (Uchiyama et al., 2006, 2012). Therefore, it appears

that the medial PFC plays an important role in perceiving sarcasm and is interconnected with DM and ventral anterior (VA) thalamic nuclei (Haber & Calzavara, 2009).

Our objective in undertaking the present case study was to describe in detail the medical history, as well as the clinical course and neurocognitive condition of a patient with bilateral thalamic infarctions who demonstrated apathy and cognitive symptoms, as well as impairment in social cognition. There are a few studies describing apathetic patients with or without cognitive impairment after thalamic lesions (Bogousslavsky et al., 1991; Engelborghs et al., 2000; Kumral et al., 2001; Winocur et al., 1984), but, to our knowledge, none to date have investigated social cognition.

PATIENT CHARACTERISTICS

PL, a 40-year-old right-handed man, was admitted to an Intensive Care Unit in 2006 due to sudden onset of coma. His previous medical history was unremarkable and the patient was working as a high school physics teacher. On admission, PL was in a comatose state (GCS = 6) with no lateralizing neurological signs. A brain CT scan was normal, whereas an MRI scan revealed bilateral thalamic lesions located in the paramedian thalamic artery territories, including the DM nucleus (Figure 1). The patient was diagnosed with bithalamic infarcts and treated accordingly with antiplatelet drugs (Clopidogrel 75 mg qd). Within 4 days, the patient’s level of consciousness improved significantly and he was transferred to the neurological ward. Further investigations revealed the presence of a patent foramen ovale, probably predisposing the patient to the occurrence of stroke, which was treated with an endovascular approach. The patient was discharged from the hospital 2 weeks later, fully alert with no focal neurological signs. In the meantime, however, it became increasingly evident that the patient presented significant personality and behavioral changes as well as a persistent amnesic disorder.

A clinical interview revealed that, contrary to the previous active and compassionate individual he had been, PL had now turned into an indifferent man with flattened affect and little interest in himself or others. It is noteworthy that when he saw his baby daughter falling off a table he neither worried nor did he make an effort to prevent this

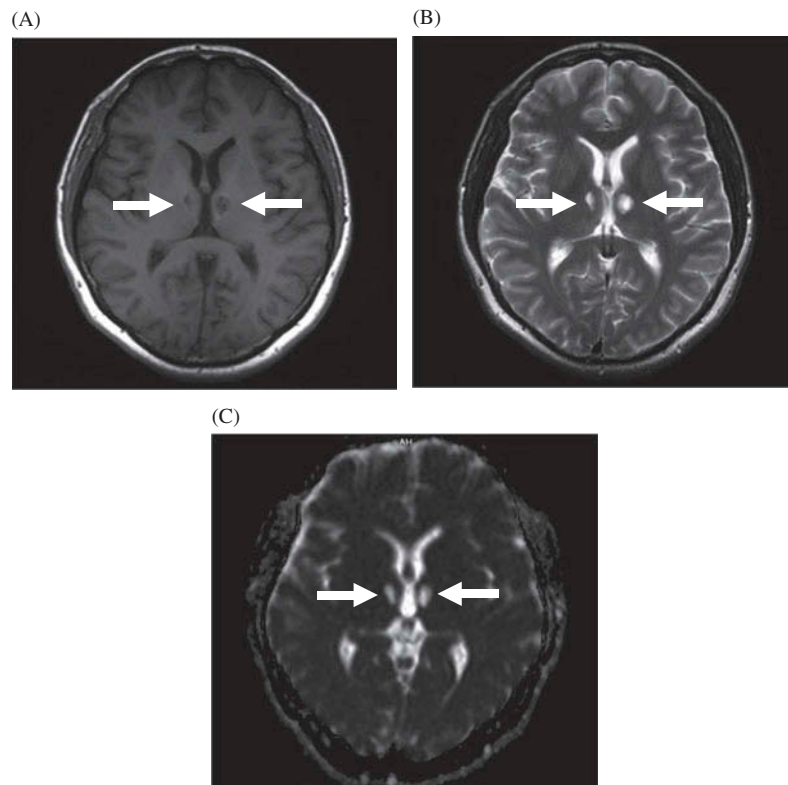


Figure 1. Axial brain MRI scans (T1-, T2-weighted images and ADC map) revealing paramedian bithalamic infarction at 5 years post-stroke: (A) TR = 500, TE = 7.7, (B) TR = 4000, TE = 97, (C) TR = 5700, TE = 139.

accident from happening. PL was able to continue his work as a high school teacher of physics despite his reduced level of functioning (his knowledge would presumably be stored in intact brain areas, e.g., the temporal cortex). Initially, his teaching hours were significantly curtailed and restricted to junior classes, whereas recently he quit teaching altogether and undertook a less demanding office position. Yet, he found no interest in his job or hobbies and he showed no concern about the future. Moreover, PL presented symptoms of anosognosia, demonstrating no awareness of his medical condition or his work-related functioning; his anosognosia persists to date. He was, therefore, particularly reluctant to seek appropriate help, but consented to receiving antidepressant and antiepileptic medication (Bupropion 300 mg qd and Donepezil 10 mg qd).

Based on the clinical observation of PL's apathy, we assessed this symptom formally for the first time 3 years post-stroke. Apathy occurring in such a clinical context often coexists with symptoms of depression. In fact, a recent exploration of Post-Stroke Depression (PSD) Hama, Yamashita, Yamawaki, and Kurisu (2011) yielded

two core syndromes, affective and apathetic PSD, each one associated with distinct neuroanatomical substrates. In order to evaluate both depressive and apathetic symptoms, we used the Lille Apathy Rating scale-LARS (Table 1). This instrument consists of 33 items falling into nine main domains of apathy giving, thus, a global measurement of all clinical manifestations of apathy including depressive symptoms. In addition, it provides a precise scoring system, making it possible not only to quantify important qualitative information, but also to differentiate between apathy and depression based on the patient's score. In a range of values from -36 to $+36$, scores between -26 and -17 are indicative of depression, scores up to -10 indicate the presence of moderate apathy, while values greater than -9 denote both severe apathy and depression (for a detailed description of the LARS see Sockeel et al., 2006). His initial score (Total LARS Score = 12) revealed the presence of severe apathy and depression. Follow-up assessment 2 years later revealed minimal improvement (Total LARS score = -10), demonstrating symptoms of moderate apathy (Sockeel et al., 2006).

TABLE 1

PL's performance 3 years (first assessment) and 5 years (follow-up) post-infarct, on general cognitive ability and behavioral measures

Test	First assessment		Follow-up	
	Raw score	Interpretation	Raw score	Interpretation
1. Mini Mental State Examination	21/30	Below cut-off	–	–
2. Lille Apathy Rating Scale	12	Severe deficit	–10	Moderate deficit
3. Rivermead Behavioral Memory Test	10/18	>–3.0 SD	7/18	>–5.0 SD

We conducted a neuropsychological assessment of the patient 3 years post-stroke to explore his cognitive deficits, as well as a follow-up evaluation 2 years later to determine any change in his condition.

During the first evaluation, we used the Mini Mental State Examination (MMSE) to assess global cognitive functioning. The patient's score (Total MMSE score = 21) was below the cut-off point (23/30) proposed in a Greek normative study (Fountoulakis, Tsolaki, Chantzi, & Kazis, 2000), suggesting some cognitive impairment. Accordingly, we conducted a more in-depth assessment to investigate his cognitive deficits in detail. We found that his performance on verbal, non-verbal, and episodic memory tests, as well as on executive functioning tests, deviated significantly from the mean performance of an age- and education-matched normative sample (Table 2).

Follow-up neuropsychological testing was more extensive than the initial evaluation and took place when PL's acute apathy symptoms had minimally improved. Compared to the previous evaluation, deficits in immediate and delayed verbal and non-verbal memory, as well as in episodic memory and executive functioning, still remained. In addition to these deficits, the second assessment also revealed impairment in attention, working memory and processing speed. Visuo-spatial perception and organization disturbances were documented as well. His performance ranged from 1.5 to 2 SDs under the mean control performance on all tests of the aforementioned cognitive abilities (Table 2); this is despite his average performance on a brief test of intellectual functioning.

Given PL's clinical profile, we wondered whether he would demonstrate difficulties in cognitive processes relevant to social interaction. To our knowledge, social cognition has not been investigated in the context of bithalamic infarction. Therefore, we explored two components of social cognition,

namely, the ability to perceive emotions in the facial expressions of others and Theory of Mind. More specifically, we examined his ability to recognize emotions in photographs of facial expressions with respect to a social context, as well as his ability to perceive sarcasm in written short scenarios (Table 2). This assessment took place only during the follow-up examination.

In order to assess emotion perception in various social contexts, we administered a test comprising 57 drawings, each one depicting an everyday scenario with one or more people, wherein the face of the protagonist was missing (Fantie's Cartoon Test; Fantie, 1989). On each item, a series of seven photographs depicting the basic emotional expressions (happiness, sadness, surprise, anger, fear, disgust, as well as a neutral expression) were presented at the bottom of the page. The patient was asked to select the facial expression among the photographs, which best matched what the protagonist (whose face was missing) must be feeling. Thus, he had to decode and interpret the social scenario in order to correctly indicate one of the seven emotional expressions that best fit the missing face. The stimuli were also divided into three conditions, according to the context: "nonsocial context" (depicting only one person), "social congruent context" (with more than one person, wherein the expression of the missing face agreed with that of the others), and "social non-congruent context" (wherein the expression of the missing face was different from those of the others in the scene). On less than half of the items (26/57), the patient chose as the correct response one that was also chosen by most healthy individuals in the normative sample. The same pattern emerged on each of the three conditions, wherein he responded according to the most popular choice on about half of the items with poorer performance on the non-social context condition relative to the other two conditions (non-social 37%,

TABLE 2

Neuropsychological performance of PL 3 years (first assessment) and 5 years (follow-up) post-infarct, as assessed with memory (1–3), working memory (4–5), attention (6–9), executive function (8–11), visuospatial perception (1, 11–12), emotion perception (13), and Theory of Mind (14) tests

Test	First assessment		Follow-up	
	Raw score	Interpretation	Raw score	Interpretation
1. Rey-Osterieth Complex Figure Test				
a. Copy	32/36	–2.0 SD	36/36	Average range
b. Immediate recall			6/36	>–2.0 SD
c. Delayed recall	13/36	–1.0 SD	4/36	>–2.0 SD
2. Word List Learning				
a. Learning (total over five trials)	–	–	23	>–3.5 SD
b. Immediate free recall	–	–	2	>–5.0 SD
c. Delayed free recall			1	>–5.0 SD
3. Hebb's Recurring Digits	–	–	0	No implicit learning
4. Digit Span				
a. Forward (span)	–	–	4	Low
b. Backward (span)	–	–	3	Low
5. Visual Patterns Test (span)	3	>–1.5 SD	6	Average range
6. Symbol Digits Modalities Test	–	–	37	Very low
7. Ruff's 2 & 7 Selective Attention Test				
a. Automatic Detection Speed	–	–	87	>–2.0 SD
b. Controlled Search Speed	–	–	77	>–2.0 SD
8. Trail Making Test				
a. Part A (seconds)	–	–	83	–2.0 SD
b. Part B (seconds)	–	–	115	–1.0 SD
9. Stroop Test				
a. Words	–	–	90	–0.5 SD
b. Colors	–	–	56	–1.0 SD
c. Color-words	–	–	26	–2.0 SD
10. Verbal Fluency				
a. Semantic	33	–2.0 SD	39	–1.5 SD
b. Phonological	11	–2.0 SD	28	–1.0 SD
11. Clock Drawing Test				
A (free draw)	–	–	14	–1.0 SD
B (pre-drawn circle)	–	–	12	–2.0 SD
C (pre-drawn, set time only)	–	–	11	Average range
D (pre-drawn, set time only)	–	–	11	Average range
E (pre-drawn, set time only)	–	–	11	Average range
12. Hooper Visual Organization Test	–	–	20	–1.5 SD
13. Fantie Cartoon Test – Total score	–	–	51%	>–1.0 SD
a. Non-social context	–	–	37%	>–2.5 SD
b. Social congruent context	–	–	56%	>–2.0 SD
c. Social noncongruent context	–	–	45%	>–1.5 SD
14. Sarcasm & Metaphor Comprehension				
a. Sarcasm (number correct)	–	–	0/6	Very low
b. Metaphor (number correct)	–	–	5/6	Average range

social congruent 56% and social noncongruent 45% [a typical pattern among healthy individuals is better performance on the social congruent than the other two conditions, which do not differ from each other]; Kosmidis, Fantie, Giannakou, & Bozikas, under review). Thus, PL had difficulty recognizing other people's emotional states, particularly when there were no social cues to aid him in interpreting the context; accordingly, he benefited from the

addition of contextual cues in the scenario, particularly if they were congruent with those of the context.

In order to investigate PL's ability to perceive sarcasm, we gave him the Sarcasm & Metaphor Comprehension Test (Bozikas et al., 2011; Giannakou, Kosmidis, Bozikas, Garyfallos, & Fokas, 2007; Kosmidis, Giannakou, Garyfallos, Kiosseoglou, & Bozikas, 2011). This task

comprised 24 short stories depicting one or two characters involved in a dialog (with adequate internal reliability: Cronbach's $\alpha = .63$). The patient was asked to judge if the final utterance in each scenario was suitable to the story and to explain what the person meant by this statement. The final utterance of these stories was sarcastic, metaphorical, literal, or a *non sequitor*. PL's ability to perceive sarcasm was impaired, despite his intact perception of metaphor.

In sum, neuropsychological testing revealed that no noteworthy improvement had taken place during the 2-year interval between the first and the second neuropsychological assessment. Most of PL's cognitive abilities had only slightly improved since the first assessment, but they still remained below normative performance of a healthy sample and were accompanied by impaired social cognition, related to emotion and sarcasm perception.

DISCUSSION

In the present case report, we described the long-term neuropsychological outcome of a patient who sustained bilateral thalamic lesions as a result of brain infarcts in the paramedian thalamic artery territories. Based on his clinical and neurocognitive profile, we suggest that circumscribed lesions in this thalamic subregion may result in persistent neuropsychological dysfunction and changes in personality including symptoms of apathy, cognitive deficits, and impaired social cognition. Therefore, the present case study may help elucidate the functions of this brain region.

In our patient, bithalamic infarcts involved the DM nucleus, an area that is strategically located within the striatal-ventral pallidal-thalamic-frontomesial limbic loop. The DM is responsible for emotional and motivational responses to sensory stimuli with afferent and efferent fibers to the prefrontal and orbital cortices as well as afferent fibers from the olfactory cortex and parts of the limbic system, and efferent fibers to the hypothalamus (van der Werf et al., 2000). It is conceivable, therefore, that defective flow of information within this loop may provide a plausible explanation for our patient's apathy symptoms.

To account for PL's cognitive deficits, we must consider the fact that the thalamus comprises a number of distinct nuclei, each contributing to different aspects of cognition. Findings regarding the role of the DM in memory are at present

contradictory. One line of research has suggested that no memory impairment results from DM lesions (van der Werf et al., 2000, 2003). Other researchers, however, have reported memory deficits after damage to the DM thalamic nucleus (Aggleton & Brown, 1999; Kumral et al., 2001). Consequently, we suggest that our patient's memory impairment may, in part, be accounted for by the damage to the DM. Moreover, damage to this nucleus has previously been shown to be connected with executive dysfunction and inattention (reviewed in van der Werf et al., 2000), thus accounting for PL's deficits in executive functioning. The same researchers have also suggested that DM damage is related to reduced initiative and poor motivation. Thus, we may alternatively propose that our patient's poor cognitive performance is generally attributed to poor motivation. We cannot rule out the latter explanation with respect to our patient, as the DM nucleus was predominantly involved. In addition, we should emphasize that apathy, as in the case of PL, may exacerbate cognitive dysfunction in such patients (Pluck & Brown, 2002).

Our patient also demonstrated an impaired ability to infer one's emotional state from pictures, but was aided by the addition of socially relevant contextual cues. At least one study (Hooker et al., 2008) has suggested the bilateral thalamic mediation of emotion recognition. Thus, PL's damage to both thalami may explain his difficulty in perceiving emotional expressions. In line with this explanation is the facial feedback hypothesis, according to which apathy secondary to thalamic infarcts leads to impaired perception and expression of one's own emotional states (Alam, Barrett, Hodapp, & Arndt, 2008). Alternatively, PL's performance may be due to disrupted transfer of information from the medial and the ventromedial PFC to the thalamus, as these areas are thought to mediate empathy for emotions (reviewed in Decety, 2011).

However, PL's impaired emotion perception may reflect, to some extent, the mode of stimulus presentation. Our test consisted of static pictures, which presumably activate the medial PFC (Kessler et al., 2011; Murphy, Nimmo-Smith, & Lawrence, 2003). This region is part of the affected neural circuit in the present case. In contrast, dynamic pictures activate additional areas, such as the superior temporal gyrus, the fusiform gyrus and the V5 visual area, which in PL's case were intact (Kessler et al., 2011). Therefore, we cannot rule out the possibility that he

may have shown better performance had we used a different mode of stimulus presentation.

Additionally, our patient showed a selective deficit in perceiving sarcasm, but not metaphor, literal or nonsequitor statements. One line of research has suggested that the medial PFC (Shamay et al., 2002; Shamay-Tsoory et al., 2005; Uchiyama et al., 2006, 2012) and its interconnection to the DM (Haber & Calzavara, 2009) may play an important role in perceiving sarcasm. Given the aforementioned finding and the fact that our patient's lesion is in the DM area, we propose that a disconnection of the pathway conveying information from the medial PFC to the thalamus may account for his specific deficit. While the interpretation of metaphors has been linked to the medial PFC, anterior caudate and thalamus (Uchiyama et al., 2012), it was intact in PL. We attribute the above finding to the fact that metaphor is based on language pragmatics, not on mentalizing ability (Giora, 2007). Therefore, it came as no surprise that the patient's interpretation of metaphors was intact.

In conclusion, the present case suggests that paramedian bithalamic infarction may result in persistent cognitive, behavioral and personality impairment. Based on our patient's profile and previous research, we proposed that his symptoms of apathy and his difficulties in perceiving emotions and sarcasm may be attributed to a possible disruption of information flow from the medial PFC to the thalamus. With respect to his cognitive deficits, we suggest that they are due to DM damage, which results in impaired memory and executive functioning and poor motivation.

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