

Neuropsychological delineation

Social cognition in developmental and adult-onset amnesia: a multiple case-control study

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Summary

Memory disorders due to medial temporal lobe lesions are well documented, but studies on social cognition in patients with amnesia are rare. This study examined social cognitive functioning in three adult amnesic patients. We report on the neurocognitive and social cognitive profiles of two patients with developmental amnesia and a patient with adult-onset amnesia, all due to hypoxic events. All cases were compared to their individual IQ-matched control groups. Both cases with developmental amnesia showed notable deficits in tasks assessing emotion recognition and theory of mind. In comparison, the patient with adult-onset amnesia showed less severe and more circumscribed impairment in social cognition. Our findings suggest that social cognition is at serious risk in patients with amnesia. The deficits may be more pronounced in developmental amnesia with hippocampal lesions than in adult-onset amnesia. Our findings highlight the importance of examining social cognitive functions in patients with memory impairment to assess the need for therapeutic interventions and counselling of patients and their relatives.

Introduction

Successful navigation through our complex social environment requires a variety of cognitive and affective processes such as recognising, recalling and manipulating the information we have about other people's mental states, thoughts and intentions. The ability to contextualise such social processes and to retrieve socially relevant information from past experiences contributes to successful social interactions. Very recent results suggest that the hippocampus plays an important role in supporting social cognitive functioning by mapping and storing social information [1–7]. Furthermore, studies in healthy adults and in patients with lesions have provided emerging evidence for the role of (episodic) memory in interpersonal emotions such as empathy [8–10] and behaviour [11, 12]. Social cognition encompasses all of the affective and cognitive functions that are needed to recognise, un-

derstand and interpret the emotions, intentions and behaviours of others, as well as to adapt one's own behaviour to them [13]. Deficits in social cognition can lead to serious conflicts in social interactions and consequently reduce quality of life in neurological and psychiatric patients [14]. Therefore, the assessment of social cognition in neurological patients is increasingly gaining attention.

Recently, the DSM-5 has included social cognition as one of the six core functional domains in the assessment of neurocognitive disorders [15]. Social cognitive functions are typically tested in two core components: emotion recognition (ER), the ability to recognise and label emotions from facial and verbal expressions [16], and theory of mind (ToM), the ability to represent and infer one's own and others' mental states such as beliefs, desires, feelings and intentions [17]. A substantial part of these social cognitive functions relies on the functional integrity of the temporal lobes [18].

Bilateral damage to the medial temporal lobe is typically associated with severe amnesia [19–21]. Similarly, unilateral lesions are often linked to memory impairment. More recently, studies have also found deficits in social cognition to be a common feature in patients with various temporal lobe pathologies: in unilateral temporal lobe epilepsy [22–25], in Urbach-Wiethe syndrome [26, 27] and in Klüver-Bucy syndrome [28]. It is therefore surprising that studies on social cognitive functioning in amnesic patients are rare.

Developmental amnesia is a rare neurological condition that is caused by an early bilateral hippocampal injury and often associated with refractory epilepsy. The majority of developmental amnesia patients suffered their bilateral hippocampal pathology during delivery owing to a hypoxic event. Hypoxia is one of the most common causes of sustained brain injury in infants and young children [29, 30]. As a result of early selective bilateral damage to the hippocampus, the clinical presentation of developmental amnesia includes



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profound amnesia for life events (episodic memory) [30, 31]. Despite these severe deficits in episodic memory, patients with developmental amnesia may have an almost average trajectory for the acquisition of a wide range of cognitive functions including intelligence, language abilities, executive functions, attention and semantic memory [32, 33].

To date, the question whether these amnesic patients have difficulties in social cognitive functions has not been systematically investigated, neither in case reports [34–37] nor in rare group studies [38, 39]. There is only one brief report mentioning social and emotional difficulties in two patients with developmental amnesia [36] and three case reports that examined social cognitive functions in patients with developmental amnesia [33, 40, 41].

Although our preceding single case study on patient BM implies reduced emotion recognition and ToM functions in amnesia, overall evidence is mixed and may be confounded by differences in general cognitive performance [40]. In line with our findings, the case report of Staniloiu et al. [33] also described difficulties in emotional processing when using tests that evaluated the recognition of emotions. However, differing findings exist regarding ToM function. Rabin et al. [41] found preserved ToM performance in an adult woman with developmental amnesia, as demonstrated in tests that examined her ability to recognise the mental state of others in tasks using texts, photographs of the eye region or visual cues. Similarly, the results of Staniloiu et al. [33] point to a largely preserved ToM ability or only mild impairment in several tasks testing the perception of mental states in photographs, short stories and video-based tasks. However, impairments were evident in tasks that assessed complex ToM functions such as social and moral judgment. There are several factors that may account for the observed differences, such as the use of different assessment tools and sex differences, but in particular different general cognitive performance levels may also account for these observed differences. Furthermore, our case study also left open whether BM's slower processing speed could be responsible for his performance in the social cognitive tests.

Apart from these few reports on developmental amnesia, some reports have studied social cognition in adult-onset amnesic patients who sustained bilateral hippocampal damage, commonly due to hypoxia in adulthood. These patients showed apparently unimpaired fear [42] and eyeblink conditioning [43] or were emotionally affected after a film [44], even though their explicit memory of the conditioning or the film is lost. Moreover, the findings of a patient with adult-on-

set hippocampal amnesia suggest that theory of mind processes appear to be preserved compared with controls [45]. By contrast, another study suggested that the empathetic ability to share and understand the feelings of others is reduced in patients with adult-onset hippocampal amnesia compared with controls [46].

However, the social cognitive functions in patients with adult-onset hippocampal amnesia are influenced by their preserved ability to recall personal and public facts learned before they suffered brain damage. It remains unclear whether these findings of adult-onset amnesic patients are comparable to patients with developmental amnesia, whose brain lesion usually occurs after a hypoxic event within the first year of life. On the one hand, neuronal reorganisation and plasticity shape the cognitive profile of patients with developmental amnesia. On the other hand, patients with adult-onset amnesia have a normal developmental history with regard to the acquisition of social skills, but there are clear age-related limitations in terms of compensatory neuronal reorganisation and plasticity after the brain injury.

Given the questions that remained unanswered from our previous study, our aim was to investigate whether our reported findings of deficits in social cognition in our case (BM) could be explained by his general intellectual disability and his lower processing speed. Therefore, we explored the neurocognitive profile of another epilepsy patient with developmental amnesia (NR), with an average cognitive performance level and processing speed. Furthermore, we contrasted these two cases of developmental amnesia with a patient (MJ) with adult-onset amnesia. All three cases were each compared to an IQ-matched control sample, using a case-control methodology [47]. We assumed that BM's impairments in tasks assessing social cognition emerged as a result of early bilateral mesial temporal lesion of the hippocampus. Therefore, we expected that NR would show similar abnormalities in our experimental tasks. Regarding adult-onset amnesia, it is not yet clear whether these patients have a similar or different profile compared to patients with developmental amnesia.

Material and methods

Case reports

We report here two cases with developmental amnesia, BM and NR, and one case with adult-onset amnesia, MJ. The selection criterion was that all cases have shown a broadly similar pattern of memory dysfunction and suffered a hypoxic episode that occurred either at

Table 1: Demographic and clinical characteristics of the three cases.

Variable/category	Clinical cases		
	BM	NR	MJ
Age	21 (T1) 23 (T2)	34	59
Years of education	11	5	13
Gender	Male	Male	Male
Handedness	Left	Right	Right
Medication	2 AEDs	2 AEDs	0 AEDs
Performance IQ	68	89	114

T1: session 1; T2: session 2; AEDs: anti-epileptic drugs.
BM was tested at two sessions.

birth, in the case of developmental amnesia, or in adulthood, in the case of adult amnesia. BM and NR were referred for neuropsychological investigation as part of a pre-surgical epilepsy evaluation due to the occurrence of repeated seizures and drug resistance. MJ was examined as part of a neuropsychological follow-up examination. An overview of the characteristics of all three cases is presented in table 1.

Case BM (see also [40]), a non-identical twin, was born after emergency caesarean section due to a nuchal cord, which resulted in a hypoxic event. Subsequently, BM was reanimated for more than 15 minutes. His development was mildly delayed compared with his older healthy twin brother. He first walked around the age of 18 months, could say sentences of three or four words by the age of 3, and received physical therapy from the age of 2.5 years because of muscle coordination problems. BM completed 6 years of primary school after repeating the first year. After primary school, BM attended three years of secondary school in a special class with fewer students. He completed a 3-year vocational training as a carpenter and has been working in the same sheltered employment setting ever since. BM is not currently involved in a romantic relationship and appears to be socially withdrawn. According to his mother, he has never really expressed any interest in a platonic or romantic relationship. BM was 11 years old when he started having complex focal and secondarily generalised seizures. As a result of his refractory epilepsy, he was considered for pre-surgical epilepsy evaluation when he was 21 years old. At that time, a neuropsychological assessment was performed as part of the evaluation and revealed pronounced verbal and non-verbal memory impairments and a reduced overall level of cognitive ability (see the results section for details). The anticonvulsant medication at that time was levetiracetam 1750 mg/d and pregabalin 500 mg/d. A follow-up neuropsychological assessment was administered two years later for relia-

bility purposes. At this second session, his medication was brivaracetam 175 mg/d, perampanel 8 mg/d, and 15 vitamin D drops as well as 25 cannabidiol drops. Seizure frequency was about five to nine seizures per month at both testing sessions. Epilepsy surgery was not performed as ictal EEG recordings demonstrated a bilateral temporal seizure origin.

Case NR was delivered following a normal pregnancy. However, cyanosis was present after birth, which was presumably the result of hypoxia and presumably contributed to the bilateral hippocampal lesion. Normal development was described until the age of 4, after which pronounced behavioural problems were reported. NR had to change schools many times because of school refusal. He completed 5 years of primary education in a specialist school and then was taught by a private teacher for a while. He started vocational training as a carpenter, but he dropped out of his training owing to his behaviour problems. Since then, he has received an invalidity pension. According to his father, NR is confronted with great difficulties in everyday life as a result of his severe memory impairment, which results in impatience and rigid behaviour. NR is neither married nor involved in a romantic relationship.

From the age of 3 years, NR developed simple and complex focal seizures and was diagnosed with temporal lobe epilepsy. According to the family history, NR's aunt was also diagnosed with epilepsy and his mother suffered from migraine. Because freedom from seizures had not been achieved with medication, the patient was considered for epilepsy surgery and neuropsychological testing was performed as part of the pre-surgical evaluation at the age of 34. The neuropsychological testing revealed an average cognitive performance level for non-verbal tasks and severe verbal and non-verbal memory deficits (see also the results section for details). At the time of the neuropsychological assessment, the anticonvulsant medication was oxcarbazepine 2100 mg/d and clobazam 5 mg/d. Since ictal EEG suggested seizure onset in both hippocampi, epilepsy surgery was not indicated, and drug therapy was continued.

Case MJ was delivered following a normal pregnancy, but blood transfusions were necessary because of rhesus incompatibility. Afterwards, he had a normal early childhood development. He completed 6 years of primary school but repeated one year at his request because he was a difficult pupil, according to his statement. During grades 3 and 4, he received remedial support for dyslexia. After primary school, MJ attended three years of secondary school and completed a 4-year apprenticeship as a geometrician. He was subsequently self-employed and a lecturer at a technical col-

lege. He has two adult children from his first marriage. He recently retired early and currently lives together with his second wife and her daughter, who attends secondary school.

At the age of 41, MJ had ventricular fibrillation resulting in cardiac arrest. He had to be electromechanically reanimated for 20 minutes and received an implantable cardioverter defibrillator afterwards. After the event, initial neurological deficits with extensor spasms and recurrent myoclonia occurred, which were followed by motor recovery. MJ subsequently spent a considerable amount of time in a neurorehabilitation clinic and received regular occupational therapy including cognitive training, but he has complained of memory difficulties ever since. A neuropsychological examination showed an isolated amnesic syndrome that is compatible with a bilateral lesion of the hippocampus typically occurring after cerebral hypoxia.

About 5 weeks after the event, a computed tomography (CT) scan did not reveal initial post-hypoxic brain lesions. Magnetic resonance imaging (MRI) was contraindicated in this patient because of the implanted cardioverter defibrillator. However, the prolonged resuscitation, the initial neurological deficits as well as the residual amnesic syndrome strongly suggest severe hypoxic encephalopathy following cardiac arrest [48]. Epileptic seizures were unknown, and he had never experienced or been told of any disturbances of consciousness, déjà-vu experiences, sudden emotional symptoms, hallucinations, repetitive movements / fidgeting, or staring. He was able to continue working part-time in his profession as a geometrician. At that time, he was in his first marriage and divorced 4 years after the event. According to his statement, he had noticed a change in the way he dealt with others after the cardiac arrest. His emotional sensitivity had changed, and he was more emotionally numb than before. This feeling was also in line with his second wife's feedback. He was unable to determine whether the described problems were a contributory cause of his divorce from his first marriage because there were already problems before the cardiac arrest. Follow-up neuropsychological testing was performed at the Swiss Epilepsy Centre when MJ was 59 years old. The testing revealed, in line with the previous neuropsychological test results, an average cognitive performance level and a severe isolated memory deficit (see the results section for details). At the time of the neuropsychological testing, the medication was Meto Zerok (metoprolol) 50 mg/d for the treatment of hypertension and tamsulosin 0.4 mg/d for the treatment of symptoms of benign prostatic hyperplasia.

Control group

For BM and NR, IQ-matched epilepsy patients were included as a reference group to control for the general effects of epilepsy, its increased risk for deficits in social cognition and its treatment with antiepileptic drugs. The first control sample was matched to BM's performance IQ and included six patients with temporal lobe epilepsy. The median performance IQ score of BM's control sample was 73 and ranged from 68 to 78. The second control sample was matched to NR's performance IQ and comprised 17 control patients with temporal lobe epilepsy. The performance IQ scores ranged from 74 to 104 (median 93). All control patients had unilateral temporal seizure onset and a unilateral lesion in the mesial temporal lobe that was located in either the left or right hemisphere due to a structural lesion or surgical resection with no additional structural cerebral pathology. Lesions were confirmed by T1-

Table 2: Demographic characteristics of the control groups.

Variable/category	Control group		
	BM	NR	MJ
N	6	16	46
Age (years)			
Mean	39	37.1	39.8
Standard deviation	11.1	14.3	16.0
Median	39	34	36.5
Range	22–52	2065	1977
Years of education			
Mean	10	11.1	14.5
Standard deviation	2.4	1.7	2.4
Median	10	12	14
Range	713	713	1120
Gender, n (%)			
Male	2 (33.3)	7 (43.8)	20 (43.5)
Female	4 (66.7)	9 (56.2)	26 (56.5)
Epilepsy duration (years)			
Mean	26.2	20.4	n.a.
Standard deviation	6.4	14.3	n.a.
Median	21	13.5	n.a.
Range	751	651	n.a.
Medication (n)			
Mean	1.7	1.9	n.a.
Standard deviation	0.5	1.2	n.a.
Median	2	2	n.a.
Range	1–2	04	n.a.
Type of lesion			
Hippocampal sclerosis	3	5	n.a.
Temporal lobe resection	3	11	n.a.
Lesion side			
Left	4	10	n.a.
Right	2	6	n.a.

n.a.: not applicable.

and T2-weighted magnetic resonance images and seizure onset by interictal and ictal video-EEG monitoring with either scalp or intracranial electrodes. For MJ, IQ-matched healthy controls were included as a reference group. The control sample comprised 46 controls. The median performance IQ score was 110.7 and ranged from 100 to 125. Data for the control groups was provided by the Swiss Epilepsy Centre. All controls provided written informed consent. An overview of the characteristics of all control groups is presented in table 2.

Measures

The neurocognitive profiles of all three cases were obtained from a wide range of neuropsychological tests. To assess general cognitive ability, the following measures were used: the subtests picture completion, block design and coding of the German version of the abbreviated Wechsler Adult Intelligence Scale (WAIS) [49]. Performance IQ was calculated on the basis of the extrapolated sum of scaled scores on the subtests and converted using the conversion table of the WAIS.

For the evaluation of verbal and non-verbal antero-grade episodic memory, we used the following tests:

- Rey Auditory Verbal learning Test (RAVLT) [49]. The RAVLT assesses verbal memory span, new learning of 15 words, delayed recall, and recognition memory for verbal material.
- The subtest Logical Memory of the Wechsler Memory Scale-Revised [50]. The subtest Logical Memory I and II assess the ability to recall information immediately from orally presented stories and after a 30-min delay.
- Rey-Osterrieth complex figure test (ROCFT) [51]. The ROCFT involves the copy of a complex figure followed by a delayed recall after 30 min; it investigates visuospatial constructional functions, visuo-graphic memory and some aspects of planning and executive function.
- Rey Visual Design Learning Test (RVDLT) [52]. The RVDLT is constructed analogous to the RAVLT. It assesses visual memory span, new learning of 15 geometric figures, delayed recall, and recognition memory for non-verbal materials.

To evaluate attention and executive functions, the following tests were administered:

- The subtest Alertness of the Test Battery for the Assessment of Attention (TAP) [53]. The Alertness subtest provide a measure of the simple reaction time in response to a visual stimulus and assesses phasic and tonic alertness.
- Trail Making Tests A and B [49]; The TMT provides information on speed of processing and mental flexibility; TMT quotient was calculated as the quotient between the time score for the TMT B and TMT A conditions.
- Stroop Test [49]; An adaptation of the colour-naming Stroop paradigm to assess inhibitory control; Stroop quotient was calculated as the quotient between the time score for the incongruent (part 3) and colour (part 1) conditions.

To assess social cognitive processes, the newly developed test battery “Networks of Emotional Processing” (NEmo) was administered, which is a comprehensive tool to evaluate aspects of social cognition, including the two subdomains emotion recognition (ER) and theory of mind (ToM) (for more details, see [54])

To assess emotion recognition, the following four tasks from the NEmo test battery were administered:

- Static facial ER task: to assess emotion recognition of static facial expressions with direct and averted gaze direction; Participants choose an emotion from a list of the six basic emotions (sadness, fear, anger, disgust, surprise, happiness) and neutral.
- Dynamic facial ER task: to estimate the recognition of emotions in dynamic facial expressions; Participants choose the corresponding emotion out of a list of six basic emotions as quickly as possible after each brief video presentation.
- Simultaneous facial ER task: to evaluate the recognition of dynamic emotional expressions of two faces presented at the same time; Participants decide whether the two dynamic facial expressions display the same or different emotions.
- Prosodic and facial ER task: to assess multimodal emotion recognition of simultaneously presented static facial and prosodic expressions; Participants decide whether the emotions in the visual and auditory modality match or differ from each other.

To assess theory of mind, we used the following three tests from the NEmo test battery:

- Recognition of irony task: a test of ToM function that assesses the ability to detect irony in short stories based on prosodic information; Participants listen to short stories and decide whether the utter-

ance at the end of each short story is ironic, empathetic/friendly or neutral.

- Faux-pas test (FPT) [17]: to evaluate affective as well as cognitive ToM ability; the shortened German adaptation was used which consists of five written short stories containing a faux-pas where someone unintentionally says something that would hurt or upset another individual; Participants are asked questions to determine whether or not they recognised the faux-pas and whether they are able to identify the feelings of one of the characters in the story.
- Movie for the Assessment of Social Cognition (MASC) [55]: a short movie of 15 minutes with multiple choice questions referring to the actors' mental states such as thoughts, intentions, and feelings; The MASC provides one correct score for accurate ToM and three error scores for excessive, reduced, and absence of ToM.

To quantify the hippocampal atrophy, an automated magnetic resonance imaging postprocessing technique, atlas-based volumetry (ABV), was used, and the results were corrected for intracranial volume (i.e. standardised to the approximate average intracranial volume of 1400 mL in adults) and transformed to Z-scores. See Huppertz et al. [56] for more details on this procedure.

Data analysis

To indirectly contrast all cases that exhibited different cognitive performance, the behavioural data of each case were compared with an IQ-matched control group. We used a modified t-test to account for the modest size of the control sample [47, 57]. This method avoids the inflation of type I errors and provides a more rigorous basis for defining behavioural deficits in single patients compared with other standard methods (e.g., comparison of Z-scores). The modified t-test is available as open-source software from the website: <https://homepages.abdn.ac.uk/j.crawford/pages/dept/SingleCaseMethodsComputerPrograms.HTM#conflims>. The test used in the current study was Singlims_ES.exe. All results are one-tailed with a significance threshold of $p < 0.05$.

Results

Imaging findings

As magnetic resonance imaging (MRI) is contraindicated in patients with implanted cardiac devices, there are no imaging findings for MJ. However, a bilateral le-

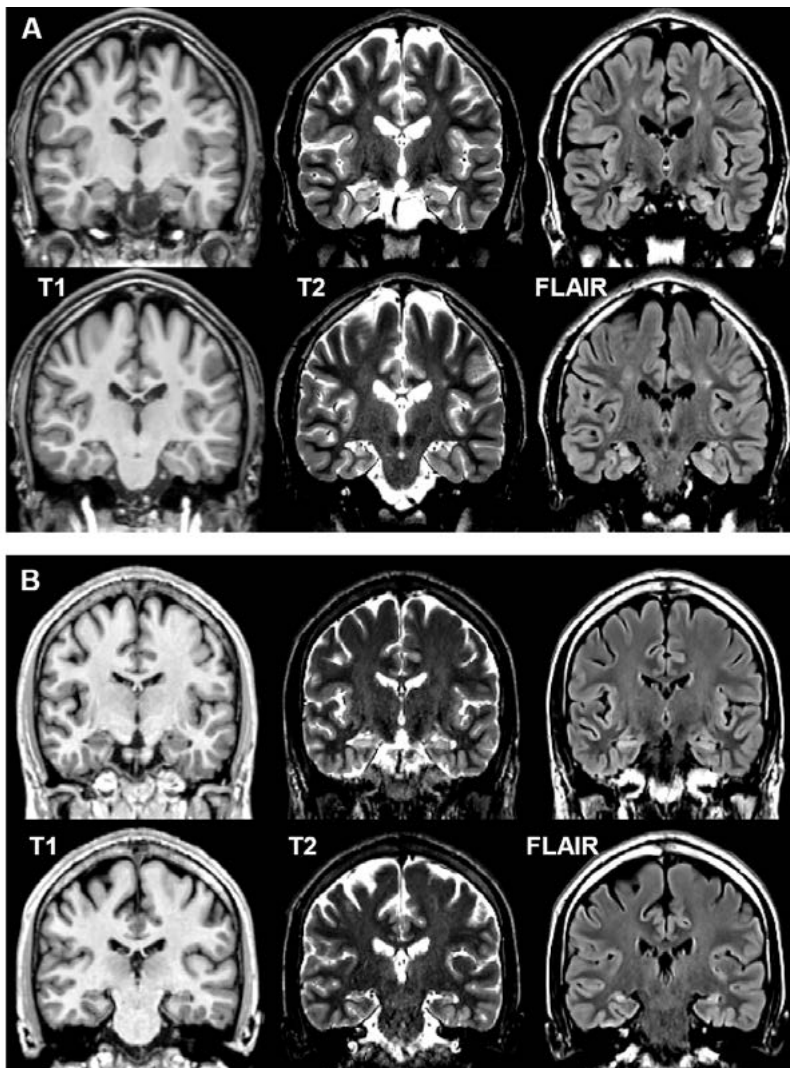


Figure 1: Coronal slices of T1-weighted, T2-weighted and FLAIR images through head (upper row) and body (lower row) of hippocampus showing bilateral volume loss and T2- and FLAIR-hyperintensity in patients BM (A) and NR (B). The findings are compatible with bilateral hippocampal sclerosis. The left side of the MR images is the right side of the patient (i.e., radiological orientation).

sion of the hippocampus after cerebral hypoxia is suspected, given the prolonged reanimation and the amnesic syndrome [48]. Therefore, the MRI results of BM and NR only are reported below.

Visual inspection of the MRI revealed bilateral hippocampal volume reduction and loss of internal structure in both cases with developmental amnesia. Moreover, an increased signal intensity of both hippocampi was visible in both patients on T2 and FLAIR sequences. Volumetric data analysis of patient BM revealed pronounced hippocampal volume reduction, more for the right (z-score = -1.8) than for the left hippocampus (z-score = -0.5). Similarly, both hippocampus volumes of patient NR were clearly below average, with z-scores of -1.7 and -1.1 for the right and left side, respectively.

The findings are compatible with bilateral mesial temporal lobe sclerosis, which – according to the hyperintensity in T2 and FLAIR images – is more clear on the right than on the left side in both cases. Apart from this, there was no evidence of any other potentially epileptogenic lesion or relevant cerebral pathology in the rest of the brain on visual inspection and morphometric MRI analysis. The T1-weighted, T2-weighted and FLAIR images of both cases are depicted in figure 1.

Neuropsychological assessment

This study set out to understand the neurocognitive and social cognitive profile of two cases with developmental amnesia, BM and NR, and compare them with a case with adult-onset amnesia, MJ. All individuals were cooperative, friendly and motivated during the neuropsychological assessment. The results of each case were compared with their IQ-matched control group.

Memory performance

With respect to anterograde memory, a variety of tests were used to confirm the amnesic syndrome. Across all three cases, the neuropsychological testing revealed a clear deficit in comparison with their control groups in all tests used to assess delayed recall in verbal and non-verbal memory (RAVLT, Logical Memory Subtest of the WMS-R, RVDLT). The only exception was the delayed recall of the Rey-Osterrieth figure, in which all cases performed within the range of their control group. In the immediate recall of two stories on the WMS-R subtest Logical Memory, the performance of all cases was comparable to their control group. Only in the immediate recall of a list of words on the RAVLT, BM and MJ performed below the level of their control group. In terms of learning, the results revealed that BM's performance in verbal learning fell significantly below his control group on the RAVLT, whereas NR and MJ had a pronounced deficit in learning non-verbal material assessed with the RVDLT as compared with their control groups. Results of all tests assessing memory function and the estimated effect sizes of all t-tests are depicted in table 3.

Cognitive (non-social) performance

Neurocognitive tests assessing general cognitive level, attention and executive function were used to account for factors that might explain possible deficits in social cognition. In terms of general cognitive level, BM's performance IQ with a score of 65 and a 95% confidence interval of 60 to 74 was below average on the Wechsler Adult Intelligence Scale and fell within the range of general intellectual disability. Even though there was no significant difference between BM and his control

Table 3: Performance on anterograde memory tests.

	Case BM	Case NR	Case MJ	Estimated effect size (z _{cc})		
				BM compared with IQ-matched control group (n = 6)	NR compared with IQ-matched control group (n = 16)	MJ compared with the normative data*
<i>Verbal memory</i>						
RAVLT Total learning (raw score)	32	35	36	-3.4	-1.3	-1.4 ^a
RAVLT Immediate recall (raw score)	3	6	2	-2.6	-0.8	-2.5^a
RAVLT Delayed recall (raw score)	0	0	2	-3.3	-2.4	-2.2^a
WMS-R LM Immediate recall (raw score)	12	9	17	-1.2	-1.4	-1.5 ^b
WMS-R LM Delayed recall (raw score)	0	0	3	-3.1	-1.9	-2.8^b
<i>Non-verbal memory</i>						
RVDLT Total learning (raw score)	12	11	15	-1.3	-1.8	-2.8^c
RVDLT Delayed recall (raw score)	1	2	2	-2.2	-2.0	-6.6^c
Rey-Osterrieth figure Delayed recall (raw score)	1	10	15	-1.5	-0.8	0.0 ^d

n.a.: not administered; RAVLT: Rey Auditory Verbal Learning Test; RVDLT: Rey Visual Design Learning Test; WMS-R LM: Wechsler Memory Scale-Revised Logical Memory. A significant difference (1-tailed, $p < 0.05$) is indicated in bold. * As the tests on memory were not performed in MJ's healthy control group, we referred to the corresponding norm data of the tests. ^a Reference group (n = 32) from the compendium of Stauss et al. (2006). ^b Reference group (n = 30) from the manual Härting et al. (2000). ^c Reference group (n = 10) from the compendium Spreen & Strauss (1991). ^d Reference group (n = 21) from the compendium of Stauss et al. (2006).

group on the individual subtests, BM's performance IQ fell below that of the control group. NR's performance IQ, with a score of 89, was in the lower average range. There was no significant difference between NR and his control group. MJ's performance IQ of 114 also fell within the average range on the Wechsler Adult Intelligence Scale. There was no significant difference between MJ and his control group. The results of the t-tests are depicted in table 4.

In terms of executive and attentional functions, BM's performance did not differ from his control group in the TAP Alertness and TMT test, but his speed was significantly slower than the controls in all three conditions of the Stroop task (Stroop colour, Stroop word, Stroop incongruent). However, there was no significant difference between BM and his control group in the Stroop quotient score derived from the ratio index (incongruent/colour), which adjusts for confounding factors such as processing speed. In contrast, the results of the neuropsychological testing of NR and MJ revealed that both cases did not significantly differ from their control group in all tasks for the assessment of attention and executive function. Only in the Stroop quotient score did MJ's performance fall below that of his control group. An overview of the t-test results is depicted in table 4.

Social cognitive performance

To assess the performance of social cognition, we used the NEmo test battery [40]. The t-test results of all cases in the tests assessing social cognitive functions are shown in table 5. BM was tested on two occasions for reliability purposes.

The neuropsychological assessment of the two cases with developmental amnesia showed that both performed significantly worse in tests assessing emotion recognition when compared with their IQ-matched control group. The results of the t-test revealed that BM and NR performed significantly worse in the emotion recognition of static emotional facial expressions. In addition, t-tests revealed that BM's performance in recognising emotions in dynamic faces fell significantly below his control group, whereas NR's performance was not different from his control group.

As for ToM functions, both cases with developmental amnesia showed a significant difference compared with their controls. BM and NR performed significantly worse than the control group in the scores for the irony recognition task. In the FPT, BM and NR showed a lower total comprehension score than the control group as well as a reduced ability to identify the person responsible for the faux pas and to understand that the social mishap was unintentional. For the MASC, t-tests showed that the performance of BM and NR fell below their control group in at least one of the four subscales. More specifically, NR scored significantly worse than his control group in the total comprehension score and in the error score that indicates hypermentalising, the overinterpretation of others' mental states. In contrast, results of the t-test showed a significant difference between BM and his control group for the error score that indicates an absence of ToM.

In contrast to BM and NR, the neuropsychological assessment of MJ, a case with adult-onset amnesia and suspected bilateral hippocampal lesions, showed more circumscribed and less prominent deficits in tests

Table 4: Performance in non-social cognitive tests.

	Case BM	Case NR	Case MJ	Estimated effect size (z _{cc})		
				BM compared with IQ-matched control group (n = 6)	NR compared with IQ-matched control group (n = 16)	MJ compared with IQ-matched control group (n = 46)
<i>General cognitive ability</i>						
WIE Picture Completion (scaled score)	5	8	11	-0.8	-0.2	0.1
WIE Block Design (scaled score)	5	10	12	-0.5	0.6	0.2
WIE Digit symbol (scaled score)	3	7	13	-1.3	-0.6	-0.2
WIE Performance IQ (standard score)	65	89	114	-2.2	-0.1	0.4
<i>Attention/ cognitive processing speed</i>						
TAP Tonic alertness (time in msec)	286	245	261	0.1	0.6	-0.4
TAP Phasic alertness (time in msec)	274	246	253	0.4	0.6	0.1
TMT A (time in msec)	46	28	20	-0.5	0.4	0.6
Stroop colour (time in msec)	25	9	9	-6.9	1.3	1.1
Stroop word (time in msec)	28	11	13	-2.8	1.2	0.2
<i>Executive function/ cognitive flexibility</i>						
TMT B (time in msec)	90	77	48	1.9	0.5	0.4
TMT quotient B/A (time in msec)	2	2.8	2.4	1.3	-0.1	0.0
Stroop incongruent (time in msec)	36	16	12	-3.7	0.9	1.4
Stroop quotient (time in msec)	1.4	1.8	2.3	1.8	0.2	-1.8

TAP: Test Battery for the Assessment of Attention; TMT: Trail Making Test; WAIS: Wechsler Adult Intelligence Scale.

A significant difference (1-tailed, $p < 0.05$) is indicated in bold.

assessing emotion recognition and ToM. Compared with his control group, MJ performed significantly worse in the test for emotion recognition in static emotional facial expressions and in the most demanding and dynamic test for assessing ToM, MASC. Apart from that, there was no significant difference between MJ and his control group (Dynamic and Simultaneous FER, Prosodic-facial ER, Detection of irony, FPT).

Taken together, the performance of social cognitive functions was significantly lower than the control group in both cases with developmental amnesia in five out of seven tests in patient BM and in four out of seven tests in patient NR. This corresponds to 71% of all tests in the case of BM and 57% in the case of NR, which can be seen as an impairment index for social cognitive function. In comparison, patient MJ showed less severe deficits in social cognition, performing worse than his control group in two out of 7 tests (28%). Thus, both cases with developmental amnesia showed notable deficits in a considerable number of tests assessing social cognition, whereas a case with adult-onset amnesia showed circumscribed and less pronounced deficits in social cognition.

Discussion

We have comprehensively evaluated and compared the performance in various tests of social cognition in two patients with developmental amnesia and in one with

adult-onset amnesia. In summary, the comparison with the IQ-matched control groups showed that both patients with developmental amnesia demonstrated significant deficits in socio-cognitive tasks assessing emotion recognition and theory of mind, despite their differing levels of overall cognitive ability. In comparison, the patient with adult-onset amnesia was less impaired compared with his IQ-matched control group and the two patients with developmental amnesia.

The neuropsychological investigation of all three cases showed reduced abilities to store and to freely recall verbal or non-verbal information after a half hour delay. A bilateral hippocampal sclerosis was confirmed by visual inspection and volumetric data analysis in both cases with developmental amnesia, BM and NR. For patient MJ, with adult-onset amnesia, a MRI was unfortunately unavailable because of a permanently implanted cardioverter defibrillator. However, given the medical history (prolonged reanimation), and the well-documented presence of an amnesic syndrome, bilateral hippocampal damage is very likely [48]. Altogether, these findings allow the diagnosis of developmental amnesia after episodes of perinatal hypoxia for the two cases BM and NR [38, 39, 58], and the diagnosis of adult-onset amnesia with suspected hippocampal lesions after hypoxia secondary to cardiac arrest for the case MJ [59].

To address the limitations of our previous findings, we compared BM with the neurocognitive profile of an

Table 5: Performance on social-cognitive tests.

	Case BM		Case NR	Case MJ	Estimated effect size (z_{cc})			
	T1	T2			BM compared with IQ-matched control group (n = 6)		NR compared with IQ-matched control group (n = 16)	MJ compared with IQ-matched control group (n = 46)
					T1	T2		
<i>Emotion recognition</i>								
Static FER (accuracy score)	57.1	60.7	69.6	70.0	-2.4	-2.0	-2.0	-3.1
Dynamic FER (accuracy score)	39.6	33.3	69.8	87.5	-4.2	-4.9	-1.0	-0.1
Simultaneous FER (accuracy score)	56.7	48.3	68.3	76.8	-0.4	-1.3	0.3	0.3
Prosodic-facial ER (accuracy score)	60	37.5	47.5	77.5	-0.1	-2.2	-1.7	0.0
<i>Theory of mind</i>								
Irony ironic (accuracy score)	16.7	83.3	100	83.3	-0.8	1.0	1.0	-0.2
Irony empathic (accuracy score)	100	0	33.3	100.0	0.7	-3.5	-1.9	0.7
Irony neutral (accuracy score)	16.7	33.3	50	83.3	-2.5	-1.7	-0.8	0.7
Irony total (accuracy score)	44.4	38.9	61.1	88.8	-1.2	-1.5	-1.3	0.6
Faux-pas 2 (raw score)	1	0	3	5.0	-1.8	-2.4	-2.3	0.4
Faux-pas 3 (raw score)	0.5	0	1.5	3.0	-1.9	-2.3	-1.7	0.9
Faux-pas 4 (raw score)	0	0	1	2.5	-2.4	-2.4	-2.1	-0.4
Faux-pas 5 (raw score)	2	0	1	5.0	-1.7	-2.1	-1.7	1.3
Faux-pas total (raw score)	2	0	6.5	15.5	-2.1	-2.5	-2.2	-0.3
MASC correct ToM (raw score)	15	n.a.	13	20	-1.3	n.a.	-2.3	-3.5
MASC more ToM (raw score)	7	n.a.	13	5	0.8	n.a.	-2.5	0.1
MASC less ToM (raw score)	12	n.a.	12	8	-0.4	n.a.	-1.4	-1.7
MASC no ToM (raw score)	12	n.a.	8	3	-2.3	n.a.	-1.3	-0.5

n.a.: not administered; FER: facial emotion recognition; ER: emotion recognition; MAS: movie for the assessment of social cognition.

A significant difference (1-tailed, $p < 0.05$) is indicated in bold. One control person from the IQ-matched group of BM was excluded from the analyses of language-dependent tests due to the foreign language background.

other case NR with a similar medical history but an average cognitive performance level. Based on the assumption that difficulties in social cognition are caused by early bilateral lesions of the hippocampus, we expected the two cases with developmental amnesia, NR and BM, to show similar social cognitive impairments in our experimental tasks. Indeed, our findings showed that NR, like BM, performed significantly worse in almost all of the tests assessing emotion recognition and theory of mind compared with their IQ-matched control group. In more detail, NR showed social cognitive deficits in four out of seven tests (57%) and BM in five out of seven tests (71%). Thus, both cases showed considerable deficits over a broad spectrum of social cognition. Furthermore, these deficits in social cognitive functioning were dissociated from other neurocognitive functions such as attention and executive function. Given the high degree of overlap between BM's and NR's difficulties in social cognition, we assume that BM's general cognitive disability and reduced processing speed cannot sufficiently explain the profound social cognitive deficits.

In terms of emotion recognition, BM and NR showed difficulty in detecting emotions in static facial expressions compared with their control groups. These find-

ings are in line with the results of Staniloiu et al. [33], who also reported difficulties with emotional processing. In addition, BM's performance also fell significantly below that of his control group in recognising emotions in dynamic faces. In contrast, NR's performance was not significantly different from that of his control group. This inconsistency might be explained by the reduced psychomotor processing speed of BM compared with his control group, which was visible in all three conditions of the Stroop test. Regardless of whether the reduction was due to the hypoxic event, post-ictal impairment, side effects of anti-epileptic drugs, or an underlying brain lesion, it is likely that reductions in the information processing speed can make it difficult to have smooth social interactions [60].

BM and NR performed significantly worse than their control group in all three tasks used to assess ToM. For instance, BM and NR showed particular difficulty in detecting a statement intended to be friendly in a task that measures the ability to recognise the intended meaning of a statement in orally presented short stories. Furthermore, both cases had difficulties in detecting social faux-pas in written short stories depicting social interactions. Similarly, BM and NR were strongly impaired in inferring mental states and emotions

from characters in the MASC, a highly complex and dynamic task based on a short movie. Contrary to our results, other reports on developmental amnesia found largely preserved core ToM function [33, 61]. The observed differences could be mediated by several factors, for example the use of different measurements, and sex differences [62, 63].

To further characterise social cognitive dysfunction in patients with developmental amnesia, we also explored the social cognitive profile of a case with adult-onset amnesia and suspected bilateral hippocampal damage, patient MJ. In contrast to the two cases with developmental amnesia, the neuropsychological assessment of MJ showed more circumscribed and less severely impaired function in tests assessing emotion recognition and ToM. MJ performed significantly worse than his reference group in a test for emotion recognition in static faces and in a video-based test for assessing ToM, MASC. It seems plausible that MJ's inability to generate episodic details and recapitulate specific aspects from a scene impairs his ability to make ToM-level judgments about the actors within it. This form of scene recall, which relies on episodic memory, is much less relevant in tasks where MJ's performance is within the norm. However, these results seem to contradict other studies suggesting that social cognitive deficits are not obvious in patients with adult-onset amnesia [42–44], and that ToM functions in particular may be independent of the hippocampal integrity [45].

There are some factors that may have contributed to the observed differences in impairments between developmental and late-onset amnesia. For one thing, it should be taken into consideration that MJ may have been able to compensate for his deficits largely through his intelligence and education, which was the highest of the three cases. For another, he had the most experience in social practice, given that he had worked as a geometrician and lecturer for many years, had been in long-term relationships, and was the father of two children. However, what is perhaps even more intriguing is that, despite those beneficial factors, MJ showed clinically significant deficits in social cognition.

Apparently, the suspected hippocampal lesion and its evident memory deficit nevertheless left traces in the network that is relevant for social cognition. Recent results from animal studies suggest that the hippocampus is important for social cognition [4–7, 64]. However, the significance of the hippocampus in humans has not yet been clarified, although our results can be interpreted as indicating that there might be a connection. We assume that early lesion onset, reduced opportunities for social practice and low intelligence are strong predictors of significant deficits. Comparatively,

adult-onset amnesia after hypoxia with suspected hippocampal damage also leads to deficits, but a high level of social practice and intelligence efficiency may partly protect social cognition.

In sum, our findings lend weight to the assumption that, besides the well-described severe episodic memory problems, social cognitive functions are impaired in patients with amnesia. In comparison, a case with adult-onset amnesia showed less severe and circumscribed impairments in social cognition than the two patients with developmental amnesia. This difference might be explained by a long developmental period of unimpaired acquisition of a multitude of social competencies before the amnesic syndrome occurred as a result of cerebral hypoxia. Therefore, patients with developmental amnesia might be at higher risk for social cognitive deficits. Our study suggests that deficits in social cognition might belong to the core symptoms of an amnesic syndrome due to suspected hippocampal damage and should be always taken into account in clinical settings.

Conclusion

Although descriptive in nature, our study contributes to the neuropsychological characterisation of social cognition in individuals with amnesia due to suspected bilateral hippocampal dysfunction acquired after a hypoxic event either early in life, as seen in developmental amnesia, or later in adulthood, as seen in adult-onset amnesia. Distinct social cognitive impairments were detected in both cases with developmental amnesia, BM and NR, in the domains of both emotion recognition and theory of mind. In comparison, a case with adult-onset amnesia, patient MJ, showed less severe and circumscribed deficits in social cognition. This study underpins the need for comprehensive diagnostics of social cognitive function, as recommended by the DSM-5 [15], in amnesic patients of different aetiologies and courses of disease, as social cognitive deficits are a significant risk factor for quality of life, relationships, and employment status [14, 65] with tremendous social and economic costs and consequences.

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