Cognitive and social impairments in patients with superficial siderosis

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Summary

Superficial siderosis of the CNS is a rare condition, caused by deposition of haemosiderin in the superficial layers of the CNS due to repeated chronic subarachnoid or intraventricular haemorrhage. Typically, the hindbrain structures, especially the cerebellum, are most affected. There is a surprising lack of studies investigating in detail the behavioural functioning of patients with such a condition. In this study, we document for the first time the cognitive, social and emotional processing of six patients with a confirmed clinical diagnosis of superficial siderosis. They were aged between 40 and 62 years, with a mean age of 50.2 years; four were male. We administered a comprehensive battery of general cognitive ability and social cognitive tasks. A review of MRI was also undertaken. The findings indicate selective cognitive impairments affecting speech production, visual recall memory and executive functions. In addition, a selective pattern of social dysfunction, affecting the ability to represent other people’s mental states, was found. These behavioural dysfunctions are reported in the context of MRI-documented lesions maximally involving the cerebellum, in particular the superior vermis, as well as the medial and inferior frontal cortex. These results suggest that superficial siderosis is associated with a distinct pattern of cognitive and social impairments. They are consistent with the recently proposed role of the cerebellum as a modulator of cognitive, social and emotional functions.

Keywords: superficial siderosis; theory of mind; cerebellum; cognitive functioning; social cognition

Abbreviations: ToM = theory of mind; MWCST = Modified Wisconsin Card Sorting Test


Introduction

Superficial siderosis of the CNS is a rare condition due to repeated or continuous leakage of blood into the CSF caused by a wide variety of pathologies. Haemoglobin is metabolized to ferritin by glia and is deposited in the superficial layers of the CNS with resulting gliosis and loss of neurons. Typically, the hindbrain structures, especially the cerebellum, are most affected. The 8th nerve is severely damaged because, unlike other true cranial nerves, central myelin extends for a considerable distance along the nerve (Tarlov, 1937). The cerebral cortex is less affected; neuropathological studies demonstrate that the inferior frontal lobes are the site of maximum damage, a fact consistent with the anosmia that all patients develop (e.g. Tomlinson and Walton, 1964; Castaigne et al., 1967; Hughes and Oppenheimer, 1969; Sherwin and Toll, 1972; Katsuragi et al., 1988), but no superficial area is totally spared. The deep nuclei are not involved. The reason for this distribution is unknown but it may be related to CSF flow and stasis. Typical clinical signs are cerebellar ataxia and dysarthria, anosmia, sensorineural deafness and pyramidal signs (e.g. Fearnley et al., 1995).

T2-weighted MRI invariably demonstrates a signal void coating the CNS, the distribution reflecting the neuropathology. Gradient echo sequences are the most sensitive at detecting the iron and show more extensive abnormality, but the relative distribution is the same as shown on routine spin echo T2-weighted scans.

To the best of our knowledge, a systematic investigation into the cognitive functioning of patients with superficial siderosis has not been reported. A few early qualitative studies reported that superficial siderosis is associated with dementia; however, no formal cognitive testing was documented (e.g. Hughes and Oppenheimer, 1969; Sherwin and
Toll, 1972; Katsuragie et al., 1988; Stevens et al., 1991; Fearnley et al., 1995). The diagnosis of dementia was often made through qualitative observation (e.g. Hughes and Opperheimer, 1969). Moreover, from these studies, the relationship between disease duration and severity of the dementia is ill understood. For example, Katsuragie et al. (1988) described one patient with superficial siderosis showing a profound dementia with progressive loss of recent memory, inability to sustain work and bizarre behaviour only 1 year after diagnosis. Conversely, Stevens et al. (1991) described a patient who developed memory problems 32 years after the onset of the disorder. Only one of the four patients of Anderson et al. (1995) had mild cognitive impairment, but no formal testing was reported, and similar results were obtained by Leussink et al. (2003).

The lack of any systematic investigation into cognitive deficits of superficial siderosis is surprising since recent literature has indicated that cerebellar pathology, the site of maximum damage in superficial siderosis, can be associated with both cognitive and social impairments. For example, Schmahmann and Sherman (1998) studied a large number of patients with cerebellar lesions due to a variety of causes (stroke, tumour and atrophy). They reported that their patients presented with a range of cognitive impairments, including deficits in language, visuospatial cognition and executive functioning. They also described anecdotal qualitative changes in the regulation of emotions and social behaviour as demonstrated by personality changes in their patients with blunting of affect or inappropriate behaviour. They concluded that the pattern of deficit in these patients is characteristic enough to suggest that it forms a recognizable syndrome, the ‘cerebellar cognitive affective syndrome’. Other clinical reports of patients with focal cerebellar lesions have described personality changes (Pollack et al., 1995; Levisohn et al., 1997) and emotional flattening (Annoni et al., 2003). These qualitative observations are in line with the results of several neuroimaging studies, reporting cerebellar activation in emotional modulation (e.g. Reiman et al., 1989; Bench et al., 1992; Dolan et al., 1992; George et al., 1995; Mayberg et al., 1995).

There is also evidence suggesting that cerebellar abnormality occurs in individuals with autism, a developmental disorder characterized by impairments in social interaction and communication (e.g. Courchesne, 1997; Bailey et al., 1998; Abell et al., 1999). Cerebellar abnormalities have been documented at autopsy and on structural MRI. In particular, abnormalities have been reported in vermal lobules VI and VII (Courchesne et al., 1988, 1994; Piven et al., 1995). Voxel-based morphometry studies have reported increased grey matter density bilaterally in the posterior lobes of the cerebellum in autism (Abell et al., 1999; Salmond et al., 2003). In these individuals, the abnormal autistic social behaviour is often interpreted in terms of ‘theory of mind’ (ToM) impairment. ToM is the ability of humans to attribute mental states, such as beliefs, intentions and desires, to others (e.g. Frith, 2001; Baron-Cohen, 1995). A variety of techniques has been developed to test this complex ability, including story comprehension tasks requiring inferences about the protagonist’s thoughts or intentions. Whilst most people carry out these tasks effortlessly, they present difficulties for individuals with autism. Functional imaging studies have indicated that the neuronal system underlying ToM is widely distributed (e.g. Frith and Frith, 2003). Typically, both medial frontal and temporal, in particular temporal poles and posterior superior temporal sulcus, have been implicated (e.g. Fletcher et al., 1995; Baron Cohen et al., 1999; Vogel et al., 2001; Siegal and Varley, 2002; Gallagher and Frith, 2003; Wicker et al., 2003). So far, lesion studies, however, have been less definitive in providing a distinct neuroanatomical correlate. For example, some studies have found greater ToM impairment in patients with left frontal damage (e.g. Channon and Crawford, 2000), others in patients with right frontal damage (e.g. Stuss et al., 2001) and others have found no laterality effects (Rowe et al., 2001). In addition, normal ToM abilities have been reported following medial frontal damage (Bird et al., 2004). To our knowledge, none of the published studies has investigated ToM abilities in patients with cerebellar damage.

If the presence of cerebellar damage contributes to the impairment of both cognitive and social (mentalizing) abilities, it might be expected that other conditions, such as superficial siderosis, which impact on cerebellar functions, may have a similar affect. The aim of the present study is to characterize the cognitive and social cognitive profiles of patients with this condition. Six patients underwent detailed cognitive and social cognitive assessments. A review of the imaging data is also undertaken.

Case reports
Six patients with a clinical diagnosis of superficial siderosis confirmed by MRI (see below) have been investigated in the Neuropsychology Department of the National Hospital for Neurology and Neurosurgery. They were aged between 40 and 62 years (mean age = 50.2; SD = 9.15). Two were female and four were male. They had 8–13 years of formal education (mean = 10, SD = 1.8).

Neurological and neuroradiological findings
Table 1 summarizes the clinical history, neurological signs and presumptive cause of the superficial siderosis in six patients. All had the classical features of this condition: neural hearing loss, ataxia and anosmia. Four had minor pyramidal signs. None had any problems with managing their daily lives or obvious cognitive or behavioural defects. The following case description gives some idea of the course of this disorder.

Description of case 2
In 1990, this 48-year-old accountant, who had had a head injury aged 3 years resulting in a skull fracture, developed tinnitus and decreased hearing, initially in the right ear then
the left. There was no significant family history of hearing loss or neurological disease. Subsequently the hearing loss progressed. In 1993, he first noticed unsteadiness of gait and clumsiness of the hands. This progressively worsened.

He was first assessed neurologically in 1993 and 1994. He was anosmic and there was marked hypermetria of saccadic eye movements on returning the eyes to the primary position. There was no nystagmus. He was noted to have a marked sensorineural hearing loss of >40 dB for all frequencies above 500 Hz on the right and above 250 Hz on the left. The stapedius reflex thresholds were normal, but there was abnormal tone decay at 2 kHz on the left. Brainstem evoked potentials and otoacoustic emissions were absent bilaterally. Caloric tests revealed a right canal paresis and diminished responses on the left. He had a moderate dysarthria and ataxia of the limbs and gait. Tone and power were normal in the upper and lower limbs with no pathological reflexes.

Extensive investigations were undertaken. An MRI of the entire neuraxis revealed superficial siderosis, and angiography of the cranial and spinal arteries was normal. The spinal fluid contained 365 red blood cells/mm³ and was xanthochromic on visual inspection. Blood clotting studies were normal. Trientene (1200 mg daily) was given in an attempt to chelate the iron.

His hearing continued to decline, and by 2001 he was totally deaf on the left and had 80 dB loss of all frequencies >250 Hz on the right. The caloric test showed no function in either horizontal canal. His ataxia especially of gait had increased such that he began to fall, and his dysarthria was severe, making his speech extremely difficult to understand. He developed a non-specific headache and dull pain in the legs responding partly to gabapentin. Hydroxychloroquin was added to his trientene in an attempt to block the production of ferritin.

In 2003, he was admitted for his last assessment. At this time, he had to give up work because of his physical incapacity; he had no problems coping intellectually with his work, could manage his personal and financial affairs, and his personality was unchanged. He was totally deaf. The eye movement abnormality was unchanged. The dysarthria was profound. He had a severe ataxia of gait and moderately severe ataxia of the limbs, greater in the legs. There were no sensory signs. CSF examination revealed 888 red blood cells/mm³, and spectroscopy demonstrated oxyhaemoglobin and breakdown products of haemoglobin. A trial of mefanemic acid did not alter the CSF findings.

In summary, this patient has followed the classical course of superficial siderosis; it is not known if the therapies given are of any value, but it is clear the bleeding continues. It is assumed the bleeding is venous in origin and perhaps related to trauma as a child (for discussion of possible causative factors, see Fearnley et al., 1995).

Table 2 summarizes the MRI findings. No quantitative measures of the iron deposition were obtained; all data are qualitative. All but one (patient 3 with a cochlear implant) had axial T2-weighted scans of the brain, and patient 6 had gradient echo sequences. All patients had extensive superficial siderosis of the hindbrain structures with atrophy of the superior and posterior parts of the cerebellum (Fig. 1). The forebrain was much less affected, with iron deposition being detected with routine T2-weighted scans only in the more inferior parts and anteriorly. In the detailed study of

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**Table 1** Summary of the clinical findings

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Duration (years) of Signs</th>
<th>Hearing loss</th>
<th>Unsteadiness</th>
<th>Anosmia</th>
<th>Hearing loss</th>
<th>Ataxia</th>
<th>Pyramidal</th>
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<tr>
<td>1</td>
<td>47</td>
<td>M</td>
<td>5</td>
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<td>22</td>
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</tr>
<tr>
<td>5</td>
<td>44</td>
<td>M</td>
<td>2</td>
<td>+ + + + + +</td>
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<td>+ + + + + +</td>
<td>+ + + +</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

0 = absent; + to +++ = mild to severe; U/K = unknown; # = fracture.

**Table 2** Summary of iron deposition detected by MRI fast spin echo (T2 weighted)

<table>
<thead>
<tr>
<th>Case</th>
<th>Cortex</th>
<th>Cerebellum</th>
<th>Brainstem Midbrain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Superior</td>
<td>Inferior</td>
<td>Superior</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>+++†</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>No contemporary scan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>+++†</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>+++</td>
<td>+</td>
</tr>
</tbody>
</table>

*Medial and inferior surface of frontal lobes; †medial temporal lobes. 0 = no deposition of iron; ± = probable deposition of iron; + to +++ = mild to severe deposition of iron.
case 2, which included gradient echo and fat sat sequences, iron deposition in the forebrain was maximal in the gyrus rectus and the medial frontal cortex (Figs 2 and 3). Lesser deposition was found in the temporal lobes, especially inferiorly, and in the insular (left greater than right), but not in the more posterior cerebral cortex or basal ganglia. Dedicated high resolution coronal slices of the medial temporal structures to look at the hippocampi were not obtained, but none of the patients has hippocampal atrophy on inspection; iron deposition involved the surface of the entorhinal cortex to the hippocampal fissure in two patients (cases 2 and 4), but the superior surface (CA1 and CA2) was not involved (Fig. 4).

Neuropsychological investigation

The six patients were administered an identical battery of standardized and published neuropsychological tests. This included general cognitive tests and tests assessing executive and social processing skills. The general cognitive battery included tasks of current intellectual functioning [Wechsler Adult Intelligence Scale-Revised (WAIS-R); Wechsler 1981]; pre-morbid optimal level of functioning [National Adult Reading Test (NART); Nelson, 1992]; visual and verbal recall and recognition memory [RMT (Warrington, 1984); paired associate learning test (Warrington, 1996); Rey Osterrieth complex figure (Osterrieth, 1944)]; nominal functions (graded difficulty naming test; McKenna and Warrington, 1983); calculation (graded difficulty arithmetic test; Jackson and Warrington, 1986) and perceptual functions (with subtests from the visual object and space perception battery; Warrington and James, 1991). Attention skills were assessed with a series of clinical tests of speed and attention [canceling 0s and digit copying (Willison and Warrington, 1992); part A of the trail making test (Reitan and Wolfson, 1985)]. Executive skills were assessed with a series of clinical tests thought to tap executive dysfunction [Hayling sentence completion test (Burgess and Shallice, 1997); phonemic fluency task (Spreen and Strauss, 1998); Stroop test (Trenerry et al., 1989); part B of the trail making test (Reitan and Wolfson, 1985); modified Wisconsin Card Sorting Test (MWCST; Nelson, 1976); proverb interpretation].

Raw scores on each test measure were converted into derived scores with reference to the available age scale normative data described in the manuals of the tests quoted above. Five derived scores were calculated as follows. (i) The intellectual functioning score was obtained using the method of Nelson and O’Connell (1978), by recoding the difference between an estimated pre-morbid IQ (from the NART IQ equivalent scores) and the measured prorated full-scale IQ. A difference ≥15 was taken as evidence of intellectual decline. (ii) The memory and naming scores were derived by converting the standardized test performance into percentile scores (Osterrieth, 1944; McKenna and Warrington, 1983; Warrington, 1984, 1996). Scores at or below the 5th percentile were taken to indicate memory or naming impairment. (iii) The perceptual scores could not be converted into percentile scores, because they were not normally distributed (Warrington and James, 1991). Thus, scores at or below the 5% cut-off were taken to indicate a perceptual impairment. (iv) Speed and attention scores were the mean time (in s) for patients to complete the tasks. Scores of 2 SDs above the standard population were taken as an impaired performance on speed and attention tasks (Reitan and Wolfson, 1985; Willison and Warrington, 1992). (v) Four different procedures were adopted to analyse the frontal test scores. (a) Word fluency, Stroop and trail making test scores were derived by converting the standardized test performance into percentile scores (Trenerry et al., 1989; Reitan and Wolfson, 1985; Spreen and Strauss, 1998). (b) Hayling sentence completion test converting raw scores into scaled scores. According to published norms, a scaled score of ≥3 indicated impairment (Burgess and Shallice, 1997). (c) Responses on the MWCST were calculated according to the number of categories achieved and the percentage of total perseverative errors (Kapur et al., 2003). Four or five categories achieved and a score of <50% perseverative errors indicated mild impairment. Less than four categories and/or a score at or above 50% indicated marked impairment. (d) A pass or fail procedure was adopted for the proverb interpretation task. Patients were classed as having a frontal impairment if
their performance was impaired on at least two tests of frontal executive functioning.

Social cognition investigation

The social cognition battery is an experimental test battery designed to investigate three aspects of social cognition: (i) the ability to represent the internal mental states of others; (ii) the ability to represent the emotions of others; and (iii) the ability to process the appropriateness of behaviour in different social contexts. This battery comprised three different tasks (advanced ToM, emotion attribution and social situation tasks; see descriptions below). Although this battery has not been standardized, it has been used previously both with adult patients with acquired neurological conditions (Blair and Cipolotti, 2000; Heims et al., 2004; Baird et al., 2005) and with adult patients with developmental psychopathy (Blair and Cipolotti, 2000). In addition, advanced ToM and social situation tasks, similar to those adopted in our battery, have been used previously in studies of autism (Dewey, 1991; Happe, 1994). Our previous investigations on patients with acquired neurological conditions have indicated that grave dysexecutive impairment without aberrant behaviour does not compromise performance on the three tasks of the social cognition battery (patient C.L.A., Blair and Cipolotti, 2000). However, both acquired frontal damage and peripheral denervation of autonomic neurons (pure autonomic failure) differentially impair test performance. In particular, we reported a patient with orbitofrontal damage and acquired sociopathy who, whilst unimpaired in the advanced ToM tasks, presented with severe difficulty in the emotion attribution and social situation tasks (patient J.S., Blair and Cipolotti, 2000). Three recently investigated patients with medial frontal lobe lesions showed deficit in the advanced ToM task only when the lesion involved the anterior cingulate cortex bilaterally. No significant deficit was present in emotion and social situation tasks (Baird et al., 2005). Six patients with pure autonomic failure were unimpaired in ToM and social situation tasks. However, they scored worse than the comparison control group on the emotion attribution task (Heims et al., 2004). The studies conducted on patients with neurodevelopmental disorders indicated that the autistic patients failed the ToM task while the developmental psychopaths were unimpaired (Happe, 1994; Blair and Cipolotti, 2000). Overall, these studies seem to suggest that these experimental tasks are able to identify different types of impairments in social functioning associated with different neurological pathologies.

Control subjects

In the social cognition investigation, the performance of the patients was compared with that of 21 healthy volunteer subjects, matched for age, who were free from neurological impairment. The group of control subjects were aged between 27 and 81 years (mean age = 52.52; SD = 18.75). Patient scores above or below 2 SDs from the control mean were considered significant.

Social cognition tasks

Advanced ToM task

In this task, the participant was presented with 14 stories describing naturalistic social situations and was asked to interpret and justify the behaviour of the main character. Three scores were manually recorded. The first indexed comprehension of the situation (maximum score = 14). The remaining two scores referred to the justification provided during interpretation of the story character’s behaviour, i.e. reference to either the character’s mental states or physical information. Of the stories correctly understood, the total number of stories justified using mental state information and total number of stories justified with reference to physical information were recorded. An example of a ToM story, with mental and physical justifications, is shown in the Supplementary material available at Brain Online.

The emotion attribution task

In this task, the participant was presented with 75 short stories describing an emotional situation and was required to provide a description of how the main character might feel in that situation. The sentences were designed to elicit attributions of happiness, sadness, fear, anger or embarrassment. There were 15 sentences for each emotion. The task was scored according to the number of correct attributions made for each emotion category, i.e. participants received a score out of 15. Examples of stories for each emotion are shown in the Supplementary material.

The social situation task

In this task, 20 short stories describing social situations incorporating behaviour that was either normative or a violation were read by the participant. Participants were required to judge the appropriateness of behaviours at various points in each story, giving a score from A to D. A indicated that the behaviour had been judged normal. Scores of B–D indicated that the behaviour had been judged as a violation and indicated the extent of the violation (B = mild, D = serious). In total, there were 17 normative situations and 20 violations. Three scores were generated. The first two indicate the number of normative situations (maximum 17) and the number of violations (maximum 20) correctly identified. The last score indicates the extent to which participants judged violations to be socially inappropriate. For each violation, the participant obtained a score between 0 and 3, matching their response of A–D (i.e. A = 0, B = 1, C = 2, D = 3). An example of a social situation story is presented in the Supplementary material.

Statistical analysis

Mann–Whitney U tests were used in order to compare mean scores between the patient and the control groups on both the ToM and social situations tasks. Differences were considered significant at the $P < 0.05$ level. Patient 1 was administered only a subset of the social cognition tests and was therefore excluded from the analysis.
General cognitive test results

Table 3 summarizes the patients' performance on general cognitive tests. All patients had a normal verbal IQ, but patient 2 had a mild weakness in his performance IQ. Verbal recognition and recall memory functions were entirely normal in all six patients. Only one patient (case 4) obtained a marginally weak score on the paired associate learning test of verbal recall memory. Similarly, all patients had normal visual recognition memory on the visual version of the recognition memory test. However, they all, except for patient 6, showed impaired performance on the delayed recall of the Rey complex figure despite normal performance on the copy condition. Although naming skills were preserved, all patients presented with mild speech production difficulties, which could be best characterized by slow, effortful and at times slightly dysprosodic speech production. Visual perception and calculation functions were generally intact, with the exception of one patient (case 5), who obtained an impaired score on the graded arithmetic test. However, it was noticeable that this patient was able to carry out complex written multi-digit addition, subtraction and multiplication problems when there was no time limit. Two patients (cases 2 and 5) had an impaired performance on a test of speed and attention. Thus, patient 5’s impaired performance on the graded arithmetic test was principally caused by his slowness in information processing. Remarkably, four patients (cases 1, 3, 4 and 5) showed clear-cut executive impairment. Indeed, their performance was impaired on at least three tests of frontal executive functioning. All patients had difficulty on tasks requiring them to initiate a response (phonemic fluency and Hayling sentence completion test part A). All but one patient (case 4) showed deficits on tasks requiring them to inhibit a dominant response (Stroop test and Hayling sentence completion test part B). In addition, two patients had difficulties on tests that require switching between categories (trail making test part B and MWCST) and one patient had problems with abstraction (proverbs interpretation). Two patients could not be classed as having an executive impairment since they failed only one test of executive function. However, it was noted that, like the other patients, they both failed the Hayling sentence completion test.

Social cognition tasks results

The individual performance of each patient and control on the three social cognition tasks is shown in Table 4. Unfortunately, due to time constraints, patient 1 was given only a half set of each of the three social cognition tasks.

### Table 3 Summary of neuropsychological test results

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient 1 (%ile)</th>
<th>Patient 2 (%ile)</th>
<th>Patient 3 (%ile)</th>
<th>Patient 4 (%ile)</th>
<th>Patient 5 (%ile)</th>
<th>Patient 6 (%ile)</th>
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<tbody>
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<td>89</td>
<td>112</td>
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<td>108</td>
<td>96</td>
<td>116</td>
<td>94</td>
<td>121</td>
</tr>
<tr>
<td>RMW</td>
<td>48 (&gt;75th)</td>
<td>47 (75th)</td>
<td>49 (90th)</td>
<td>46 (50–75th)</td>
<td>46 (75th)</td>
<td>50 (&gt;95th)</td>
</tr>
<tr>
<td>RMF</td>
<td>43 (25–50th)</td>
<td>41 (25th)</td>
<td>43 (5–50th)</td>
<td>45 (50–75th)</td>
<td>42 (50th)</td>
<td>41 (25–50th)</td>
</tr>
<tr>
<td>PAL T1</td>
<td>19 (25–50th)</td>
<td>20 (50–75th)</td>
<td>20 (50–75th)</td>
<td>15 (10–25th)</td>
<td>16 (25–50th)</td>
<td>23 (&gt;90th)</td>
</tr>
<tr>
<td>PAL T2</td>
<td>22 (25th)</td>
<td>22 (25th)</td>
<td>24 (&gt;75th)</td>
<td>20 (5–10th)</td>
<td>22 (50th)</td>
<td>24 (&gt;90th)</td>
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<td>Rey copy</td>
<td>36/36 (100th)</td>
<td>NT</td>
<td>35/36 (90th)</td>
<td>36/36 (100th)</td>
<td>30/36 (20th)</td>
<td>36/36 (100th)</td>
</tr>
<tr>
<td>Rey recall</td>
<td>11/16 (5th)</td>
<td>NT</td>
<td>14/36 (5th)</td>
<td>13/36 (&lt;5th)</td>
<td>12/36 (&lt;5th)</td>
<td>25/36 (50–75th)</td>
</tr>
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<td>25 (&gt;75th)</td>
<td>23 (75th)</td>
<td>20 (50th)</td>
<td>25 (75th)</td>
<td>22 (50–75th)</td>
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<td>20 (5–5th)</td>
<td>20 (5–5th)</td>
<td>20 (5–5th)</td>
<td>20 (5–5th)</td>
</tr>
<tr>
<td>CA</td>
<td>10 (&gt;5th)</td>
<td>10 (5–5th)</td>
<td>10 (&gt;5th)</td>
<td>10 (&gt;5th)</td>
<td>9 (&gt;5th)</td>
<td>10 (&gt;5th)</td>
</tr>
<tr>
<td>Cancel 0s</td>
<td>62 (&lt;1 SD)</td>
<td>77 (&gt;2 SD)</td>
<td>52</td>
<td>48</td>
<td>96 (&gt;2 SD)</td>
<td>40</td>
</tr>
<tr>
<td>Digit copy</td>
<td>51 (10–25th)</td>
<td>36 (50–75th)</td>
<td>43 (10–25th)</td>
<td>48 (25–50th)</td>
<td>41 (&gt;75th)</td>
<td>41 (&gt;75th)</td>
</tr>
<tr>
<td>TMTA</td>
<td>36 (25–50th)</td>
<td>26 (50–75th)</td>
<td>25 (50–75th)</td>
<td>78 (10–25th)</td>
<td>31 (50–75th)</td>
<td>31 (50–75th)</td>
</tr>
<tr>
<td>Hayling</td>
<td>18 (6)</td>
<td>8 (1)</td>
<td>11 (3)</td>
<td>13 (4)</td>
<td>8 (1)</td>
<td>12 (3)</td>
</tr>
<tr>
<td>Fluency</td>
<td>FAS = 27 (&lt;10th)</td>
<td>FAS = 49 (70–80th)</td>
<td>FAS = 22 (&lt;10th)</td>
<td>FAS = 34 + 5p (10–20th)</td>
<td>FAS = 20 (&lt;10th)</td>
<td>FAS = 69 (&gt;95th)</td>
</tr>
<tr>
<td>Stroop</td>
<td>73 (2–3th)</td>
<td>112 (100th)</td>
<td>97 (19th cut-off)</td>
<td>109 (44th)</td>
<td>56 (2–4th)</td>
<td>112 (100th)</td>
</tr>
<tr>
<td>TMTB</td>
<td>73 (50–75th)</td>
<td>61 (50–75th)</td>
<td>66 (50–75th)</td>
<td>150 (&lt;10th)</td>
<td>263 (&lt;5th)</td>
<td>62 (90th)</td>
</tr>
<tr>
<td>MWCST</td>
<td>6/6</td>
<td>6/6</td>
<td>6/6</td>
<td>6/6</td>
<td>6/6</td>
<td>6/6</td>
</tr>
<tr>
<td>PE</td>
<td>50%</td>
<td>0%</td>
<td>50%</td>
<td>25%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Proverbes</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>F</td>
<td>P</td>
<td>P</td>
</tr>
</tbody>
</table>

VIQ = verbal IQ; PIQ = performance IQ; FSIQ = full-scale IQ; NART = National Adult Reading Test; RMW = recognition memory test for words; RMF = recognition memory test for faces; PAL = paired associate learning; GNT = graded naming test; GDA = graded arithmetic test; OD = object decision; IL = incomplete letters; CA = cube analysis; PD = position discrimination; TMTA = trail making test part A; TMTB = trail making test part B; MWCST = Modified Wisconsin Card Sorting Test; PE = perseverative errors; NT = not tested.
provided by the control group (physical state, $U = 0.00$, $P < 0.0001$; mental state, $U = 0.00$, $P < 0.0001$). Of note, they used a higher number of physical justifications and less mental justifications. In contrast, no significant difference was found between the patient group and the control group on the number of stories correctly understood (patient and controls: $U = 52.0$, NS). These findings suggest that the ability to judge the internal mental states of others is impaired in the patient group.

**Emotion attribution task**

No significant difference was found between the performance of the patient group and controls in their attribution of the emotions of happiness, sadness, fear, embarrassment or anger to the story characters compared with the control group.

**Social situation task**

The patient group and control group did not differ in their ability to identify normative situations (patient and control group: $U = 42.50$, NS). Moreover, scores reflecting the extent of social violations (appropriateness scores) did not differ significantly between the patient group and the control group, indicating an intact ability to process the appropriateness of behaviour in different social situations (patient and control group: $U = 37.50$, NS). The only exception was patient 4, who identified significantly fewer violations on the behavioural judgement tasks.

**Discussion**

Our study provides the first detailed analysis of the imaging, cognitive, social and emotional functioning of six patients with superficial siderosis. The five patients for whom there were contemporary MRI data had the classical distribution of superficial siderosis. In particular, the superior and posterior cerebellum, especially the vermis, was severely affected. In comparison, the inferior cerebellum showed no atrophy and lesser deposition of iron. The cerebral cortex was maximally involved in the inferior frontal regions, with lesser deposition of iron in the inferior temporal lobe on inspection of spin echo T2-weighted MRI. The basal ganglia were not involved (see Figs 1, 2 and 4). However, superficial siderosis

![Fig. 2 Coronal T2 (fat sat)-weighted MRI of frontal lobes (case 2). There is decreased signal return from the surface of the inferior frontal gyri including the gyrus rectus (white arrow) and lower part of the medial frontal lobe (white arrowhead).](image-url)
involves all peripheral areas of the CNS and caution must be exercised in attributing the neuropsychological defects in our patients to particular anatomical regions; nevertheless, some areas are much more severely affected than others.

The neuropsychological investigation revealed that all six patients showed remarkably similar cognitive profiles characterized by speech production, visual recall and executive impairments. Indeed, all patients had mild speech production and visual recall memory impairments, as shown by the Rey complex figure test. All patients also showed impairments on tests of ‘executive’ function. Interestingly, the two most commonly impaired executive tests were the Hayling sentence completion and the word fluency tests. Difficulties were also present, although to a much lesser extent, on the MWCST and the trail making test part B.

In contrast, general intellectual functioning was well preserved, the only exception being patient 2, who showed a mild weakness on the non-verbal part of the WAIS-R. Similarly, all patients had intact naming, literacy, calculation, visual perceptual and visuospatial skills. Verbal and visual

![Fig. 3](image1.png) Gradient echo MRI from case 2 showing extensive iron deposition frontally and lesser deposition in the temporal lobes and insula with sparing of the posterior cerebral cortex.

![Fig. 4](image2.png) T2-weighted (fast spin echo) coronal scan at the level of the head of the hippocampi showing iron deposition over the medial temporal cortex sparing the superior surface of the hippocampi. The hippocampi appear of normal size (case 4).
recognition memory and verbal recall functions were also generally intact. Speed of information processing was relatively preserved. Only two patients (cases 2 and 5) showed a selective impairment on one of the three tests used to assess speed of information processing. Quite clearly our data indicated that our patients did not present with dementia. This is not in good accord with previous studies suggesting that dementia is associated with superficial siderosis (see Fearnley et al., 1995). However, it may well be that dementia is associated with the later stages of the condition. Indeed, the patients with superficial siderosis described in the early reports, many of whom were diagnosed at autopsy, are likely to have had the advanced condition (e.g. Fearnley et al., 1995; Messori et al., 2004).

Interestingly, the impairments in speech production, visual recall memory and executive functions reported in our study have been documented previously in a sample of patients with cerebellar lesions (Schmahmann and Sherman, 1998). These patients were shown to have significant impairment on speech production, visual recall memory test (Rey complex figure) and frontal executive tests. Like our patients, these patients had most difficulty on the word fluency task, whilst the MWCST was much less impaired. Schmahmann and Sherman (1998) attributed their findings to the disruption of the anatomically defined cerebrocerebellar pathways that link the associative and paralimbic regions of the cerebral cortex with the cerebellum. They suggested that the cerebellum is incorporated into the neural circuits that subserve higher order behaviour such as linguistic processing, memory and executive functions (Schmahmann, 1991, 1996).

Schmahmann and Sherman (1998) also described qualitative changes in the regulation of emotions and social behaviour in their patients. In our study, we attempted to carry out an objective and quantitative assessment of the emotional and social behaviour of our patients. We found a highly selective social impairment. Our patients performed entirely satisfactorily on the emotion attribution and the social situation tasks, the only exception being patient 4, who identified significantly less violations on the behavioural judgment task. In contrast, all patients failed the ToM task. Analysis of the errors revealed that they tended to use more physical state justifications rather than mental state justifications on this task. This finding suggests that our patients have a mentalizing impairment. This impairment could not easily be explained by a generalized intellectual and/or a verbal comprehension impairment. Our sample performed well on tests of general intelligence. They also have no difficulties in understanding other story-type stimuli such as the social situation or emotion attribution tasks. Importantly, they all performed well on the control comprehension question of the ToM task. Thus it is unlikely that a generalized executive impairment could account for our patients’ mentalizing deficit. The two patients with a milder executive impairment (cases 2 and 6) were as impaired as the patients with a more severe executive impairment (e.g. cases 4 and 5). There is an increasing literature suggesting that executive functioning and ToM are dissociable (e.g. Blair and Cipolotti, 2000; Fine et al., 2001; Bird et al., 2003).

It is of interest to note that there is a dissociation in our patients between impaired performance on a ToM task and spared performance on the emotion attribution and social situations tasks. In this context, we note that our previously reported case of acquired sociopathy following orbitofrontal damage was unimpaired in ToM, but impaired on emotion attribution and social situations tasks (Blair and Cipolotti, 2000). Similarly, patient E.V.R. who presented with profound emotional and behavioural changes following a lesion of the orbitofrontal cortex was unimpaired in a test which requires representation of potential mental states (Saver and Damasio, 1991). These data seem to suggest that it is inappropriate to postulate a unitary social cognitive module. Rather, it appears that there are dissociable, perhaps interlocking, systems involved in social cognition. Brain damage can selectively impair the functioning of one of such systems.

Our finding of a mentalizing impairment in a condition that maximally affects the cerebellum raises the possibility that this anatomical region may be not only necessary for the normal acquisition of ToM but also essential for the implementation of ToM. It is of interest to note that autopsy studies of patients with autism found the posterior cerebellar vermis (the area of lobules VI and VII) to be the most abnormal (Courchesne et al., 1988, 1994). Furthermore, Bauman and Kemper (1985, 1990) reported a reduction in the numbers of Purkinje cells in the posterior vermis and cerebellar hemispheres in patients with autism. This is in keeping with our finding that the cerebellum, especially the superior and posterior vermis, is the most affected area in our patient sample. Interestingly, the behavioural changes described by Schmahmann and Sherman (1998) were reported to be clinically most prominent in patients with lesions involving the vermis. Alternatively, it is possible that the ToM deficit observed in our patients is underpinned by their more extensive cerebral damage, rather than by cerebellar damage. Our patients had abnormal signal return from the surface of the inferior and medial frontal lobes and, to a lesser extent, medial and inferior temporal lobes on T2-weighted scans, and in the one patient studied with gradient echo sequences there was more extensive abnormality in the inferior part of the temporal lobes. Furthermore, autopsy studies show that no superficial area of the cerebral cortex is spared, although maximal damage, including atrophy, is always in the hindbrain structures and frontal lobes inferiorly. These studies show gliosis underlying the iron deposition. However, this is always extremely superficial and has maximal depth in inferior frontal regions of the cortex. In addition, functional imaging studies have shown activations in these latter areas as well as in posterior regions (superior temporal sulcus and temporal pole) in healthy subjects performing ToM tasks (e.g. Castelli et al., 2002; Siegal and Varley, 2002; Frith and Frith, 2003; Gallagher and Frith, 2003; Samson et al., 2004). This has led to the hypothesis that one or more neuronal systems are dedicated to ToM (Frith and Frith, 2003).
Since superficial siderosis involves some of the cortical areas thought to be critical for ToM, it remains possible that the mentalizing deficit observed in our patients may be caused by the cortical rather than the cerebellar pathology. In this respect, our data do not allow us to distinguish unambiguously between these two interpretations. However, our data raise the possibility that the cerebellum may be critical in ToM.

In summary, our findings identify a consistent pattern of behavioural abnormalities in patients with superficial siderosis. Mild speech production, visual recall memory, executive and ToM impairments are associated with this condition. Our results concur with previously reported patterns of cognitive profiles in patients with cerebellar lesions (e.g. Schmahmann and Sherman, 1998; Riva and Giorgi, 2000). They suggest that the cerebellum may contribute not only to cognition but also to social cognition. This combination of cognitive and social dysfunction lends greater credibility to the notion of the ‘cerebellar cognitive affective syndrome’, but studies of much more localized lesions will be necessary to confirm this, since in superficial siderosis the damage is too widespread to come to a definitive conclusion.

Acknowledgements

We wish to thank Naomi Martin for her invaluable help with the preparation of the manuscript.

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