Degradation of emotion processing ability in corticobasal syndrome and Alzheimer’s disease

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Disturbed emotion processing and difficulty with social interactions are present to variable degrees in dementia. They are characteristic features of frontotemporal dementia, whereas these deficits tend to be mild in Alzheimer’s disease, reflecting the different patterns of neurodegeneration seen in these disorders. Corticobasal syndrome is an atypical parkinsonian disorder clinically and pathologically related to frontotemporal dementia. Corticobasal syndrome typically presents as a motor disturbance, although cognitive and behavioural changes are now recognized. Pathological changes are found in frontoparietal cortical regions and in the basal ganglia; regions that are heavily involved in emotion processing. Despite the overlap with frontotemporal dementia and the observed regions of brain atrophy, emotion processing has not been systematically explored in corticobasal syndrome. This study aimed to (i) comprehensively examine emotion processing in corticobasal syndrome in comparison to Alzheimer’s disease, to determine whether emotion processing deficits exist in this syndrome, beyond those seen in Alzheimer’s disease; and (ii) identify the neural correlates underlying emotion processing in corticobasal syndrome and Alzheimer’s disease. Sixteen patients with corticobasal syndrome, 18 patients with Alzheimer’s disease and 22 matched healthy control subjects were assessed on a comprehensive battery of face and emotion processing tasks. Behavioural analyses revealed deficits in both basic face processing and high-level emotion processing tasks in patients with corticobasal syndrome. Notably, the emotion processing disturbance persisted even after controlling for face processing deficits. In contrast, patients with Alzheimer’s disease were impaired on high-level complex and cognitively demanding emotion recognition tasks (Ekman 60, The Awareness of Social Inference Test) only. Neuroimaging analyses using FreeSurfer revealed that emotion processing deficits in corticobasal syndrome were associated with basal ganglia volume loss as well as cortical thinning of the left paracentral gyrus/precuneus region. In Alzheimer’s disease, however, emotion processing deficits were associated with atrophy in a different set of brain regions, including the right cingulate and the bilateral insulae, as well as the hippocampi, right amygdala and nucleus accumbens bilaterally. Our results demonstrate that patients with corticobasal syndrome experience widespread deficits in emotion processing, and these deficits are related to changes in brain regions known to be crucial for emotion processing. These findings have important clinical implications for the treatment and management of these patients.
Introduction

Disturbed emotion processing and difficulty engaging in social interactions are hallmark features of frontotemporal dementia (Kipps et al., 2009; Piguet et al., 2011; Kumfor and Piguet, 2012). Emotion processing, however, is not equally affected across different dementia syndromes, with emotion processing and social graces relatively spared in Alzheimer’s disease (Bucks and Radford, 2004; Kumfor and Piguet, 2013). The extent that deficits in emotion processing are present is determined by the pattern of neurodegeneration (Rosen et al., 2006; Kumfor et al., 2013). Cortical regions within the frontal lobe are integral for decoding emotional signals, whereas subcortical regions including the basal ganglia and amygdala are involved in both automatic and controlled emotion processing (for review see Adolphs, 2002). Thus, syndromes where these brain regions are disproportionately affected, such as in frontotemporal dementia, show profound emotion processing deficits (Kumfor and Piguet 2012; Kumfor et al., 2013). Research characterizing the emotion processing disturbance in typical frontotemporal dementia and Alzheimer’s disease syndromes has made significant advances. Presence of such deficits in atypical presentations of these dementias, however, is not known.

Corticobasal syndrome (CBS) is clinically and pathologically related to frontotemporal dementia. Patients with CBS typically present with a constellation of motor and sensory symptoms including asymmetrical ideomotor and limb kinetic apraxia and cortical sensory loss leading to an alien limb. Cognitive impairment and behavioural disturbances are also present and resemble those seen in frontotemporal dementia (Ling et al., 2010; Burrell et al., 2014). On neuroimaging, asymmetrical atrophy and hypometabolism has been reported in the basal ganglia and frontoparietal cortex (Eidelberg et al., 1991; Burrell et al., 2013), regions that play an important role in emotion processing. Association between CBS and the typical corticobasal degeneration pathology varies between 20% and 50%. Recent studies have reported the presence of other tauopathies including frontotemporal lobar degeneration, progressive supranuclear palsy and Alzheimer’s disease pathology, and even in some cases frontotemporal lobar degeneration with TARDBP inclusions, or a combination of Pick’s disease and Alzheimer’s disease pathology (Boeve et al., 2003; Murray et al., 2007; Ling et al., 2010; Rusina et al., 2013). The severity of pathology in the basal ganglia and frontoparietal cortex appear to play a central role in the emergence of the clinical phenotype of CBS, regardless of the type of pathology (Whitwell et al., 2010). Here, we use the term CBS to refer to the clinical syndrome, which is a clinical diagnosis made in accordance with consensus criteria (Belfor et al., 2006; Mathew et al., 2012).

Cognitive and behavioural changes are varied in CBS. Impairments include expressive language deficits due to dysarthria, as well as frank non-fluent aphasia (Graham et al., 2003a). Reductions in visuospatial and/or constructional abilities together with executive dysfunction are also often observed (Soliveri et al., 1999; Kertesz et al., 2000; Graham et al., 2003b; Bak et al., 2006; Kertesz and McMonagle, 2010; Burrell et al., 2013). Behaviourally, patients with CBS show increased levels of depression, anxiety, apathy and irritability as well as behavioural changes that resemble those observed in the behavioural variant of frontotemporal dementia (Litvan et al., 1998; Kertesz et al., 2000). Crucially, the pattern of neurodegeneration seen in CBS and its clinical overlap with frontotemporal dementia, suggest that deficits in emotion processing are likely.

Anecdotal evidence indicates that the ability to express emotions appropriately is compromised in CBS, with flat prosodic speech reported in some individuals (Arima et al., 1994; Kertesz and Munoz, 2003; Kertesz and McMonagle, 2010). Facial apraxia, which manifested as the inability to display emotional expressions, together with a severe impairment in recognizing facial emotional expressions in others, was reported in another patient diagnosed with CBS (Kluger and Heilman, 2007). No systematic investigation of emotion processing ability has been undertaken in CBS to date. Moreover, the relationships between the structures that are the predominant site of brain atrophy (prefrontal cortex and basal ganglia) and emotion processing have not been investigated in this clinical syndrome.

This study aimed to redress this gap in the literature, by comprehensively examining emotion processing ability in CBS. Performance in CBS was compared with Alzheimer’s disease, the most common form of dementia. Although pathological overlap is found in CBS and Alzheimer’s disease, neurodegeneration in Alzheimer’s disease is typically seen more posteriorly and includes the precuneus, posterior cingulate and subcortical regions including the hippocampus, with emotion processing and social graces usually relatively spared, although deficits can emerge with disease progression (Lavenu and Pasquier, 2005; Kumfor and Piguet, 2013; Kumfor et al., 2014). Comparison of CBS with Alzheimer’s disease, as a disease control group, has the added advantage of ensuring that any emotion processing deficits seen in CBS do not simply reflect more generalized cognitive impairment, as a result of neurodegeneration. Based on the evidence reviewed above, we hypothesized that patients with CBS would show deficits in emotion processing compared to patients with Alzheimer’s disease and healthy control subjects.

The second aim of this study was to examine the relationship between regional changes in brain integrity with emotion processing ability to identify the neural correlates of emotion processing in CBS compared with Alzheimer’s disease. While sharing some neural substrates, we predicted that changes in emotion processing in CBS would be associated with atrophy of the frontal cortices together with subcortical regions, specifically the basal ganglia. In contrast, in Alzheimer’s disease, we hypothesized that atrophy in posterior brain regions would be associated with emotion processing ability.
Materials and methods

Participants

Sixteen patients with CBS and 18 with Alzheimer’s disease were recruited for this study. An experienced behavioural neurologist examined all patients and diagnosis was reached by consensus of the multidisciplinary team based on current diagnostic criteria (McKhann et al., 2011; Mathew et al., 2012). Eleven of 16 CBS participants underwent a Pittsburgh compound B (PiB) PET scan at the Austin Hospital, Melbourne, Australia. A mean standardized uptake value > 1.5 was applied to determine whether the scan was positive for PiB uptake, in accordance with previous studies (Leyton et al., 2011). Nine of 11 CBS participants’ scans were PiB negative, confirming absence of underlying amyloid pathology in these cases.

In addition, 22 age- and education-matched healthy control subjects were recruited from the local community. All participants underwent a comprehensive neuropsychological assessment and structural MRI. The cognitive assessment included a general screening measure of cognition [Addenbrooke’s Cognitive Examination-Revised (ACE-R); Mioshi et al., 2006], tests of attention and working memory (Digit Span, Trail Making Test; Wechsler, 1997; Tombaugh, 2004), language (Sydney Language Battery; Savage et al., 2013) and episodic memory ( Rey Complex Figure; Meyers and Meyers, 1995). The Cambridge Behavioural Inventory-Revised was completed by each participant’s informant to measure behaviour change (Wear et al., 2008). We focussed on the subscales investigating loss of motivation and presence of abnormal behaviour, as these measure the behavioural changes typically seen in frontotemporal dementia (Wedderburn et al., 2008). For patients and controls, exclusion criteria included: significant history of neurological or psychological disorders including significant traumatic brain injury with loss of consciousness, and/or use of neuroleptics or other drugs with CNS effects. Patients were also excluded if they scored < 50/100 on the ACE-R and controls if they scored < 88/100 (Mioshi et al., 2006).

The Southeastern Sydney Local Health District and the University of New South Wales ethics committees approved the study. Participants or their Person Responsible provided informed consent in accordance with the Declaration of Helsinki. All participants volunteered their time, but were reimbursed for any travel expenses.

Emotion processing assessment

A comprehensive emotion processing assessment was used to assess face processing, facial emotion recognition and dynamic emotion recognition.

Facial emotion recognition task

Four tasks were used to study the different cognitive processes involved in facial emotion recognition as described previously (Miller et al., 2012) (Fig. 1).

The face-perception task is a simple discrimination task where participants view 40 pairs of neutral faces one at a time, and need to determine whether the faces are identical or different.

Face-Matching, Emotion-Matching, and Emotion-Selection Tasks consisted of 42 trials each, and faces displayed one of the six basic emotions (anger, disgust, fear, sadness, surprise, or happiness) or were neutral.

The Face-Matching Task examines the ability to identify a face across different emotions. Participants are shown pairs of faces expressing different emotional expressions and need to indicate whether the faces belong to the same person.

The Emotion-Matching Task measures the ability to match facial emotions across different faces. Participants view pairs of different faces, displaying emotional expressions and need to indicate whether the two faces are showing the same emotional expression.

The emotion-selection task measures the ability to select a facial expression based on a verbal label. Participants view arrays of seven faces of the same person displaying the six basic emotions (anger, disgust, fear, sadness, surprise, happiness) and a neutral expression. Participants are instructed to point to the face corresponding to the label spoken by the examiner (e.g. ‘Point to the happy face’). For participants with motor deficits or apraxia, verbal responses are also accepted. Faces and position of emotions on the screen vary across trials, and are adequately spaced to minimize the need for precise motor control.

Images were selected from the NimStim stimulus set (www.macbrain.org). Faces were cropped so that non-facial features (e.g. hair) were removed, and for each task, faces were displayed in greyscale on a computer screen. Responding was untimed and no feedback was provided. Scores were available for 14 patients with CBS, 18 patients with Alzheimer’s disease and 21 control subjects on this task.

Ekman 60 Task

This task evaluates the recognition of six basic emotions (anger, disgust, fear, sadness, surprise, happiness), using stimuli from the Pictures of Facial Affect series (Young et al., 2002). The 60 items use six different models, and pictures are randomly presented. Each image appears for 5 s, and participants are instructed to select the label that best describes the emotional expression. Participants may answer either verbally or by pointing to the label with their hand or the mouse.

The Awareness of Social Inference Test

This test assesses the ability to recognize dynamic displays of emotion, by combining facial, vocal, and behavioural expressions (McDonald et al., 2003). Participants watch short videos (15–60 s) and are instructed to identify the dominant emotion of the person in the scene (anger, revulsion/disgust, anxiety/fear, sadness, surprise, happiness, neutral). Twenty-eight scenes are presented, and participants provide their response verbally or by completing a response sheet. Scores were available for 13 patients with CBS, 18 with Alzheimer’s disease and 22 control subjects on this task.

Brain image acquisition and processing

MRI scan

All participants underwent whole brain structural MRI with a 3 T Phillips scanner using a standard 8-channel head coil. MRI scans were obtained on average, within 2 months of the behavioural assessment. 3D high-resolution turbo field echo T1-weighted sequences were acquired with the following parameters: coronal orientation, matrix 256 x 256, 200 slices, 1 mm2 in-plane resolution, slice thickness 1 mm, echo time/repetition time 2.6/5.8 ms, flip angle a = 19°. Before analyses, the two T1 volumes were merged and averaged to increase the signal to noise ratio and the grey matter-white matter contrasts in brain structures.

The T1 volumes were processed using FreeSurfer version 5.1 (http://surfer.nmr.mgh.harvard.edu). This software is a set of automated tools for reconstruction of the brain’s cortical surface and subcortical nuclei from structural MRI data (Fischl and Dale, 2000). Briefly, images were
Statistical analyses

Behavioural analyses

All statistical analyses were performed using SPSS Statistics, 20.0 (IBM). Demographic variables were analysed using univariate ANOVA. Neuropsychological tests were analysed using multivariate ANOVA followed by Sidak correction for multiple comparisons. For the Ekman 60 and The Awareness of Social Inference Test (TASIT), two separate repeated measures analyses were conducted with Emotion (anger, disgust, fear, sadness, surprise, happiness) as the within subjects variable and Diagnosis (CBS, Alzheimer’s disease, control) as the between subjects variable. Post hoc analyses using Sidak correction for multiple comparisons were conducted to examine interaction and main effects. Statistical significance was set at $P = 0.05$.

Finally, Pearson correlations were conducted to examine the relationship between emotion processing performance and cognitive or behavioural variables.

Cortical thickness analyses

Sets of vertex-by-vertex analyses were performed using general linear models aimed to examine in the first instance differences in cortical thickness between groups and then to estimate the neural correlates for the emotion processing tasks where both CBS and Alzheimer’s disease groups were impaired compared to controls (Ekman 60, TASIT). In the first set of analyses, overall cortical thickness of both hemispheres was modelled according to diagnostic group. In the second set of analyses, we created two separate general linear models, one for each emotion processing task. Each model included the following regressors: diagnosis (CBS and Alzheimer’s disease), the behavioural variable (either Ekman 60 or TASIT) and the interaction between diagnosis and the behavioural variable. To determine behavioural associations with cortical thickness specific to diagnosis group, we focused on the interaction effect between diagnosis and the behavioural variable. To determine behavioural associations with cortical thickness specific to diagnosis group, we focused on the interaction effect between diagnosis and the behavioural variable. The correlations in both groups combined are reported in Supplementary Table 2 and Supplementary Fig. 3. Statistical significance was set at $P = 0.001$ uncorrected for multiple comparisons. In addition, we used a conservative cluster extent threshold of $k > 50 \text{mm}^2$. This approach is designed to minimize Type I error while balancing the risk of Type II error (Lieberman and Cunningham, 2009). Effect sizes for each cluster were also calculated according to the formula by Cohen, in line with previous studies (Hilti et al., 2013).

Subcortical volumes analysis

Subcortical volumes were extracted for the following regions of interest: thalamus, caudate, putamen, pallidum, hippocampus, amygdala and nucleus accumbens and corrected for intracranial volume using the following formula: (Volume of interest/total intracranial volume) × 1000. Pearson correlations were conducted in each patient group combined with controls to determine whether different subcortical volumes correlated with performance on the Ekman 60 and TASIT, according to diagnostic group. This approach was taken to maximize statistical power. Correlation analyses were corrected for multiple comparisons using Bonferroni ($\alpha/k$: $P < 0.003$).

Results

Demographics and neuropsychological performance

All groups were matched for sex, age and education and patient groups were matched for disease duration (Table 1).

Performance on standard neuropsychological tests was consistent with the cognitive profiles typically seen in CBS and Alzheimer’s disease (Table 2). In brief, the CBS group was impaired compared to controls on tasks of general cognition (ACE-R), visuospatial ability (Rey Complex Figure Copy), visuomotor processing speed (Trails A), working memory (Digit Span Forwards), and language (Sydney Language Battery). Specifically,
the CBS group performed below control subjects on tasks assessing word repetition, confrontation naming, word comprehension and semantic association. The Alzheimer’s disease group was also impaired across most neuropsychological tests, but showed worse performance than the CBS group on tasks of memory (ACE-R Memory subscale, Rey Complex Figure Recall) and were less impaired than patients with CBS on a task of visuomotor speed (Trails A). Behavioural changes were present in both patient groups, with both CBS and Alzheimer’s disease showing increased abnormal behaviour and increased apathy. No difference, however, was observed between CBS and Alzheimer’s disease (Table 2).

### Emotion processing performance

#### Facial emotion recognition task

Patients with CBS performed worse than controls on the facial emotion recognition tasks, whereas patients with Alzheimer’s disease showed relatively intact performance. Specifically, a significant effect of Diagnosis was identified on each of the four tasks [Face-Perception: $F(2,50) = 4.037$, $P = 0.024$; Face-Matching: $F(2,50) = 3.388$, $P = 0.042$; Emotion-Matching: $F(2,50) = 7.691$, $P = 0.001$; Emotion-Selection: $F(2,50) = 11.132$, $P < 0.001$]. Post hoc analyses revealed that the CBS group performed worse than controls on the Face-Perception, Emotion-Matching and Emotion-Selection Tasks (all $P$-values $< 0.05$). No difference between CBS and controls was present on the Face-Matching Task ($P > 0.05$). In contrast, the Alzheimer’s disease group performed at the same level as controls on the Face-Perception, Face-Matching and Emotion-Matching Tasks (all $P$-values $> 0.05$), although a trend for worse performance on the Emotion-Selection Task was observed ($P = 0.059$) (Fig. 2A).

### Table 1 Demographic characteristics of the patients with CBS, Alzheimer’s disease and control subjects

<table>
<thead>
<tr>
<th></th>
<th>CBS $n = 16$</th>
<th>Alzheimer’s disease $n = 18$</th>
<th>Controls $n = 22$</th>
<th>F</th>
<th>Post hoc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male:female</td>
<td>8:8</td>
<td>12:6</td>
<td>11:11</td>
<td>1.37a</td>
<td>ns</td>
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<tr>
<td>Age (years)</td>
<td>64.8±6.2</td>
<td>65.7±7.0</td>
<td>65.0±5.7</td>
<td>0.10</td>
<td>ns</td>
</tr>
<tr>
<td>Education (years)</td>
<td>11.3±3.0</td>
<td>11.9±3.2</td>
<td>12.2±1.7</td>
<td>0.59</td>
<td>ns</td>
</tr>
<tr>
<td>Disease duration (months)</td>
<td>52.5±35.2</td>
<td>43.2±27.6</td>
<td>–</td>
<td>0.75</td>
<td>ns</td>
</tr>
</tbody>
</table>

Values are: mean ± standard deviation. Statistical significance was set at $P < 0.05$; ns = not significant.

*Pearson $\chi^2$ value.

### Table 2 Cognitive and behavioural performance in patients with CBS, Alzheimer’s disease and control subjects

<table>
<thead>
<tr>
<th></th>
<th>CBS $n = 16$</th>
<th>Alzheimer’s disease $n = 18$</th>
<th>Controls $n = 22$</th>
<th>F</th>
<th>Post hoc</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-R</td>
<td></td>
<td></td>
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<tr>
<td>Total (100)</td>
<td>78.3±11.6</td>
<td>77.7±11.0</td>
<td>94.7±3.0</td>
<td>***</td>
<td>Patients &lt; controls; CBS = AD</td>
</tr>
<tr>
<td>Attention (18)</td>
<td>17.0±1.3</td>
<td>16.4±1.6</td>
<td>17.8±0.4</td>
<td>**</td>
<td>AD &lt; controls</td>
</tr>
<tr>
<td>Fluency (14)</td>
<td>7.3±4.6</td>
<td>8.2±3.1</td>
<td>12.4±1.4</td>
<td>***</td>
<td>Patients &lt; controls; CBS = AD</td>
</tr>
<tr>
<td>Memory (26)</td>
<td>20.5±4.2</td>
<td>16.2±5.2</td>
<td>24.1±1.7</td>
<td>***</td>
<td>Patients &lt; controls; CBS = AD</td>
</tr>
<tr>
<td>Language (26)</td>
<td>21.6±2.8</td>
<td>22.6±2.8</td>
<td>25.1±1.3</td>
<td>***</td>
<td>Patients &lt; controls; CBS = AD</td>
</tr>
<tr>
<td>Visuospatial (16)</td>
<td>12.0±3.0</td>
<td>14.4±2.9</td>
<td>15.3±1.0</td>
<td>***</td>
<td>CBS &lt; controls</td>
</tr>
<tr>
<td>Digit Span</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Forwards span</td>
<td>5.9±1.6</td>
<td>5.8±1.3</td>
<td>6.9±1.4</td>
<td>*</td>
<td>AD &lt; controls</td>
</tr>
<tr>
<td>Backwards span</td>
<td>3.9±1.0</td>
<td>4.1±1.1</td>
<td>5.0±1.3</td>
<td>**</td>
<td>CBS &lt; controls</td>
</tr>
<tr>
<td>Trails</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Part A (s)</td>
<td>115.3±90.9</td>
<td>69.8±43.2</td>
<td>32.8±13.1</td>
<td>***</td>
<td>CBS &gt; controls</td>
</tr>
<tr>
<td>Part B (s)</td>
<td>181.1±73.7</td>
<td>150.6±76.9</td>
<td>83.6±25.5</td>
<td>***</td>
<td>Patients &gt; controls; CBS = AD</td>
</tr>
<tr>
<td>SYDBAT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naming (30)</td>
<td>22.3±3.0</td>
<td>21.6±3.7</td>
<td>27.0±2.2</td>
<td>***</td>
<td>Patients &lt; controls; CBS = AD</td>
</tr>
<tr>
<td>Comprehension (30)</td>
<td>26.0±3.7</td>
<td>27.1±2.2</td>
<td>28.9±1.7</td>
<td>**</td>
<td>CBS &lt; controls</td>
</tr>
<tr>
<td>Repetition (30)</td>
<td>28.7±1.2</td>
<td>29.3±0.8</td>
<td>30.0±0.2</td>
<td>***</td>
<td>CBS &lt; controls</td>
</tr>
<tr>
<td>Semantic (30)</td>
<td>24.8±2.1</td>
<td>25.7±2.3</td>
<td>27.7±1.8</td>
<td>***</td>
<td>Patients &lt; controls; CBS = AD</td>
</tr>
<tr>
<td>Rey Complex Figure</td>
<td></td>
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<tr>
<td>Copy (36)</td>
<td>23.0±8.4</td>
<td>27.5±9.4</td>
<td>31.8±3.9</td>
<td>**</td>
<td>CBS &lt; controls</td>
</tr>
<tr>
<td>Recall (36)</td>
<td>11.7±4.9</td>
<td>4.4±4.5</td>
<td>17.1±4.8</td>
<td>***</td>
<td>Patients &lt; controls; AD &lt; CBS</td>
</tr>
<tr>
<td>CBI</td>
<td></td>
<td></td>
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<tr>
<td>Abnormal behaviour</td>
<td>15.6±17.0</td>
<td>10.9±10.6</td>
<td>2.2±3.7</td>
<td>**</td>
<td>Patients &gt; controls</td>
</tr>
<tr>
<td>Loss of motivation</td>
<td>46.0±31.5</td>
<td>30.0±31.1</td>
<td>1.0±2.1</td>
<td>***</td>
<td>Patients &gt; controls</td>
</tr>
</tbody>
</table>

Values are: mean ± standard deviation. Values in parentheses indicate maximum scores.

F test: $^* P < 0.05$; $^{**} P < 0.01$; $^{***} P < 0.001$. Post hoc: Sidak correction.

AD = Alzheimer’s disease; CBI = Cambridge Behavioural Inventory-Revised.

Missing scores or test discontinued: Trails A: one CBS, one Alzheimer’s disease; Trails B: six CBS, four Alzheimer’s disease; SYDBAT: one control; Rey Complex Figure Copy: one control, five CBS; Rey Complex Figure Recall: one control, seven CBS. CBS patients who were unable to adequately control a pencil, were not administered the Rey Complex Figure. Cambridge Behavioural Inventory-Revised: two Alzheimer’s disease, one control.
Given the significant difficulty the CBS patients demonstrated on the Face-Perception task, we re-analysed the data including this score as a covariate, to determine the extent that face perception difficulties were contributing to performance on the emotion recognition tasks. The main effect of Diagnosis remained significant on the Emotion-Matching \((P = 0.003)\) and Emotion-Selection \((P < 0.001)\) Tasks, with CBS performing significantly worse than controls on both tasks \((P\text{-values} < 0.05)\) indicating that deficits in face perception alone, do not account for the emotion recognition deficits observed in these patients. The Alzheimer’s disease group also showed a trend to perform worse than controls on the Emotion-Selection task after covarying for Face Perception performance \((P = 0.056)\) (Fig. 2B).

**Ekman 60 Task**

On the Ekman 60, a main effect of Diagnosis was present \([F(2,53) = 11.699, \ P < 0.001]\), with CBS \((P < 0.001)\) and Alzheimer’s disease \((P = 0.002)\) performing worse than control subjects. No difference between CBS and Alzheimer’s disease groups was present, averaged across emotions \((P > 0.05)\). The main effect of Emotion was significant \([F(4,206) = 40.678, \ P < 0.001]\), with positive emotions typically recognized better than negative emotions. An Emotion \(\times\) Diagnosis interaction was also present \([F(8,206 = 3.373, P = 0.001)\]. Both CBS and patients with Alzheimer’s disease performed worse than controls on all negative emotions \((all\ P\text{-values} < 0.05)\), but within normal limits for recognition of surprise and happiness \((P > 0.05)\). No difference was observed between CBS and Alzheimer’s disease groups on each of the individual emotions \((all\ P\text{-values} > 0.05)\) (Fig. 3).

**The Awareness of Social Inference Test**

On the TASIT, a task that examines the ability to recognize emotions under ecologically valid conditions, the overall effect of Diagnosis was again significant \([F(2,50) = 17.388, \ P < 0.001]\), with CBS \((P < 0.001)\) and Alzheimer’s disease \((P < 0.001)\) performing worse than controls. No difference in performance between patient groups was observed \((P > 0.05)\). An overall effect of Emotion was significant \([F(5,228) = 11.350, P < 0.001]\), although the Diagnosis \(\times\) Emotion interaction was not significant \([F(9,228) = 0.856, P > 0.05]\). Post hoc analyses revealed that the CBS group performed worse than controls for the emotions disgust/revulsion, anxiety/fear, sadness, surprise, and happiness \((all\ P\text{-values} < 0.05)\) and also demonstrated a trend for worse recognition of anger \((P = 0.064)\), while recognition of neutral vignettes was within normal limits \((P > 0.05)\). In contrast, patients with Alzheimer’s disease performed worse than controls for the recognition of disgust/revulsion, sadness, surprise and happiness \((P < 0.05)\), but not anger, anxiety/fear or neutral displays of emotion \((P\text{-values} > 0.05)\) (Fig. 3).

**Correlations with cognitive and behavioural performance**

Correlations between emotion processing and cognitive and behavioural variables are reported in Supplementary Table 3. The results revealed distinct associations according to patient group. In CBS, the only significant correlation was between performance on the Face-Perception task and visuospatial performance on the Rey Complex Figure copy \((r = 0.867, P = 0.001)\). In contrast, the only significant association in the Alzheimer’s disease group was between the Emotion-Selection task and word comprehension subtest of the Sydney Language Battery \((r = 0.774; P < 0.001)\).

**Pittsburgh compound B status**

Given the variable pathology associated with a clinical diagnosis of CBS, we examined whether performance differed on the cognitive and emotion processing tasks, according to the individual’s PiB status. Examination of performance on the ACE-R, Emotion-Selection task, Ekman 60 and TASIT revealed no clear differences in profiles of performance according to PiB status and results from

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**Figure 2** (A) Facial emotion recognition performance on the Face-Perception task, Face-Matching Task, Emotion-Matching Task and Emotion-Selection Task in patients with CBS, Alzheimer’s disease and controls. (B) Estimated marginal means on the facial emotion recognition tasks after covarying for Face-Perception performance. Scores missing for two patients with CBS and one control participant. *Post hoc* between group comparisons \(P < 0.05\). Sidak correction for multiple comparisons. A trend for worse performance in the Alzheimer’s disease group compared with controls was present for the Emotion-Selection Task \((P = 0.059)\) and this remained after covarying for Face-Perception ability \((P = 0.056)\).
the statistical analyses remained largely the same after excluding the two PiB positive cases (Supplementary Fig. 1).

**Neural correlates of emotion processing**

FreeSurfer analyses examining discrete neural correlates in CBS and Alzheimer’s disease revealed distinct regions associated with performance on the high-level emotion processing tasks (Ekman 60, TASIT) according to diagnosis (Fig. 4 and Table 3). In CBS, worse performance on the Ekman 60 was associated with cortical thinning in the left paracentral gyrus/precuneus region. No significant cortical clusters were found on the TASIT; however, significant correlations were observed between TASIT performance and several subcortical volumes: left caudate (r = 0.538; P = 0.001), left putamen (r = 0.603; P < 0.001) and left hippocampus (r = 0.562; P < 0.001) (Fig. 5 and Supplementary Table 3). No significant associations were observed between subcortical regions and Ekman 60 performance in CBS.

In the Alzheimer’s disease group, performance on the Ekman 60 was associated with cortical thinning in the insula bilaterally. Performance on the TASIT was also associated with cortical thinning in the right insula, together with the right anterior cingulate (Fig. 4 and Table 3). Performance on the Ekman 60 was also significantly associated with the right hippocampus volume (r = 0.510, P = 0.001). In addition, TASIT performance correlated with hippocampal volume bilaterally (Left: r = 0.591; P < 0.001; Right: r = 0.582; P < 0.001), together with the right amygdala (r = 0.493; P = 0.001), bilateral accumbens (Left: r = 0.492; P = 0.001; Right: r = 0.466; P = 0.002) and bilateral putamen (Left: r = 0.482; P = 0.002; Right: r = 0.469; P = 0.002) (Fig. 5 and Supplementary Table 3).

Patterns of cortical thickness and subcortical volumes according to diagnostic group are presented and discussed in the Supplementary material.

**Discussion**

Here, we systematically examined emotion processing in CBS compared to Alzheimer’s disease and revealed the presence of an emotion processing disturbance in CBS, affecting basic and high-level facial and dynamic emotion recognition. These emotion recognition deficits seem to be more pronounced than those seen in Alzheimer’s disease. Importantly, our neuroimaging analyses reveal that these high-level emotion processing deficits in CBS are associated with atrophy of the paracentral gyrus/precuneus region, as well as the basal ganglia. In contrast, Alzheimer’s disease performance was impaired on the complex and cognitively demanding high-level emotion processing tasks only (Ekman 60, TASIT). In this group, correlations with brain atrophy revealed associations between emotion processing task performance and cortical thickness in the anterior cingulate and insula, together with the hippocampus, amygdala and nucleus accumbens. Here, we discuss how our results inform understanding of the socio-emotional deficits in CBS with respect to Alzheimer’s disease.

Patients with CBS showed widespread impairment of emotion recognition, more so than patients with Alzheimer’s disease, with a tendency for negative emotions to be more affected than positive emotions. This profile resembles the pattern of performance typically seen in patients with frontotemporal dementia (Fernandez-Duque and Black, 2005; Kumfor and Piguet, 2012). Importantly, the deficits in CBS were present despite the fact that, compared to Alzheimer’s disease, this group showed less extensive brain atrophy and similar levels of disease severity and cognitive ability. This finding suggests that impaired emotion recognition in CBS is not simply an artefact of reduced cognitive ability or of disease severity. Marked visuospatial functioning deficits have been previously reported in CBS (Bak et al., 2006). Our results indicate that these deficits may also impact upon CBS patients’ basic facial perception abilities, with a significant association between visuospatial ability and basic face perception ability observed in this group. Although no associations were observed for the other emotion processing tasks, it is plausible that CBS performance is influenced by the visual complexity of the stimuli. Future studies may consider examining the relationship between visuospatial functioning and emotion processing in these patients. Although impaired face processing in CBS contributed to emotion processing performance, it did not fully account for the degradation of emotion processing in these patients. Interestingly, a similar pattern was observed in a CBS case study investigating emotion processing. While this individual exhibited basic face processing deficits, performance on high-level facial and dynamic emotion recognition.

**Figure 3** Ekman 60 and TASIT performance in CBS, Alzheimer’s disease and controls. *Post hoc between group comparisons P < 0.05. Sidak correction for multiple comparisons. Ang = anger; Dis = disgust/revulsion; Foa = fear/anxiety; Sad = sadness; Sur = surprise; Hap = happiness; Neu = neutral. Scores missing for three patients with CBS on the TASIT. A trend for worse recognition of anger on the TASIT was present in the CBS group (P = 0.064).
high-level emotion processing tasks was in comparison more greatly affected (Kluger and Heilman, 2007), providing additional support for a central emotion processing deficit in CBS.

The primary emotion processing deficit uncovered in CBS is corroborated by our neuroimaging investigations. Investigation of the role of subcortical regions in emotion processing revealed that the integrity of the basal ganglia and hippocampus are critical for high-level emotion processing in CBS. Growing evidence now supports the crucial role of the basal ganglia in recognising emotions. Studies on patients with focal lesions involving the basal ganglia or on patients diagnosed with Huntington’s disease indicate that this structure is important for emotion processing and may play a specific role in disgust recognition (Sprengelmeyer et al., 1996; Adolphs et al., 2000; Adolphs, 2002). Indeed, our results are remarkably consistent with a case study of an individual with a focal caudate lesion who showed specific deficits in recognition of negative emotions, empathy and affective theory of mind (Kemp et al., 2012). The authors postulated that disconnection in frontostriatal loops, specifically between frontocortical structures and the caudate, were responsible for these deficits. Notably, the ventromedial portion of the caudate projects to the pallidum, thalamus and orbitofrontal cortex (Alexander et al., 1986; O’Callaghan et al., 2014), which has been associated with disturbed facial emotion recognition in patients with frontotemporal dementia (Kumfor et al., 2013). When examining the cortical mantle, the paracentral gyrus/precuneus region was the only neural correlate associated

Figure 4  Regions of significant correlations between cortical thickness and performance on the Ekman 60 and TASIT in CBS (blue) and Alzheimer’s disease (AD, red) participants. Statistical significance was set at $P < 0.001$ uncorrected for multiple comparisons.

Table 3  Regions of cortical thickness significantly associated with emotion processing in patients with corticobasal syndrome and Alzheimer’s disease

<table>
<thead>
<tr>
<th>Anatomical location</th>
<th>Side</th>
<th>Cluster size (mm$^2$)</th>
<th>Number of vertices</th>
<th>Talairach coordinates</th>
<th>t value</th>
<th>$P$-value</th>
<th>Effect size (Cohen’s d)</th>
<th>Effect size ($r$)</th>
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<tbody>
<tr>
<td><strong>Ekman 60</strong></td>
<td><strong>Corticobasal syndrome</strong></td>
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<tr>
<td>Paracentral gyrus/precuneus</td>
<td>Left</td>
<td>173.1</td>
<td>390</td>
<td>$(x, y, z) = (-9.3, -37.0, 61.2)$</td>
<td>-4.3</td>
<td>0.0001</td>
<td>1.58</td>
<td>0.62</td>
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<tr>
<td>Alzheimer’s disease</td>
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<tr>
<td>Inferior insula</td>
<td>Left</td>
<td>89.7</td>
<td>256</td>
<td>$(x, y, z) = (-39.4, -10.3, -12.4)$</td>
<td>4.3</td>
<td>0.0001</td>
<td>1.58</td>
<td>0.62</td>
</tr>
<tr>
<td>Inferior insula</td>
<td>Right</td>
<td>76.5</td>
<td>239</td>
<td>$(x, y, z) = (40.5, -6.2, -14.4)$</td>
<td>3.93</td>
<td>0.0005</td>
<td>1.43</td>
<td>0.58</td>
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<td><strong>TASIT</strong></td>
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<td>Corticobasal syndrome</td>
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<td>No significant clusters</td>
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<td>Alzheimer’s disease</td>
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<tr>
<td>Middle anterior cingulate</td>
<td>Right</td>
<td>198.0</td>
<td>527</td>
<td>$(x, y, z) = (12.3, 10.9, 33.6)$</td>
<td>4.8</td>
<td>$&lt;0.0001$</td>
<td>1.84</td>
<td>0.68</td>
</tr>
<tr>
<td>Inferior insula</td>
<td>Right</td>
<td>68.7</td>
<td>204</td>
<td>$(x, y, z) = (42.4, -6.6, -14.8)$</td>
<td>4.1</td>
<td>0.0003</td>
<td>1.59</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Effect size was computed according to the formula by Cohen. Clusters were thresholded at $P < 0.001$ (uncorrected for multiple comparisons), with a cluster extent threshold of $k > 50$ mm$^2$. Coordinates and $P$-values refer to the maximum vertex within the cluster.
with emotion recognition in CBS. Functional neuroimaging studies have previously reported the involvement of the precuneus in aspects of self-awareness and self-consciousness (for review see Cavanna and Trimble, 2006) and during emotional state attributions to one self and to others (Ochsner et al., 2004). Notably, the precuneus projects to the caudate and striatum (Cavanna and Trimble, 2006), regions which were also associated with emotion processing deficits in CBS here. It is possible that disconnection between cortical and subcortical structures underlies the emotion processing deficits seen in CBS (Choi et al., 2012). Investigations of functional and structural connectivity in these patients will be important in testing this hypothesis further.

In Alzheimer’s disease, emotion processing deficits were present on the complex and cognitively demanding emotion recognition tasks only (Ekman 60, TASIT), whereas behavioural performance on the simple face processing and Emotion-Matching Tasks was within normal limits. The Ekman 60 and TASIT require the participant to match a real-world emotional display with the appropriate emotional word. In contrast, the Facial Emotion Recognition tasks provide concrete examples of the emotional display, and therefore require less abstraction to perform successfully, placing less demand on the participant. The finding that patients with Alzheimer’s disease show higher-level emotion processing deficits only, is consistent with the view that emotion processing deficits in Alzheimer’s disease tend to be mild and seem to emerge in the latter stages of the disease (Lavenu and Pasquier, 2005; Kumfor and Piguet, 2013) as neurodegenerative changes become more widespread. Volume loss in the amygdala, hippocampus and nucleus accumbens was associated with poorer emotion recognition performance in Alzheimer’s disease. The crucial role of the amygdala in processing negative emotions, particularly fear, is well recognized (Adolphs et al., 1994; Phan et al., 2002). The nucleus accumbens is typically associated with reward processing, although this region, together with the amygdala and hippocampus, has also been shown to activate in response to positive, social emotions, suggesting it is also involved in some aspects of emotion processing (Britton et al., 2006). In the Alzheimer’s disease group, cortical thickness analyses indicated that emotion processing deficits were associated with thinning of the insula and anterior cingulate. These regions are known to activate in healthy adults during the recognition of negative emotions (Phan et al., 2002, 2004), confirming the important role these regions play, in high-level emotion processing. In addition to these regions, the anterior cingulate was the only cortical region that was associated with emotion processing ability in both patient groups combined. The anterior cingulate is part of the limbic system and is implicated in attention and emotion (Bush et al., 2000). Interestingly, the anterior cingulate is also associated with the emotion recognition deficits in typical frontotemporal dementia (Kumfor et al., 2013). Together, our results indicate that the emotion processing deficits seen in CBS are more widespread than those seen in Alzheimer’s disease. Further, these emotion processing deficits are due to both common and distinct cortical and subcortical regions that are implicated in emotion processing.

Although absence of pathological confirmation in CBS cases may seem to be a potential limitation of the present study, in vivo pathological investigations with PiB-PET showed a highly homogeneous study sample. Nine of 11 patients showed negative PiB-PET results, with only two positive for underlying Alzheimer’s pathology, which nevertheless falls broadly under the tauopathy umbrella. Further correlation between clinical features and underlying histopathology, for example whether emotion processing
differs in CBS due to different underlying pathologies, cannot be specifically addressed by the present study. Nonetheless, it is reassuring that the main findings were unchanged when the two CBS cases due to Alzheimer’s pathology were excluded. Importantly, all CBS cases included here demonstrated the core features of the syndrome consistently (e.g. asymmetrical parkinsonism and limb apraxia), in accordance with the newly proposed diagnostic criteria (Mathew et al., 2012). One interpretation of this observation is that the clinical phenotype is a reflection of the distribution of neuropathology, rather than the specific molecular abnormality per se (Whitwell et al., 2010). A second issue to consider is that our neuroimaging results were reported uncorrected for multiple comparisons at $P < 0.001$, as they did not survive conservative corrections. To guard against the potential risk of false positive results we applied an additional conservative cluster extent threshold of $k \geq 50 \text{mm}^2$. This approach reduces the risk of type I error while balancing the potential risk of type II error, without compromising the statistical power of the study (Forman et al., 1995; Lieberman and Cunningham, 2009). In addition, we calculated effect sizes for our neuroimaging results, which were all in the medium-high range, providing further support for our findings.

Perhaps unsurprisingly, previous studies in CBS have focussed on the motor disturbance and more recently the cognitive changes experienced by these patients. In this study, we comprehensively examined emotion processing and demonstrated a consistent impairment in the ability to interpret static and dynamic emotional expressions in this clinical syndrome, which are associated with changes in brain regions known to be necessary for successful emotion processing. These findings have important clinical implications for the treatment and management of these patients. The presence of neuropsychiatric features in CBS, including depression, apathy, irritability and agitation have been reported in a large number of patients (Litvan et al., 1998). It is possible that these features are in part due to a global disturbance of emotion processing. Difficulties in understanding subtle social signals, together with a reduced capacity to participate meaningfully in social interactions may impact on the overall mood and behaviour of patients with CBS, which future studies will need to investigate further. The deficits in emotion processing may also contribute to a lack of insight in these patients. A previous study which examined the relationship between cognitive and emotional abilities and insight in CBS, progressive supranuclear palsy and frontotemporal dementia, reported that reduced metacognitive and anticipatory awareness was associated with poor emotion recognition ability in these groups combined, suggesting that deficits in emotion recognition may also impact on insight, foresight and the ability to make social judgements (O’Keeffe et al., 2007). Our results provide convincing grounds to more closely examine socioemotional processing in CBS, with the view to better understanding how these deficits impact on mood, functioning and behaviour.

In summary, this study has comprehensively examined emotion processing in CBS and demonstrated that pervasive deficits in these abilities exist in these patients, which are due to degradation of the paracentral gyrus/precuneus region and subcortical basal ganglia structures including the caudate. These results reveal that CBS affects not only motor and cognitive abilities, but also significantly impacts upon emotion processing.

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Supplementary material

Supplementary material is available at Brain online.

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