

## Research article

### Pronounced impairment of activities of daily living in posterior cortical atrophy

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**Short title:** Activities of daily living in PCA

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Attention; Memory.

1 **Abstract**

2 **Introduction:** The impact of several dementia syndromes on activities of daily living (ADLs)  
3 has been well documented, but no study has yet investigated functional ability in posterior  
4 cortical atrophy (PCA). The primarily visual nature of deficits in this condition is likely to  
5 have a pronounced impact on ADLs.

6 **Objective:** To profile functional change in PCA and identify predictors of change.

7 **Method:** 29 PCA patients and 25 patients with typical Alzheimer’s disease (AD) and their  
8 caregivers were included in this cross-sectional study. ADLs were assessed using the  
9 Disability Assessment for Dementia (DAD), administered to caregivers, assessing basic  
10 ADLs (e.g. eating, dressing) and instrumental ADLs (e.g. managing finances, meal  
11 preparation). The predictive utility of cognitive domains (ACE), behavioural impairment  
12 (CBI-R) and demographic variables on ADL ability was also examined.

13 **Results:** PCA patients showed significantly reduced total ADL scores compared to AD  
14 patients (medium effect size,  $d = -0.7$ ;  $p < 0.05$ ), with significantly more impairment on basic  
15 ADLs (large effect size,  $d = -0.8$ ;  $p < 0.05$ ), but similar impairment on instrumental ADLs  
16 (medium effect size,  $d = -0.5$ ;  $p > 0.05$ ). A model combining patient mood, disinhibition,  
17 apathy, symptom duration, and memory and attention/orientation scores explained the  
18 variance of scores in functional decline (61.2%), but the key factor predicting ADL scores  
19 was attention/orientation ( $p = .048$ ).

20 **Conclusion:** This study shows the profound impact of PCA on ADLs and factors  
21 underpinning their disability. Attention/orientation deficits were found to correlate and  
22 contribute to variance in ADL scores. Future work to develop tailored interventions to  
23 manage ADL impairment in PCA should take these findings into account.

24

25 **Introduction**

26

27 Establishing a diagnosis of dementia requires observation of a decline in cognition, and this  
28 decline must be severe enough to interfere with functional ability. Recently published  
29 consensus criteria for posterior cortical atrophy (PCA) (1) require this same evidence,  
30 representing a decline from a previous higher level of independent functioning. PCA is  
31 defined by a constellation of symptoms that fall broadly into the visual, perceptual and  
32 visuospatial domains (2, 3), alongside atrophy, hypometabolism or hypoperfusion  
33 predominantly in parieto-occipital or temporo-occipital cortices.

34

35 Assessing ADLs reduces misdiagnosis based on over-interpretation of a change in cognition  
36 or sub-normal test scores, particularly in early stages. Functional measures have been shown  
37 to support early diagnosis of syndrome specific cognitive changes (4, 5), track the  
38 longitudinal course of disease (6, 7), inform tailored interventions to support independent  
39 living (8), and indicate caregiver outcomes (8). Regulatory guidelines for pharmacological  
40 trials in dementia recommend the incorporation of ADL scales to detect meaningful and  
41 ecologically valid change, as well as assess the efficacy of an intervention.

42

43 ADLs are typically divided into basic activities, (e.g. eating) and instrumental activities,  
44 comprising more complex tasks (e.g. managing finances) (9). The impact of several dementia  
45 syndromes on ADLs has been well documented, showing broadly that instrumental ADLs are  
46 more affected than basic ADLs (e.g. (4)). Few studies have been undertaken to describe how  
47 a diagnosis of PCA impacts ADLs. Shakespeare et al. (10) used the Cambridge Behavioural  
48 Inventory to show a loss of independence in everyday skills and self-care, and cases studies  
49 (11, 12) support this finding of a loss of autonomy. The primarily visual nature of deficits in

50 PCA are likely to have a pronounced impact on ADLs and thus a more extensive profile of  
51 impairment is needed.

52

53 The aim of this study was to determine (i) the profile of functional change in PCA, and (ii)  
54 the predictive utility of cognition, behavioural and demographic variables on overall ADL  
55 ability.

56

## 57 **Materials and Methods**

58

### 59 *Participants*

60

61 29 PCA patients and caregivers were recruited through the Oxford Cognitive Disorders Clinic  
62 at the John Radcliffe Hospital, Oxford, UK between 2014 and 2017. PCA patients were  
63 compared with 25 tAD patients, included as a patient control group, recruited from the Early  
64 Onset Dementia Clinic, at Addenbrooke's Hospital, Cambridge, UK, from May 2004 to  
65 2006. The data from these tAD patients have previously been published(4). Diagnosis was  
66 established by a senior behavioural neurologist (CRB, ST or MH in Oxford, and JRH in  
67 Cambridge). All patients fulfilled consensus criteria for PCA (1) or tAD (13, 14), based upon  
68 clinical assessment, brain imaging and detailed neuropsychological assessment. Clinical  
69 magnetic resonance imaging (MRI) confirmed hallmark focal atrophy in the occipital and  
70 parietal lobes in PCA and bilateral medial temporal lobe atrophy in tAD. Patient groups were  
71 matched for age, years of education, gender distribution and symptom duration, *i.e.* time  
72 since the first symptom was noticed (all p values >.05; Table 1).

73

74 Patients were included into the study if they (i) had a caregiver, defined as a person who was

75 able to give a reliable account of the patient's routine, either from sharing a residence or close  
76 involvement in the patient's everyday life; and (ii) did not have any additional physical  
77 disability that would confound assessment of ADLs.

78

79 *-Table 1 here-*

80

### 81 *Assessment measures*

82

83 *Functional assessment.* ADLs were assessed using the Disability Assessment for Dementia  
84 (DAD; (9)), an informant-based scale consisting of 40 items which has been extensively used  
85 in dementia cohorts (e.g. frontotemporal dementia, Alzheimer's disease (4), primary  
86 progressive aphasia (6)) and atypical parkinsonian syndromes (15). Seventeen items relate to  
87 basic ADLs, divided into questions about hygiene, dressing, continence and eating. Twenty-  
88 three items relate to instrumental ADLs asking about meal preparation, telephoning, going on  
89 an outing, finance and correspondence, medications and leisure and housework. Lower scores  
90 on the DAD denote greater impairment. Non-applicable questions are excluded from the total  
91 score, avoiding gender bias toward activities (e.g., cooking, house chores, finances), and  
92 scores are converted to percentages. Caregivers responded by considering the patients' ability  
93 to conduct each activity independently, without help or reminder, in the last two weeks.

94 *Brief cognitive assessment.* The Addenbrooke's Cognitive Examination-III (ACE-III) (16)  
95 assesses five domains: attention and orientation, memory, verbal fluency, language and  
96 visuospatial abilities.

97 *Behavioural outcomes.* Questions pertaining to abnormal behaviour, mood and motivation  
98 from the Cambridge Behavioural Inventory-Revised (CBI-R; (17)) were used to assess  
99 behavioural change. CBI-R scores were converted to percentages for ease of comparison

100 across domains that have an unequal number of questions. Higher percentages denote more  
101 impairment.

102

### 103 *Statistical analyses*

104

105 Demographic and cognitive characteristics of patient groups (PCA vs tAD) were explored  
106 using independent sample t-tests and nonparametric Mann-Whitney tests for pairwise  
107 comparisons, as appropriate. Chi-squared test was used to explore gender differences  
108 between groups.

109

110 Further analysis was restricted to the PCA group as the patient group of interest and due to  
111 lack of available comparison data in the AD group. The predictive value of cognitive (ACE  
112 memory, fluency, attention/orientation, language and visuospatial skills), behavioural (CBI-R  
113 domains, namely: disinhibition, apathy and mood) and demographics variables (age and  
114 symptom duration) was explored using univariate linear regression analyses, and any  
115 variables not normally distributed were log transformed for this purpose. Significant  
116 predictors were subsequently entered into a multiple linear regression analysis (Enter  
117 method) to determine the relative contribution of each predictor to total DAD score.

118 For all between group comparisons, Cohen's  $d$  was used to estimate effect size:  $d = 0.2$   
119 (small effect size);  $d = 0.5$  (medium effect size);  $d = 0.8$  (large effect size) (18). Significance  
120 level was set at  $p \leq 0.05$ , 95% Confidence Interval (95%CI). All analyses were performed  
121 using the Statistical Package for the Social Sciences (SPSS) 21.0 version (IBM Inc., Chicago,  
122 Illinois, USA).

123

### 124 *Data availability*

125 Anonymized data, related documents such as study protocol, and statistical analysis will be  
126 shared for legitimate research, by direct request from the principal author at  
127 [samrah.ahmed@ndcn.ox.ac.uk](mailto:samrah.ahmed@ndcn.ox.ac.uk).

128

## 129 **Results**

130

### 131 *Profile of ADLs in PCA compared to AD*

132

133 *DAD total scores.* PCA patients showed significantly lower DAD scores than tAD patients,  
134 reflecting more severe disability to perform ADLs independently (*medium effect size,  $d = -0.7$ ,*  
135  *$p < 0.05$* ) (Table 1).

136

137 *Basic ADLs and Instrumental ADLs.* PCA patients were significantly more impaired than  
138 tAD patients on basic ADLs (*large effect size,  $d = -0.8, p < 0.05$* ), but there was no significant  
139 difference between groups on instrumental ADLs performance (*medium effect size  $d = -0.5,$*   
140  *$p > 0.05$* ). Examining the difference between basic ADLs and instrumental ADLs within each  
141 group, PCA and tAD patients were both significantly more impaired on instrumental ADLs  
142 compared to basic ADLs, as expected.

143

144 To investigate the clinical implications of these dementia subtypes on everyday living,  
145 patients were classified according to their level of impairment on basic ADLs and  
146 instrumental ADLs. The method of classification was as follows (4): 100% = ‘no change’;  
147 70-99% = ‘marginal to mild impairment’; 30-69% = ‘moderate to severe impairment’; 0-29%  
148 = ‘severe to very severe impairment’. Of note, both dementia subgroups had similar duration  
149 of symptoms (Table 1).



150

151 While the majority of patients with PCA (~60%) had no change or mild impairment in basic  
152 ADLs, 20% of patients had severe impairment in basic ADLs. By contrast, no AD patient had  
153 severe impairment in basic ADLs in this study. The great majority of patients with AD and  
154 PCA had moderate to severe impairment in instrumental ADLs (Figure 1b). Of note, one  
155 PCA patient did not have any impairment in ADLs on the DAD. Close inspection of the data  
156 revealed that this person was very early in the disease course (less than 24 months) and both  
157 patient and carer were still in paid employment. The carer may not therefore have judged  
158 there to be marked ADL impairment.

159

160

- *Insert Figure 1 here* -

161

### 162 ***Qualitative patterns of disability in patients with PCA***

163 For a greater understanding of clinical and care issues in patients with PCA, we plotted  
164 patients according to their levels of performance in ten different types of ADLs, according to  
165 their scores on the DAD: hygiene, continence, eating, dressing, leisure and housework,  
166 managing medications, going on an outing, telephoning, meal preparation and managing  
167 finances and correspondence. In addition, we split the patients into three groups according to  
168 their length of symptoms (1-3 years; 4-6 years; 8 years+).

169

170 Figure 2 shows that early in the disease course, patients with PCA are likely to have greater  
171 difficulties in the management of finances and correspondence, as well as meal preparation,  
172 with a gradient of difficulties on other basic activities. Later in the disease progression, this  
173 gradient seems to flatten and patients seem to be largely impaired across both instrumental  
174 and basic ADLs, confirming a greater level of dependency to perform ADLs.

175

176

- *Insert Figure 2 here* -

177

178 ***Predictors of ADL ability in patients with PCA***

179 Univariate regression analyses were used to investigate the utility of cognitive (ACE  
180 domains: attention/orientation, memory, fluency, language and visuospatial skills), behavioral  
181 (CBI-R domains: disinhibition, mood and apathy) and demographic variables (age and  
182 symptom duration) to predict ADL performance (DAD total) in patients with PCA. ACE  
183 attention/orientation ( $p=.004$ ), ACE memory ( $p=.024$ ), CBI-R disinhibition ( $p=.003$ ), CBI-R  
184 mood ( $p=.006$ ), CBI-R apathy ( $p=.008$ ) and symptom duration ( $p=.001$ ) were significantly  
185 correlated with total DAD score. Next, a multiple regression analysis was run to predict DAD  
186 total score from these significant factors. Overall, the model significantly predicted DAD  
187 total scores ( $F(6,13)=3.424$ ,  $p=.030$ ,  $R^2=.612$ ), accounting for 61.2% of the variance. Only  
188 ACE attention/orientation score added significance to the overall prediction of the model  
189 ( $p=.048$ ). Secondary exploratory analysis was conducted to examine whether floor/ceiling  
190 effects on the ACE subdomains may have skewed the association with the DAD.  
191 Representative scatterplots (Figure 3) show that there was variability in cognitive  
192 performance across domains, however, visuospatial assessment did suffer from a floor effect.  
193 This is likely to be a contributory factor to the lack of association between ADL and  
194 visuospatial measures.

195

196

- *Insert Figure 3 here* -

197

198 **Discussion/Conclusion**

199

200 This study details a novel investigation of how everyday functional ability is affected by  
201 PCA. PCA patients were impaired in ADLs to a greater extent than the tAD group despite the  
202 two groups being matched for symptom duration. On basic ADLs, a larger proportion of PCA  
203 patients showed impairment than tAD patients. These changes were also more severe in PCA,  
204 where 41.4% of patients had ‘moderate to very severe’ impairment compared to only 8% of  
205 tAD patients, and no tAD patients showed ‘severe to very severe’ impairment. All tAD  
206 patients were impaired on instrumental ADLs. The majority of PCA patients showed  
207 ‘moderate to severe impairment’, with a higher proportion than tAD showing the most severe  
208 impairment. Both patient groups were more impaired on instrumental ADLs than on basic  
209 ADLs, as would be expected given the more complex requirements of instrumental ADLs.

210

211 We predicted that these changes in ADLs would be, in some part, related to the salient visual  
212 deficits in PCA. However, no relationship between ADLs and the visuospatial scores was  
213 identified. Examination of individual scores showed that several patients scored at floor on  
214 visuospatial assessment, compared to more varied scores in other domains. As such, it is not  
215 possible to conclude that impaired visuospatial scores are not a predictor of ADL scores. The  
216 brief visuospatial assessment in the ACE is not able to capture the variability of visual  
217 deficits in PCA. A broader visuospatial assessment is likely to have drawn out a relationship  
218 with ADLs. Memory scores and, in particular, attention/orientation were predictive of overall  
219 DAD score. We have recently demonstrated that attention and memory may be impaired  
220 *early on* in PCA (19-21), perhaps related to the crucial role of the parietal lobes in these  
221 cognitive functions. Such cognitive changes would intuitively interfere with a person’s ability  
222 to undertake everyday tasks. The clinical implications are compelling, highlighting the need  
223 to examine changes in attention and memory in PCA, in addition to the salient and defining

224 visual disorder, in order to be able to predict and potentially monitor disease impact on  
225 ADLs.

226

227 ADLs were significantly associated with disease duration, showing that as disease progresses  
228 over time, proficiency in instrumental ADLs and basic ADLs decreases. This shows that  
229 functional assessment can be used as an indicator of functional deterioration from the early  
230 stages to later more severe stages of impairment in PCA. Sensitivity to early changes within a  
231 short duration of symptoms was particularly striking and highlights the detrimental impact of  
232 the initial symptomatology in PCA on a range of everyday tasks, both basic and complex.  
233 This information is particularly useful for healthcare professionals and families by indicating  
234 where PCA patients will encounter problems early in the disease process and thus where  
235 early interventions can be targeted.

236

237 Finally, behavioural changes contributed to the model explaining the variance of overall  
238 DAD scores in PCA patients. Low mood is a common accompaniment to dementia (22) and  
239 in PCA specifically, is considered as being reactive to diagnosis (1). The significant  
240 relationship with overall ADL ability suggests that assessment and monitoring of depressive  
241 symptoms in patients should be considered, and a low threshold for treatment to help prevent  
242 premature loss of independence in ADLs. Likewise, apathy is a commonly associated with  
243 several conditions (see (23) for a recent review), including Alzheimer's disease. Apathy is  
244 related to poor outcomes for both the patient and caregiver, including predicting functional  
245 impairment in AD (24) and other dementias (8), and here we show a similar relationship with  
246 independent function in PCA. Apathy may be amenable to intervention (25), and again the  
247 potential clinical implications warrant more research.

248

249

250 One limitation of the study was that pathological confirmation of diagnosis was not available  
251 in PCA, in particular. Although the most common underlying cause is Alzheimer's pathology  
252 (26), in a minority of cases alternative aetiologies, including corticobasal degeneration,  
253 dementia with Lewy bodies and prion disease, are implicated (1). Different aetiologies may  
254 well have a differential impact on ADLs. Furthermore, informant-based measures are subject  
255 to bias and may over- or underestimate a patient's actual ability, although the DAD is a  
256 widely used and well-validated measure. Further work should consider acquiring supportive  
257 data from performance-based measures to gain an independent and more accurate measure of  
258 ADL performance.

259

260 In summary, this study shows the pronounced impact of PCA on ADLs. The DAD emerges  
261 as a sensitive tool to assess functional impairment in PCA and one that may be able to  
262 monitor change as disease progresses. ADL measures tend to benefit from a relative absence  
263 of gender, language and cultural bias since their ratings are based on the individuals'  
264 premorbid functioning, further broadening its clinical utility in improving diagnostic and  
265 outcome assessment. Further work is warranted to determine how ADL measures can be used  
266 to assist the development of tailored interventions and management strategies for PCA  
267 patients.

268

269

270 **Statements**

271 **Acknowledgements**

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274

275 **Statement of Ethics**

276 The study was approved by the National Research Ethics Service South Central - Hampshire

277 B and Oxford C. Secondary Cambridge data collection (tAD) was approved through the

278 Cambridge Local Research Ethics Committee. All participants provided written informed

279 consent in accordance with the Declaration of Helsinki.

280

281 **Disclosure statement**

282 JRH is a member of the advisory boards for Nature Reviews and Neurology, both in a non-

283 profit capacity; serves on the editorial boards of Aphasiology (2000 - ), Cognitive

284 Neuropsychology (2002- ), Nature Reviews (2005 - ), Journal of Alzheimer's Disease,

285 Associate Editor (2010 - ), Acta Neuropsychologica (2011 - ), ALS Journal (2011- ), an

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290

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294

295 **Author contributions**

296 SA contributed to the design and conceptualization of the study, analysis and interpretation of  
297 data, data collection, drafting and revision of the manuscript and study supervision. SC  
298 contributed to analysis of data, data collection, and drafting and revision of the manuscript.  
299 CBD contributed to data collection, and drafting and revision of the manuscript. JRH  
300 contributed to the drafting and revision of the manuscript. CB contributed to drafting and  
301 revision of the manuscript and study supervision. EM contributed to the design and  
302 conceptualization of the study, analysis and interpretation of data, data collection, drafting  
303 and revision of the manuscript and study supervision.

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## FIGURE LEGENDS

### Figure 1.

**Title:** IADLs and BADLs in PCA and tAD. **Legend:** Distribution of patient according to severity of impairment on (A) Basic activities of daily living; and (B) Instrumental activities of daily living. **Abbreviations:** PCA Posterior cortical atrophy; tAD typical Alzheimer's disease.

### Figure 2.

**Title:** ADLs stratified by symptom duration. Lower scores (%) denote greater impairment.

**Legend:** Comparison of BADLs and IADLs in PCA, stratified by symptom duration.

**Abbreviations:** BADLs Basic Activities of Daily Living, IADLs Instrumental Activities of Living.

### Figure 3.

**Title:** Scatterplots depicting association between DAD total score and ACE subdomains in PCA patients.

