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## RESEARCH PAPER

# Co-occurrence of depressive symptoms and executive dysfunction after stroke: associations with brain pathology and prognosis

Elles Douven,<sup>1</sup> Pauline Aalten,<sup>1</sup> Julie Staals,<sup>2</sup> Syenna H J Schievink,<sup>1</sup> Robert J van Oostenbrugge,<sup>2,3</sup> Frans R J Verhey,<sup>1</sup> Sebastian Köhler<sup>1</sup>

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<sup>1</sup>Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience (MHeNs), Alzheimer Center Limburg, Maastricht University, Maastricht, The Netherlands

<sup>2</sup>Department of Neurology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Center, Maastricht, The Netherlands

<sup>3</sup>Department of Neurology, School for Mental Health and Neuroscience (MHeNs), Maastricht University, Maastricht, The Netherlands

## Correspondence to

Dr Sebastian Köhler, School for Mental Health and Neuroscience, Maastricht University, PO BOX 616 (DRT12) 6200 MD Maastricht, The Netherlands; [s.koehler@maastrichtuniversity.nl](mailto:s.koehler@maastrichtuniversity.nl)

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## ABSTRACT

**Objective** To examine, first, whether the co-occurrence of executive dysfunction (ED) and poststroke depression (PSD) shows different associations with neuroimaging markers and the course of depression and executive function, and second, whether it is associated with a different course on other cognitive domains and quality of life.

**Methods** The present study included 245 stroke patients (35.9% female, mean age 67.5 years (SD=11.9)). All patients completed neuropsychological and neuropsychiatric assessment 3 months poststroke, which were repeated at 6-month and 12-month follow-up. A subset (n=186) received 3-Tesla brain MRI at baseline to evaluate lesion-related imaging markers, white matter hyperintensity volume, global brain atrophy and total cerebral small vessel disease burden.

**Results** Patients with 'depression–executive dysfunction syndrome' (DES) showed higher white matter hyperintensity volumes compared with all other groups and more frequently showed left-sided lesions compared with ED only and PSD only. They also had more frequently old infarcts and higher total cerebral small vessel disease burden compared with PSD only and patients with neither ED nor PSD, and more global brain atrophy compared with PSD only. Longitudinal analyses showed that patients with DES had a more chronic course of depressive symptoms relative to PSD only, and a stable pattern of worse cognitive performance similar to patients with ED only.

**Conclusions** The co-occurrence of ED and PSD is associated with a worse prognosis of depression, persistent cognitive impairment and a higher amount of vascular and degenerative brain pathology. Future studies are needed to examine whether these patients represent a more severe subtype within the PSD spectrum.

**Clinical trial registration** NCT02585349;Results.

## INTRODUCTION

Poststroke depression (PSD) occurs in almost a third of stroke survivors,<sup>1</sup> with a cumulative incidence of 55% over a 15 year period.<sup>2</sup> Cognitive impairment is also frequent after stroke<sup>3</sup> and may co-occur with PSD.<sup>4</sup> The relationship between cognitive impairment and depression appears to be complex, as the direction of the association can go both ways, and they share common risk factors.<sup>5</sup>

It has been suggested that patients who present with both executive dysfunction (ED) and late-onset depression (first manifestation after age 60 or 65 years) show a worse course and clinical presentation, which has been called 'depression–executive dysfunction syndrome of late life' (DES).<sup>6</sup> DES is characterised by persistence of depressive symptoms<sup>7</sup> and unstable remission.<sup>8</sup> In a longitudinal study with 116 patients with first-ever stroke, the DES group showed less recovery from ED and depression after 2 years compared with patients with ED only or PSD only, respectively.<sup>9</sup> Whether DES after stroke has a distinct course regarding other cognitive domains is unknown. Furthermore, as both PSD<sup>10</sup> and cognitive impairment<sup>11</sup> are known to have a negative impact on quality of life (QoL), the co-occurrence of ED and PSD might be associated with an even worse course of QoL.

With respect to underlying brain pathology, it has been suggested that DES is related to damage in frontal-subcortical brain circuits,<sup>6</sup> which are known to be involved in mood regulation and executive function.<sup>12</sup> This was confirmed in a cross-sectional study of 158 patients with stroke,<sup>13</sup> which showed that frontal and subcortical lesions were more frequent in the DES group. Furthermore, DES may be also associated with more widespread brain changes, like higher degree of white matter hyperintensities (WMH),<sup>14</sup> which are a consequence of cerebral small vessel disease (cSVD). Total cSVD burden score<sup>15</sup> and generalised brain atrophy<sup>16</sup> have been shown to be predictors of decline in executive function. However, whether these imaging markers are also associated with DES remains to be studied.

The aim of the present 1-year follow-up study was first to examine whether the co-occurrence of ED and PSD shows different associations with neuroimaging markers and a different course of depression and executive function compared with patients with PSD only or ED only relative to a comparison group (patients without PSD and ED). Second, we examined whether the co-occurrence of ED and PSD is associated with a different course on other cognitive domains and QoL. Considering the literature, we hypothesised that the co-occurrence of ED and PSD would be associated with more severe lesion-related and general brain pathology and with a worse course of depression, cognitive performance and QoL over the 1-year follow-up period.



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## METHODS

### Patient population and data collection

Participants were enrolled in the Cognition and Affect after Stroke: a Prospective Evaluation of Risks study, a prospective clinical cohort study that aims to examine predictors of post-stroke cognitive impairment, depression and apathy.<sup>17</sup> Patients admitted for a non-fatal ischaemic or haemorrhagic stroke to the stroke unit or outpatient clinic of Maastricht University Medical Center or Zuyderland Hospital, the Netherlands, between June 2013 and November 2015, were approached for participation. Patients signed informed consent before participation. Exclusion criteria were: insufficient knowledge of the Dutch language, age <40 years, preexisting cognitive impairment or dementia, Mini-Mental State Examination (MMSE) score<sup>18</sup> <15, mental retardation, neurological or psychiatric diseases other than depression that are known to affect cognition, too severe aphasia to understand the study procedure, history of stroke of <3 years or residual symptoms from previous stroke, blindness and post-surgery stroke/postanoxic encephalopathy (study details are described elsewhere<sup>17</sup>).

### Procedure

Appointments for baseline measurements (T0) were scheduled around 3 months poststroke (mean (SD)=2.93 (0.46) months) to avoid interference with acute care and rehabilitation. At T0, sociodemographic information was recorded, and patients received 3-Tesla (3T) structural brain MRI if they had no contraindications and were able to visit the hospital. All patients completed neuropsychological assessment and neuropsychiatric questionnaires at T0, which were repeated 9 months after stroke (T1; mean (SD)=9.20 (0.65) months) and 15 months after stroke (T2; mean (SD)=15.1 (0.69) months).

### Magnetic resonance imaging

Participants underwent a 3T brain MRI at T0 (Philips Achieva, Philips Medical Systems, Best, the Netherlands). The MR protocol consisted of axial T1-weighted, T2-weighted, fluid-attenuation inversion recovery (FLAIR), diffusion weighted and susceptibility weighted sequences (for details, see Douven *et al.*<sup>17</sup>). Images were anonymised and analysed blinded for the patient's neuropsychiatric and cognitive status. Freesurfer software<sup>19</sup> was used to segment cortical grey and white matter on T1-weighted scans. WMH were segmented on FLAIR images with a semiautomated segmentation tool for WMH,<sup>20</sup> using a T1-weighted sequence for anatomical reference. WMH segmentation was corrected manually and normalised to intracranial volume (ICV). Global brain atrophy was calculated as 1 minus the ratio of brain parenchymal volume to total ICV. Stroke location, laterality and presence of old infarcts or lacunes were visually rated by an experienced neurologist (JS). The stroke lesion was segmented manually, normalised to ICV and divided into tertiles (ie, small, medium and large). Total cSVD burden was based on a well-validated ordinal scale,<sup>21</sup> which is based on the counting of presence of WMH, microbleeds, lacunes and enlarged perivascular spaces in the basal ganglia on MRI resulting in a total score ranging from 0 to 4 (details in online supplementary S1).

### Neuropsychological assessment

Executive function was measured with the Trail Making Test (TMT) part B (mental flexibility),<sup>22</sup> the 1min fluency test (animals and professions categories)<sup>23</sup> and the Behavioral Assessment of the Dysexecutive Syndrome (BADS) Zoo Map and Key search subtasks.<sup>24</sup> Global cognition was measured with

the MMSE,<sup>18</sup> episodic verbal memory (immediate and delayed recall) with the Dutch adaptation of the Rey Verbal Learning Test<sup>23</sup> and information processing speed with the TMT part A<sup>22</sup> and Digit Symbol Substitution Test.<sup>25</sup> Test scores were converted to z-scores, adjusted for age, sex and highest level of education based on available norms.<sup>25-28</sup> Raw scores on the BADS subtasks were converted to profile scores ranging from 0 to 4. ED was defined as a z-score on the TMT-B, or verbal fluency (animals or professions) <-1.0 or a BADS Zoo Map or Key Search profile score <1. For each cognitive domain, compound scores were created by averaging the available z-scores of the tests within this domain.

### Questionnaires

Patients fulfilling criteria for major or minor depression on the Mini International Neuropsychiatric Interview (MINI)<sup>29</sup> or with a Montgomery-Åsberg Depression Rating Scale (MADRS)<sup>30</sup> score ≥7 were classified as having PSD. The Barthel Index<sup>31</sup> was administered to measure impairment in activities of daily living, and the Stroke Specific Quality of Life (SS-QoL) scale was used to measure health-related QoL.<sup>32</sup>

### Statistical analyses

Statistical analyses were performed with Stata V.13.1 for Mac OS X. A P value <0.05 (two sided) was defined as statistically significant. Patients fulfilling criteria for both ED and PSD were grouped in the DES group. Patients with only ED were grouped in the ED-only group, patients with only PSD were grouped in the PSD-only group and patients with neither ED nor PSD were grouped in the none group, which was the reference group in all analyses.

Baseline group differences were tested using logistic and linear regression analyses. For imaging variables, models were corrected for age, sex and highest level of education. The MADRS scores (square root transformation), QoL scores and MMSE scores (logarithmic transformation) required data transformations to normalise skewed distributions. Linear mixed models were performed, corrected for age at baseline, sex and highest level of education and included a group (four levels: none, ED only, PSD only and DES) by time (three levels: T0, T1 and T2) interaction to study group differences in the course of depression, executive function, other cognitive domains and QoL over time. All models included a random intercept, and a random slope with an unstructured correlation matrix was added if this gave the best fit according to likelihood ratio tests. Sensitivity analyses were performed to examine whether the inclusion of history of depression as covariate is of influence to the results.

## RESULTS

Of the 250 participants, 246 completed neuropsychological assessment and the MADRS or MINI. One patient was excluded because of unreliable test results. Of the 245 remaining patients, 211 (86.1%) completed assessments at T1 and 217 (88.6%) completed assessments at T2 (online supplementary figure S1). Patients lost to follow-up (n=25) did not differ from patients who completed all measurements (n=220) (online supplementary table S1).

Fifty-five patients (22.5%) fulfilled criteria for DES, 38 (15.5%) patients had PSD only, 88 (35.9%) patients had ED only and the remaining 64 (26.1%) patients showed neither PSD nor ED. Patients who only fulfilled depression criteria of the MADRS but not the MINI (n=66) did not differ from patients who fulfilled the MINI criteria (n=27) with respect

**Table 1** Baseline characteristics separate for the four subgroups

Characteristic	None (n=64)	ED only (n=88)	PSD only (n=38)	DES (n=55)
Age (in years), mean (SD)	65.9 (11.0)	69.9 (11.4)*†	64.7 (11.3)	67.7 (13.5)
Male sex, n (%)	48 (75.0)	67 (76.1)	15 (39.5)*‡	27 (49.1)*‡
Low education, n (%)	25 (39.1)	37 (42.1)	13 (34.2)	26 (47.3)
Middle education, n (%)	23 (35.9)	29 (33.0)	16 (42.1)	18 (32.7)
High education, n (%)	16 (25.0)	22 (25.0)	9 (23.7)	11 (20.0)
Barthel Index, mean (SD)	19.8 (1.1)	19.4 (1.7)	19.6 (0.9)	18.9 (1.7)*†‡
Prestroke depression, n (%)	12 (18.8)	9 (10.2)	19 (50.0)*‡	15 (27.3)†‡
Family history of depression, n (%)	5 (7.9)	10 (11.4)	10 (26.3)*‡	9 (16.4)
Quality of life score, mean (SD)	4.4 (0.6)	4.3 (0.6)	3.8 (0.7)*‡	3.4 (0.7)*†‡
MMSE score, mean (SD)	28.8 (1.4)	27.8 (1.8)*†	28.8 (1.0)	27.5 (1.8)*†
MADRS score, mean (SD)	2.0 (2.0)	2.8 (2.0)	11.6 (5.0)*‡	11.7 (5.5)*‡
MINI minor or major depression, n (%)	0 (0.0)	0 (0.0)	10 (26.3)*‡	17 (30.9)*‡
MDD	0 (0.0)	0 (0.0)	5 (13.2)*‡	7 (12.7)*‡
MIND	0 (0.0)	0 (0.0)	5 (13.2)*‡	10 (18.2)*‡
PSD based on MADRS score ≥7	0 (0.0)	0 (0.0)	38 (100.0)*‡	51 (92.7)*‡

\*P<0.05 compared with the none group.

†P<0.05 compared with the PSD-only group.

‡P<0.05 compared with the ED-only group.

Results are based on logistic or linear regression models.

DES, depression–executive dysfunction syndrome; ED, executive dysfunction; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; MIND, minor depression; MINI, Mini International Neuropsychiatric Interview; MMSE, Mini-Mental State Examination; PSD, poststroke depression.

to demographic or imaging variables, except for lesion side, as patients with PSD based on the MADRS had more frequently left-sided stroke lesions ( $\chi^2=10.01$ ;  $df=1$ ;  $P=0.002$ ). Table 1 shows the baseline characteristics separately for the four subgroups. Patients with DES were more frequently female compared with ED only and the none group and had a lower Barthel Index and QoL score compared with all other groups. They had more frequently a history of depression compared with ED only, but less frequently compared with PSD only, and a lower MMSE score compared with PSD only and the none group.

A subset (n=186) received 3T brain MRI and differences between the subgroups with respect to imaging markers are

shown in table 2. Patients with DES had more frequently left-sided lesions compared with ED only ( $\chi^2=6.03$ ;  $df=1$ ,  $P=0.014$ ) and PSD only ( $\chi^2=5.77$ ;  $df=1$ ,  $P=0.016$ ) and had higher WMH volumes compared with the none group ( $F(1,158)=5.37$ ,  $P=0.022$ ), ED-only group ( $F(1,158)=5.71$ ,  $P=0.018$ ) and PSD-only group ( $F(1,158)=8.67$ ,  $P=0.004$ ). They showed more global brain atrophy compared with PSD only ( $F(1,158)=6.15$ ,  $P=0.014$ ) and had more frequently old infarcts or lacunes compared with PSD only ( $\chi^2=5.15$ ;  $df=1$ ;  $P=0.023$ ) and the none group ( $\chi^2=4.22$ ;  $df=1$ ;  $P=0.040$ ). A higher total cSVD burden score was found in the DES group compared with PSD only ( $F(1,137)=5.80$ ,  $P=0.017$ ) and the none group ( $F(1,137)=5.57$ ,  $P=0.020$ ).

**Table 2** Imaging characteristics for the four subgroups

Characteristic	None (n=54)	ED only (n=68)	PSD only (n=27)	DES (n=37)
Lesion characteristics				
Ischaemic stroke, n (%)	50 (92.6)	63 (92.7)	26 (96.3)	35 (94.6)
Left hemispheric stroke, (n=175), n (%)	24 (44.4)	27 (39.7)	6 (22.2)	23 (62.2)*†
Frontal or basal ganglia lesion, (n=136), n (%)	14 (31.8)	24 (47.1)	4 (28.6)	10 (37.0)
Infratentorial lesions, (n=136), n (%)	4 (9.1)	9 (17.7)	2 (14.3)	4 (14.8)
Stroke lesion volume, (n=166), n (%)				
Small	12 (25.5)	19 (32.2)	12 (50.0)	12 (33.3)
Medium	23 (48.9)	19 (32.2)	4 (16.7)	10 (27.8)
Large	12 (25.5)	21 (35.6)	8 (33.3)	14 (38.9)
Background damage on MRI				
Lacunae and other old infarcts, n (%)	18 (33.3)	29 (42.7)	7 (25.9)	20 (54.1)†‡
Cerebral microbleeds, (n=145), n (%)	24 (58.4)	34 (65.4)	12 (57.1)	15 (48.4)
WMH volume (% ICV) (n=166), mean (SD)	0.53 (1.03)	0.61 (0.79)	0.31 (0.43)	0.97 (1.17)*†‡
Global atrophy (% ICV) (n=166), mean (SD)	0.33 (0.04)	0.33 (0.04)	0.31 (0.03)	0.34 (0.05)†
cSVD burden ordinal score (0–4), (n=145), mean (SD)	1.41 (0.97)	1.71 (1.30)	1.33 (0.91)	1.97 (1.45)†‡

\*P<0.05 compared with the ED-only group.

†P<0.05 compared with the PSD-only group.

‡P<0.05 compared with the none group.

Results are based on logistic or linear regression models corrected for age, sex and highest level of education.

cSVD, cerebral small vessel disease; DES, depression–executive dysfunction syndrome; ED, executive dysfunction; ICV, intracranial volume; PSD, poststroke depression; WMH, white matter hyperintensities.

## Cerebrovascular disease

**Table 3** Mean differences (and 95% CI) in baseline depression, cognition and quality of life and in change in depression, cognition and quality of life (slopes) from baseline between those with depression–executive dysfunction syndrome (DES, n=55), executive dysfunction only (ED only, n=88), poststroke depression only (PSD only, n=38) and those without PSD and ED at baseline as reference group (n=64)

Outcome	Baseline difference		Change baseline to 6-month follow-up		Change baseline to 12-month follow-up		Group × time*
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	
	<b>Time</b>						
<b>Depression</b>							
ED only	0.40†	0.12 to 0.68	−0.00	−0.44 to 0.44	−0.01	−0.54 to 0.52	0.00
PSD only	2.17†	1.82 to 2.52	−0.80†	−1.33 to −0.25	−0.56	−1.20 to 0.08	8.33‡
DES	2.22†	1.91 to 2.53	−0.47	−0.95 to 0.01	−0.36	−0.94 to 0.22	3.70
<b>Executive function</b>							
ED only	−0.82†	−1.02 to −0.61	0.10	−0.07 to 0.26	0.10	−0.07 to 0.26	1.75
PSD only	0.12	−0.14 to 0.37	−0.04	−0.24 to 0.16	−0.12	−0.32 to 0.09	1.28
DES	−0.97†	−1.20 to −0.74	0.14	−0.03 to 0.32	0.20‡	0.01 to 0.38	4.63
<b>Global cognition</b>							
ED-only	0.14†	0.05 to 0.23	−0.02	−0.12 to 0.08	0.03	−0.07 to 0.13	0.85
PSD-only	0.03	−0.08 to 0.14	0.00	−0.12 to 0.13	−0.01	−0.13 to 0.11	0.03
DES	0.18†	0.08 to 0.28	0.02	−0.09 to 0.13	0.02	−0.09 to 0.13	0.25
<b>Memory</b>							
ED only	−0.49†	−0.86 to −0.12	0.09	−0.37 to 0.37	−0.14	−0.44 to 0.16	2.11
PSD only	0.14	−0.33 to 0.61	−0.00	−0.37 to 0.37	0.02	−0.34 to 0.38	0.02
DES	−0.88†	−1.30 to −0.46	−0.06	−0.39 to 0.28	−0.21	−0.54 to 0.12	1.57
<b>Processing speed</b>							
ED only	−0.49†	−0.76 to −0.22	−0.02	−0.22 to 0.19	−0.15	−0.36 to 0.05	2.55
PSD only	−0.01	−0.35 to 0.34	0.18	−0.08 to 0.43	0.17	−0.08 to 0.42	2.50
DES	−0.84†	−1.15 to −0.53	−0.04	−0.27 to 0.19	−0.03	−0.26 to 0.19	0.13
<b>Quality of life</b>							
ED only	0.07	−0.07 to 0.21	0.11	−0.02 to 0.24	0.07	−0.07 to 0.21	2.90
PSD only	0.45†	0.28 to 0.63	0.10	−0.06 to 0.26	0.03	−0.14 to 0.20	1.62
DES	0.64†	0.48 to 0.79	0.02	−0.13 to 0.16	0.05	−0.11 to 0.20	0.35

\* $\chi^2$  test (2 df) of overall interaction between subgroup and time (baseline, 6-month follow-up and 12 month follow-up) omnibus test of the null hypothesis of no difference in rate of change over time between subgroups.

† $P < 0.01$ .

‡ $P < 0.05$ .

MADRS, Montgomery-Åsberg Depression Rating Scale; MMSE, Mini-Mental State Examination; PSD, poststroke depression; SS-QoL, Stroke-Specific Quality of Life.

Table 3 gives the results for the analyses comparing patients on the course of executive function, depression, memory, information processing speed and QoL.

### Course of depression by subgroup

Overall, a significant group difference in the course of depressive symptoms was found ( $\chi^2 = 12.96$ ;  $df = 6$ ;  $P = 0.044$ ). In the PSD-only group, depressive symptoms on average improved over time compared with the none group ( $\chi^2 = 8.33$ ;  $df = 2$ ;  $P = 0.016$ ), whereas depressive symptom levels in the DES group remained stable over time compared with the none group ( $\chi^2 = 3.70$ ;  $df = 2$ ;  $P = 0.157$ , figure 1A).

### Course of executive function by subgroup

A significant group difference in the course of executive function was found from T0 to T2 ( $\chi^2 = 9.63$ ;  $df = 3$ ;  $P = 0.022$ ). Further analyses suggested that this was due to opposing trajectories for the DES and PSD only group ( $\chi^2 = 8.35$ ;  $df = 1$ ;  $P = 0.004$ ), with a modest improvement in the former paralleled by a modest decline in the latter (figure 1B). However, using the none group as reference, improvement in the DES group on executive function was not significant ( $\chi^2 = 4.63$ ;  $df = 2$ ;  $P = 0.099$ ). Notably, there were no differences in cognitive trajectories between DES and ED only, suggesting they had a more or less similar course of

stable and comparatively worse performance on executive function over time (figure 1B). Results with respect to performance on the individual test instruments measuring executive function showed that the ED-only group was more likely to show improvement over time compared with the DES group on the TMT-B and TMT index (see online supplementary table S2).

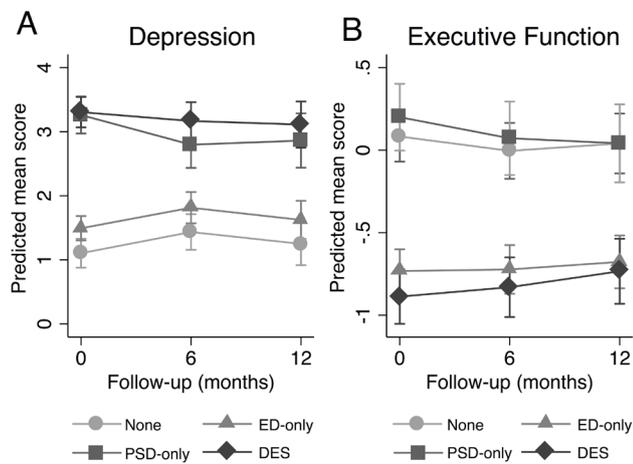
### Course of other cognitive outcomes and QoL by subgroup

#### Global cognition

At T0, patients with DES and ED only showed lower MMSE scores compared with patients in the none group (table 3). Overall, no significant difference in the course of MMSE scores was found between the four groups ( $\chi^2 = 1.77$ ;  $df = 6$ ;  $P = 0.939$ ), indicating that DES and ED-only scored consistently lower on the MMSE over the course of 12 months (figure 2A).

#### Memory

The DES group and ED only performed significantly worse on memory compared with the none group at T0 (table 3). Overall, no significant difference in the course of memory performance was found between the four groups ( $\chi^2 = 4.09$ ;  $df = 6$ ;  $P = 0.664$ ), indicating that DES and ED only scored lower on memory over the course of 12 months (figure 2B).



**Figure 1** Change over time in executive function and depression scores by subgroup. (A) Course of depressive symptoms measured with the MADRS by subgroup. (B) Course of executive function performance by subgroup. Based on random-effects analysis adjusted for age at T0, sex, level of education, group and group by time interaction. Predicted mean scores are estimated marginal means for subgroup by time, with all covariates fixed at their means. Higher mean scores indicate a higher level of depression and better performance on executive function, respectively. DES, depression–executive dysfunction syndrome; ED, executive dysfunction; MADRS, Montgomery–Åsberg Depression Rating Scale; PSD, poststroke depression.

### Information processing speed

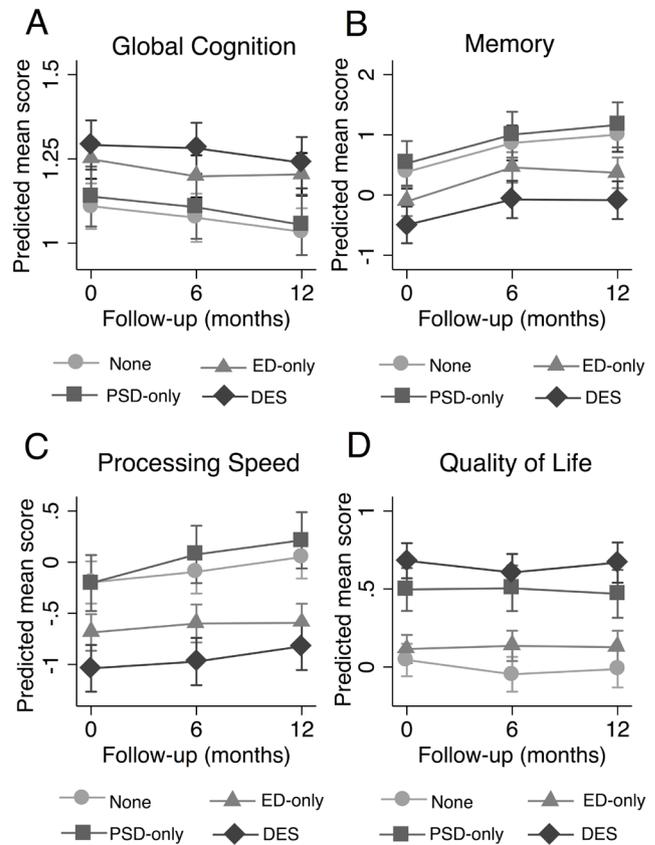
The DES group and ED only performed worse on information processing speed compared with the none group at T0 (table 3). Overall, no significant difference was found between the four groups ( $\chi^2=8.69$ ;  $df=6$ ;  $P=0.192$ ), while time-stratified analyses showed a trend for significant differences in the course of performance from T0 to T2 ( $\chi^2=7.40$ ;  $df=3$ ;  $P=0.060$ ), which was due to a relative improvement in performance in the PSD-only group compared with the ED-only group ( $\chi^2=7.19$ ;  $df=1$ ;  $P=0.007$ ). There was no significant difference in cognitive trajectory between the DES group and the none group ( $\chi^2=0.13$ ;  $df=2$ ;  $P=0.939$ ), suggesting stable low performance over time in the DES group (figure 2C).

### Quality of life

The SS-QoL score of the DES group and PSD-only group was significantly lower compared with the none group at T0 (table 3). Overall, no significant group difference was found in the course of QoL ( $\chi^2=4.67$ ;  $df=6$ ;  $P=0.587$ ), suggesting that QoL scores remained relatively stable in all four groups, with DES and PSD only scoring lower over the course of 12 months (figure 2D).

### Sensitivity analysis

To account for the fact that the relation between brain markers and depression could have existed before the stroke, a sensitivity analysis was conducted with history of depression added as a covariate to the analyses. For the association with imaging markers (online supplementary table S3), this changed the result for lesion side: patients with DES now also had more frequently left-sided strokes compared with the none group ( $\chi^2=23.87$ ;  $df=1$ ;  $P=0.049$ ), while differences with ED only and PSD only remained. With respect to the prognostic markers (online



**Figure 2** Change over time in performance on global cognition, memory, and processing speed and quality of life scores by subgroup. (A) Course of performance on global cognition measured with the MMSE by subgroup. (B) Course of memory performance by subgroup. (C) Course of performance on information processing speed by subgroup. (D) Course of quality of life scores by subgroup. Based on random-effects analysis adjusted for age at T0, sex, level of education, group and group by time interaction. Predicted mean scores are estimated marginal means for subgroup by time, with all covariates fixed at their means. Higher mean scores indicate better performance on memory and processing speed. For global cognition and quality of life, higher scores indicate worse performance and worse quality of life, respectively. DES, depression–executive dysfunction syndrome; ED, executive dysfunction; MMSE, Mini-Mental State Examination; PSD, poststroke depression.

supplementary table S4), this did not alter the results for change in depressive symptoms or cognition from T0 to T2.

### DISCUSSION

The present study aimed to examine whether the co-occurrence of PSD and ED is associated with different neuroimaging correlates and a different prognosis. The results showed that DES was associated with left-sided lesions, higher WMH volume, more global brain atrophy, higher frequency of old infarcts and higher cSVD burden. Furthermore, patients with DES showed more functional impairment at baseline and had a more chronic course of depressive symptoms relative to patients with PSD only, on average. Patients with DES also showed a non-improving pattern of poor cognitive performance similar to the ED-only group.

Depressive symptoms improved in the PSD-only group but remained stable in the DES group, suggesting a more chronic

course of depression. This is in agreement with earlier findings in patients with late-life depression,<sup>8</sup> in which ED was associated with relapse and recurrence of depression. A smaller study in 116 patients with first-ever stroke<sup>9</sup> also found that patients with DES showed a chronic course of depressive symptoms after 2 years.

Patients with DES generally showed a stable course of executive function, which did not differ significantly from ED only. This is consistent with a previous study<sup>9</sup> in which about 50% of patients with ED only or DES were still impaired in executive functions after 2 years. However, they only evaluated whether ED was present at follow-up, not whether there was a change in severity of ED over time. Results of the individual test instruments showed that the ED-only group was in fact more likely to show improvement over time compared with the DES group on some tests. On global cognition, information processing speed and memory, the DES group performed worst, and performance remained stable low over time. QoL scores were lowest in the DES group as well and remained stable over time.

DES was associated with increased WMH volume, which is in contrast to the study of Vataja *et al*,<sup>13</sup> in which no association with degree of WMH was found. However, Vataja *et al*<sup>13</sup> did not make use of a segmentation tool to determine WMH volume, so the discrepancy in methodology may be an explanation for the difference in results. Nevertheless, our results seem consistent with findings in depressed geriatric patients, particularly late-onset depression, who tend to show white matter changes in frontal-subcortical circuits.<sup>6</sup> Indeed, it has been shown that WMH in older adults with major depressive disorders relate to more severe impairment in executive functions and memory.<sup>33</sup> DES was also associated with a higher frequency of old infarcts, higher cSVD burden and more global brain atrophy, compared with PSD only, which suggests that DES is associated with increased generalised (vascular) brain pathology. This may provide support for a biological origin of depression in DES compared with PSD only, for which psychosocial factors like a psychological response to the stroke itself might be more involved.<sup>34</sup> DES therefore seems to denote a subtype of depressed stroke patients with a distinct aetiology and poor prognosis and may ask for a different treatment approach as some studies found worse response to antidepressants in depressed older adults with executive impairment.<sup>35</sup> However, the evidence base is still weak<sup>36</sup> and lacking for DES after stroke.

Important strengths of the present study include the relatively large sample with minimal dropout, the longitudinal design with serial assessments of cognitive and neuropsychiatric functioning and the use of linear mixed models, which provide the opportunity to study group differences over time. Yet, some limitations need to be addressed. The exclusion of patients with prestroke cognitive impairment, severe aphasia and comorbid neurological conditions that are known to affect cognition may limit the generalisability of our results. Next, imaging markers were only available for a subset of patients, which hampered the possibility to study associations with specific lesion locations. Also, relatively mild criteria were adopted for defining PSD. The preferred method would be to adopt the MINI criteria, which are based on the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). However, as only a small number of patients fulfilled the MINI criteria (n=27), we also included patients with a MADRS score  $\geq 7$ . This MADRS cut-off score is frequently used in stroke studies<sup>37</sup> but is lower compared with cut-offs that are commonly used in clinical practice. Therefore, the results of the study should be interpreted carefully, as the severity levels of PSD ranged from mild to severe, resulting in

heterogeneous groups. However, when we compared demographic and imaging characteristics between patients with PSD based on the MINI or on the MADRS, only a difference in frequency of left-sided lesions was found. A sensitivity analysis applying more strict criteria for PSD (MADRS >12 or major depressive disorder on the MINI) could not be performed as this yielded only a small PSD group (n=28) resulting in lack of low power. Hence, our results can be generalised to stroke patients with mild to moderate depressive symptoms but need validation for patients with major depression. Furthermore, history of depression was more frequent in patients with PSD (62%) compared with patients without PSD (31%), but a sensitivity analysis suggested this did not explain the reported differences between these groups. In addition, antidepressant use might have had an influence on cognitive functioning, as previous studies indicated that it is linked to the development of cognitive impairment and/or dementia.<sup>38</sup> However, as the number of participants using antidepressants was very low (7%), we expect this influence to be low as well. Lastly, the study had a follow-up length of 12 months. While some differences in course over time were found in this medium-term follow-up period, longer follow-up periods may show clearer demarcation of trajectories in cognition and depression and would allow examining additional outcome parameters like incident dementia and mortality, as a 12-year follow-up stroke population study indicated that DES was associated with poor long-term survival<sup>39</sup> and a population-based cohort study with non-demented elderly found an increased risk for dementia in patients with DES over a 9-year follow-up.<sup>40</sup>

In conclusion, the co-occurrence of ED and PSD, or DES, is associated with a worse prognosis of depression and cognition and a higher amount of vascular and degenerative brain pathology. Screening for the co-occurrence of ED and PSD might be helpful in clinical practice, as it might identify patients with stroke who are in need of special treatment. However, future studies are needed to examine whether DES denotes a more severe subtype within the PSD spectrum.

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