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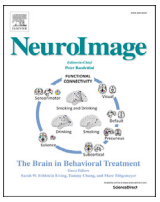

The effect of semantic memory degeneration on creative thinking: A voxel-based morphometry analysis

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ABSTRACT

Increasing attention is being directed towards explicating the neurocognitive mechanisms of divergent thinking. While neuroimaging studies have tended to dominate the contemporary creativity literature, lesion studies provide important converging evidence by revealing the regions that are not only implicated in, but essential for, task performance. Here we explored the capacity for divergent thinking in semantic dementia (SD), a neurodegenerative disorder characterised by the progressive degeneration of the conceptual knowledge base. The performance of 10 SD patients on a divergent thinking task was contrasted with that of 15 patients with the behavioural variant of frontotemporal dementia (bvFTD) and 20 healthy control participants. In addition, all participants underwent neuropsychological testing and structural MRI. Relative to controls, both patient groups generated significantly fewer responses on the divergent thinking task, with disproportionate impairment in the SD group. Further, the responses generated by patient groups were less original and reflected less flexible thinking when compared with controls. For SD patients, fluency of responses correlated with performance on a measure of semantic association, and originality of responses correlated with semantic naming and comprehension ability. In bvFTD, originality of ideas correlated with letter fluency and response inhibition. Voxel-based morphometry analyses revealed two grey matter clusters consistently associated with diminished Fluency of ideas, namely a left medial temporal lobe cluster centred on the left anterior hippocampus, and a left middle frontal gyrus cluster. Our study highlights the importance of distinct temporal and prefrontal contributions to divergent thinking via a lesion approach, and underscores the pivotal role of semantic processes in creative cognition.

1. Introduction

An important aspect of human cognition is the capacity to adjust one's behaviour in response to an ever-changing environment. Such cognitive flexibility allows us to override a prepotent response, configure a new response, and implement this new response in a task at hand (Dajani and Uddin, 2015). An inflexible cognitive style has been linked to poor outcomes across a range of clinical populations including autism spectrum disorder and schizophrenia (Champagne-Lavau et al., 2012; Geurts et al., 2009; Nemoto et al., 2007). Here, we explore how the degradation of anterior temporal and prefrontal brain regions in neurodegenerative disorders impacts the capacity for flexible thought, as indexed by measures of divergent thinking.

Divergent thinking tasks are widely used to measure an individual's capacity for creativity and require individuals to find many varied and original solutions to problems (Acar and Runco, 2019; Runco and Acar, 2012). The canonical example of this is the Alternate Uses Task (AUT) during which participants generate as many alternate uses for an object as possible (Gilhooly et al., 2007). Successful performance on the AUT relies upon a number of distinct, though interacting, cognitive mechanisms including bottom-up episodic and semantic memory processes (Kenett and Faust, 2019; Madore et al., 2015; Madore et al., 2019; Mednick, 1962; Volle, 2018), and the top-down implementation of executive control (Beaty et al., 2014; Benedek et al., 2014; Leon et al., 2014). Accordingly, the retrieval of conceptual knowledge and past episodic experiences provides the basic elements upon which executive functions such as disengagement, set shifting, inhibition and working memory operate (Beaty and Silvia, 2012; Benedek et al., 2012; Nusbaum and Silvia, 2011). This coordinated interplay between bottom-up and top-down processes ensures that the concepts generated are monitored

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and constrained according to task demands (Beaty et al., 2016; Volle, 2018).

The contribution of semantic knowledge to creative thought is of particular interest in this context (Kenett, 2018; Kenett and Faust, 2019; Kenett et al., 2018). Theoretical and empirical research has demonstrated the role of semantic memory in the creative process, whereby concepts are combined to form novel and useful ideas (Abraham, 2014; Kenett, 2018; Kenett and Faust, 2019; Mednick, 1962). Functional neuroimaging studies of creativity suggest an important role for the temporal lobe in integrating semantic information to establish novel associations. In addition, medial temporal regions enable individuals to draw on personal experiences when engaging in creative cognition (Beaty et al., 2017; Beaty et al., 2018; Madore et al., 2019; Shen et al., 2017). The prefrontal cortex is also consistently implicated in mediating flexible thought and exerting top-down control processes to inhibit salient responses and control creative thinking (Beaty et al., 2019; Benedek and Fink, 2019; Chrysikou, 2019; Gonen-Yaacovi et al., 2013). Moreover, recent meta-analyses have concluded that both parieto-temporal and prefrontal regions work in concert to support divergent thinking (Gonen-Yaacovi et al., 2013; Wu et al., 2015).

While functional neuroimaging studies have tended to dominate the contemporary creativity literature, lesion studies continue to offer an important adjunct to neuroimaging studies by demonstrating the regions that are not only implicated in but *essential* for task performance (Abraham, 2018; Bendetowicz et al., 2017; Irish and van Kesteren, 2018; Ovando-Tellez et al., 2019). To date, most lesion studies have focused on how frontal lobe damage disrupts creative thought. For example, patients with varying degrees of lateral and medial prefrontal cortical damage have been shown to generate fewer ideas on a divergent thinking task and the ideas produced are rated as lacking in originality (Abraham et al., 2012). Similarly, in Parkinson's disease, frontal lobe dysfunction has been shown to disrupt the generation of ideas on divergent thinking tasks (Tomer et al., 2002).

Patients with frontal lobe atrophy, as a result of the behavioural variant of frontotemporal dementia (bvFTD), have been observed to generate fewer ideas on verbal divergent thinking tasks compared to controls (Hart and Wade, 2006). However, this study pooled bvFTD with Alzheimer's disease participants, limiting our capacity to make disease-specific conclusions. A later study revealed that bvFTD patients performed in line with control participants on a non-verbal figure--drawing task that involved divergent thinking (Rankin et al., 2007). In contrast, a study by De Souza et al. (2010) revealed global impairments in divergent thinking in bvFTD and implicated hypoperfusion of prefrontal cortical regions in these deficits. Collectively, these studies provide important convergent evidence for the role of prefrontal regions in divergent thinking, with the suggestion that prefrontal damage impacts the originality of the ideas generated (Abraham et al., 2012).

In contrast, studies attempting to explicate the role of semantic processing in divergent thinking using a lesion approach remain remarkably absent from the literature (Ovando-Tellez et al., 2019). The syndrome of semantic dementia (SD) is particularly well-suited to investigate the contribution of semantic knowledge to cognitive processes (Hodges and Patterson, 2007; Irish et al., 2012). The hallmark feature of SD is a pan-modal deterioration of semantic knowledge due to anterior temporal lobe degeneration that gradually spreads to include medial temporal and orbitofrontal regions (Gorno-Tempini et al., 2011). Despite these profound semantic impairments, patients with SD perform in line with controls on tests which bypass verbal and conceptual demands, such as tests of visual memory (Bozeat et al., 2000b Irish et al., 2016) and spatial navigation (Pengas et al., 2010; Tu et al., 2015).

Research involving SD patients has served to clarify the contribution of semantic processes to a range of internally-driven cognitive functions including autobiographical memory (Graham et al., 1999; Irish et al., 2011), episodic future thinking (Duval et al., 2012; Irish et al., 2012a, 2012b) and scene construction (Irish et al., 2017; reviewed by Irish and Piolino, 2016). As such, it has been suggested that semantic memory provides the necessary *scaffold* for a host of flexible expressions of cognition, most importantly that of imagination (Abraham and Bubic, 2015; Irish, 2016). To our knowledge, only two studies to date have assessed creative cognition in SD. In a study focusing on visual art production in dementia, Rankin et al. (2007) documented marked impairments in 9 cases of SD on a non-verbal divergent thinking task. This finding is interesting as it suggests a fundamental impairment in divergent thinking that is not primarily driven by verbal deficits in this patient group. More recently, Ruggiero et al. (2019) used a similar figure drawing task to reveal compromised divergent thinking in a mixed sample of 8 bvFTD and 3 SD patients, however, the precise nature of performance deficits in the SD group was not explored.

The evidence to date converges to suggest marked impairments in the capacity for divergent thought in SD, likely attributable to anterior temporal lobe atrophy, and in bvFTD patients likely arising as a consequence of frontal lobe damage. Formal investigation of the neural substrates of divergent thinking impairments in these syndromes is lacking. The objective of this study, therefore, was to explore the capacity for divergent thinking in well-characterised and separate cohorts of SD and bvFTD patients. In addition, both patient groups completed a comprehensive neuropsychological battery covering the main cognitive domains and underwent structural magnetic resonance imaging (MRI). This provided us with a rich dataset to explore, for the first time, the cognitive and neural substrates of divergent thinking performance in these unique patient groups.

2. Materials and methods

2.1. Participants

A total of 45 participants were recruited through the FRONTIER frontotemporal dementia research group at the Brain and Mind Centre, The University of Sydney, Australia. Of those, 15 individuals met clinical criteria for probable bvFTD (Rascovsky et al., 2011), 10 met clinical criteria for SD (Gorno-Tempini et al., 2011), and 20 were healthy control participants. Diagnosis was established by consensus between a senior neurologist and a neuropsychologist based on the results of clinical investigation, comprehensive cognitive assessment, and evidence of atrophy on structural neuroimaging.

Patients diagnosed with bvFTD were characterised by marked changes in behaviour, executive dysfunction, loss of insight, socioemotional dysfunction, apathy, and functional decline. In addition, prominent bilateral prefrontal and anterior temporal atrophy was evident on MRI. Patients diagnosed with SD presented with marked language disturbances manifesting in impaired naming and comprehension, in the context of intact phonology and fluency of speech. The majority of SD patients ($n = 7$) displayed the classic left-lateralised presentation, with focal language disturbances reflecting atrophy commencing in the left anterior temporal lobe and evolving to a left-predominant, yet bilateral pattern of atrophy on structural MRI. Notably, 3 cases were diagnosed with the less prevalent right-sided SD syndrome, presenting clinically with prosopagnosia and behavioural changes, and characterised by predominant right-lateralised anterior temporal atrophy, which encroached into the contralateral hemisphere to a lesser degree. SD patients were combined into a single cohort to maximise power. Disease severity in all patients was measured using the Clinical Dementia Rating Frontotemporal Lobar Degeneration Scale (CDR-FTLD; Knopman et al., 2008) and the Frontotemporal dementia Rating Scale (FRS; Mioshi et al., 2010). Controls were recruited through the FRONTIER research volunteer panel and all scored 88 or above on the Addenbrooke's Cognitive Examination – Third Edition (ACE-III; Hsieh et al., 2013; So et al., 2018).

Exclusion criteria for all participants included a history of significant head injury, presence of another neurological or psychiatric condition, substance abuse, and limited English proficiency. Ethics approval was obtained from the University of New South Wales and the South Eastern Sydney Health Service ethics committee. Informed consent was provided

by all participants, or by the person responsible for their care. Participants volunteered their time and were reimbursed for any travel expenses incurred.

2.2. Assessment of divergent thinking

The Alternate Uses Task (AUT) was used to index divergent thinking and was derived from a commonly used measure in recent literature (Gilhooly et al., 2007). Briefly, participants were provided with the name of an everyday object and the usual use for that object. They were then required to generate as many alternative uses for that object as possible. One example item was given with the instructions (i.e., newspaper: used for reading) along with suggested alternative uses (i.e., swatting flies, to line drawers, to make a paper hat). Prior to commencing the task, participants were provided with an opportunity to ask questions and to clarify task instructions. Once they indicated that they understood the task requirements, six test items were presented one at a time (brick, car tyre, barrel, pencil, shoe, hanger). Throughout the task, the experimenter checked the responses made by participants to ensure they were adhering to the task requirements. Participants were encouraged to be creative and to generate as many ideas as possible. At the start of each trial, participants received a short reminder of the task instructions and the name of the object was shown on a computer screen (see also Madore et al., 2016). The cue remained on screen for the duration of each trial.

Participants had 2 min to complete each item, although they were not advised of the time limit and were automatically moved on to the next item if required. Two minutes was chosen as an appropriate time limit that would allow enough time for older adults to respond whilst minimising the potential for fatigue in the patient groups over the entire testing session. Participants provided all responses verbally, and these were digitally recorded by the experimenter for subsequent transcription and scoring.

2.3. Scoring

AUT Responses were scored in line with standard scoring methods (Barbot et al., 2019) focusing on three main outcome measures: Fluency, Originality and Flexibility. (i) Fluency represents our primary measure of interest and refers to the total number of adequate uses produced by each participant across the six trials; (ii) Originality was measured by rating the uniqueness of each use provided on a scale from 1 to 4 (lower scores denoted more commonplace responses and higher scores signified more unique responses). To control for potential confounds of fluency and generativity, an average Originality score was computed for each participant (Silvia et al., 2008); (iii) Flexibility reflected the total number of distinct categories under which each use could be subsumed. Responses were excluded if they were vague, implausible or a repetition of a previous response. Responses were scored by the first author (TP), who was blind to diagnoses. A second rater (GS) scored a subset (n = 10) of AUT responses blind to diagnoses and study hypotheses. High inter-rater reliability was achieved for Originality (Cronbach's alpha = .98) and Flexibility (Cronbach's alpha = .80). Fluency was not scored by the second rater as it was simply a sum of responses provided.

2.4. Neuropsychological testing

All participants completed the ACE-III (Hsieh et al., 2013) as a global measure of cognition covering the domains of attention and orientation, memory, fluency, language, and visuospatial abilities. Letter fluency was assessed using the letters F, A, and S (Strauss et al., 2006). Digit Span Forward and Backward subtests of the WAIS-III were used as measures of attention and working memory, respectively (Wechsler, 1997). The Trail Making Test Part B (TMT-B; Reitan, 1958) was used as a measure of executive function. Non-verbal memory was measured using the 3-min delayed recall of the Rey-Osterrieth Complex Figure (Rey, 1941). For bvFTD patients only, verbal memory was assessed using the Rey Auditory Verbal Learning Test (RAVLT; Schmidt, 1996) and inhibition was measured using the Hayling Sentence Completion Task (Burgess and Shallice, 1997). These tasks were not administered to SD patients, due to their heavy semantic loading (see Supplementary Materials Table 1). SD patients, however, completed additional tests of language function including the naming, repetition, comprehension and semantic association subtests from the Sydney Language Battery (SYDBAT; Savage et al., 2013).

2.5. Statistical analyses

Behavioural data were analysed using SPSS version 25.0. Group differences on categorical variables (e.g., sex) were examined using chi-square tests. For continuous variables, normality of data distribution was assessed using a combination of Shapiro-Wilk tests and box-and-whisker plots. Where data were normally distributed (e.g., demographic data and AUT Fluency scores), group differences were assessed using a between-subjects ANOVA with Sidak correction for post-hoc comparisons adjusting for small sample sizes. Effect sizes for all ANOVA statistics are denoted using partial eta-squared values (η_p^2). For non-normally distributed data (e.g., ACE-III measures and AUT Flexibility and Originality scores), Kruskal-Wallis tests were used to examine group differences with Bonferroni-adjusted post-hoc pairwise comparisons. Finally, two-tailed Pearson's correlation analyses were conducted to examine associations between general neuropsychological performance and the AUT measures in the patient groups, and between ACE-III subscales and AUT performance in controls.

2.6. Image acquisition

Participants underwent whole-brain structural MRI on a GE Discovery MR750 3 Tesla scanner equipped with an 8-channel head coil. High resolution 3D BRAVO T1-weighted images were acquired using the following parameters: imaging matrix of 256 × 256 × 200, 1 mm isotropic voxel resolution, echo time = 2.5 ms, repetition time = 6.7 ms, inversion time = 900 ms, flip angle = 8°. Structural MRI data were available for all patients and a subset of control participants (n = 15).

2.7. Data pre-processing

Voxel-based morphometry (VBM) was conducted using SPM12 (Wellcome Department of Cognitive Neurology, London, UK), in Matlab R2017b (Mathworks, Natick, Massachusetts, USA). First, T1-weighted images were segmented into five tissue probability maps in the native space. Both the original T1-weighted and the segmented maps were screened by DR during image quality control to ensure that no artefact (such as head motion during acquisition or bad contrast between brain tissues) or image processing errors biased the output images and could impact the statistical results. One bvFTD patient was removed from analysis due to excessive head movement during image acquisition. A Diffeomorphic Anatomical Registration using Exponentiated Lie (DARTEL) algebra template was computed using the grey and white matter probability maps of healthy control participants, then grey and white matter probability maps of patients were warped to the template. Grey matter probability maps of patients and control participants were spatially normalized to the Montreal National Institute (MNI) space according to the transformation parameters from the corresponding DARTEL template. Images were modulated and smoothed with a Gaussian filter of full width at half maximum of 8 mm.

2.8. Voxel-based morphometry analysis

Patterns of grey matter atrophy were explored using a whole-brain general linear model comprising bvFTD and SD patients as well as control participants, with age, sex and total intracranial volume (to account

for individual differences in head size) as regressors of non-interest. The total intracranial volume was assessed in the patient's space prior to spatial normalization by summing thresholded grey matter, white matter and corticospinal fluid probability maps (threshold = 0.2) and counting non-zero voxels. Voxel-wise differences in grey matter intensity between groups were assessed across the entire brain using *t*-tests, where statistical analyses combined a $p_{uncorrected} < .001$ at the voxel level with a cluster size threshold of 500 contiguous voxels, followed by a multiple comparison correction (Family Wise Error or FWE) of $P_{FWE} < .05$ at the cluster level.

Next, correlation analyses were performed between grey matter intensity and each of the three main outcome measures on the AUT (Fluency, Originality, Flexibility) using separate models. These analyses were corrected for age, sex and total intracranial volume, and bvFTD, SD and control groups were considered separately in the statistical model (i.e., one vector per group) to account for atrophy between groups. The clusters that consistently emerged across the three correlation analyses at a statistical threshold of $p_{uncorrected} < .001$ at the voxel level were extracted as regions of interest, with a cluster size threshold of 500 contiguous voxels.

Finally, since a correlation could be significant across- but not within-groups, within-group correlation analyses were conducted between grey matter intensity of each of the selected clusters (corrected for age, sex, total intracranial volume) and the total Fluency subscore of the AUT in bvFTD and SD patient groups separately. Correlations were corrected for multiple comparisons using Bonferroni correction (corrected *p* value: .05/4 = .0125).

3. Results

3.1. Demographic and clinical information

As displayed in Table 1, participants did not differ in terms of age [$F(2, 42) = 1.22$; $p = .31$; $\eta_p^2 = .055$] or years of education [$F(2, 42) = 0.93$; $p = .40$; $\eta_p^2 = .04$], however a marginally significant group difference was evident for sex distribution [$\chi^2 = 6.13$; $p = .047$]. Disease duration (years elapsed since onset of symptoms) did not differ between the patient groups [$F(1, 21) = 0.998$, $p = .33$; $\eta_p^2 = .045$] nor did disease severity [CDR-FTLD SoB: $F(1, 22) = 0.56$, $p = .46$, $\eta_p^2 = .03$]. Both bvFTD and SD patient groups displayed significant impairments on the global measure of cognitive function relative to Controls [ACE-III total: $F(2, 42) = 37.01$; $p < .001$; $\eta_p^2 = .64$], with SD patients showing significant impairments relative to bvFTD, due to the heavy semantic loading of this task ($p = .01$). Importantly, however, bvFTD patients demonstrated disproportionate functional impairment relative to the SD group [FRS Rasch score: $F(1, 18) = 6.33$; $p = .02$; $\eta_p^2 = .26$], suggesting a comparable level of disease severity.

3.2. Cognitive profiles

Characteristic profiles of cognitive impairment were evident across the subscales of the ACE-III in the patient groups relative to controls (Table 1). Briefly, bvFTD patients displayed significant impairments in attention and orientation ($p = .01$), memory ($p < .001$), fluency ($p = .003$), and visuospatial function ($p = .006$), in the context of relatively intact language function ($p = .11$). In contrast, SD patients displayed significant impairments on memory, fluency, and language (all *p*-values $< .001$) while attention and orientation ($p = .16$), and visuospatial function ($p = 1.0$) were largely intact. Direct comparison of the patient groups revealed disproportionately poorer language function in SD relative to bvFTD ($p < .02$), with no other differences evident between the patient groups (all *p*-values $> .08$).

Table 1
Demographic and clinical profile of study groups (standard deviation in parentheses).

	Controls	bvFTD	SD	Group effect (*p* value)	Post hoc (direction of effect)
N	20	15	10		
Sex (M: F)	7:13	10:5	2:8	.047	-
Age (years)	66.8 (7.8)	62.9 (7.2)	64.9 (6.2)	n.s.	-
Education (years)	13.6 (3.0)	12.3 (3.2)	12.4 (3.5)	n.s.	-
Disease duration (years since onset)	-	5.8 (3.0)	4.7 (1.7)	n.s.	-
Disease severity (CDR-FTLD SoB)	-	5.8 (4.6)	4.6 (2.8)	n.s.	-
Disease severity (FRS Rasch Score)	-	−0.59 (1.20)	1.05 (1.65)	.022	SD > bvFTD[a]
ACE-III Attention	17.0 (1.2)	14.5 (2.8)	15.6 (1.6)	.006	Controls, SD > bvFTD
ACE-III Memory	24.5 (1.8)	18.1 (4.6)	15.3 (6.2)	<.001	Controls > bvFTD, SD
ACE-III Fluency	12.3 (1.3)	9.0 (2.7)	6.2 (3.4)	< .001	Controls > bvFTD, SD
ACE-III Language	25.2 (0.9)	22.8 (3.5)	15.4 (5.3)	< .001	Controls, bvFTD > SD
ACE-III Visuospatial	15.5 (0.8)	13.9 (1.9)	15.1 (1.3)	.007	Controls, SD > bvFTD
ACE-III Total (Max: 100)	94.4 (3.3)	78.3 (8.4)	67.6 (14.2)	<.001	Controls > bvFTD > SD

Note - n.s. = not significant ($p > .05$); bvFTD = behavioural variant of frontotemporal dementia; SD = semantic dementia; ACE-III = Addenbrooke's Cognitive Examination – Third Edition. Data missing for 1 bvFTD and 1 SD patient on disease duration (years since symptom onset). Data missing for 1 SD patient on CDR-FTLD SoB. Data missing for 1 bvFTD and 4 SD patients on FRS Rasch Score.
[a]Denotes milder functional impairment in SD relative to bvFTD patients.

3.3. Assessment of divergent thinking

A summary of the three outcome measures of interest on the AUT for all three groups is displayed in Fig. 1 and Table 2.

3.3.1. Fluency

Fluency represents the total number of adequate responses generated by each participant on the AUT, and is the primary measure of interest in this study. A between-subjects ANOVA revealed a significant main effect of group on AUT Fluency, $F(2, 42) = 38.40$; $p < .001$; $\eta_p^2 = .65$, reflecting significant impairments in both bvFTD and SD groups relative to controls (all *p* values $< .001$). Sidak-corrected comparisons between the patient groups revealed disproportionate impairments on AUT Fluency in SD relative to the bvFTD group (Mean difference = 8.1; 95% CI for mean difference = 0.65, 15.48; $p = .03$).

3.3.2. Originality

A Kruskal-Wallis test revealed a significant main effect of group on Originality ratings, $H(2,42) = 16.44$; $p < .001$. Bonferroni adjusted post-hoc pairwise comparisons revealed that, on average, bvFTD and SD patients produced ideas that were less original compared to controls (both *p*-values = .001). Originality of ideas did not differ significantly between the patient groups ($p = .54$).

3.3.3. Flexibility

A Kruskal-Wallis test revealed a significant main effect of group on Flexibility, $H(2, 42) = 34.69$; $p < .001$. Bonferroni adjusted post-hoc pairwise comparisons indicated that bvFTD and SD patients produced ideas that fell into fewer categories compared to controls (both *p*-values $< .001$), with no significant difference between the patient groups ($p =$

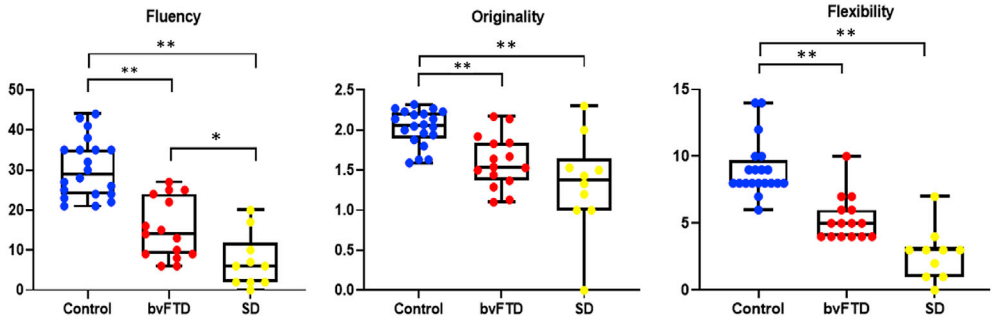

Fig. 1. Performance across participant groups on the Alternate Uses Task. Fluency measured as total number of alternate uses produced over the six trials; Originality measured as the average rating for ideas produced; Flexibility measured as the total number of categories the uses fell under. *significant difference $p < .05$. ** significant difference $p < .01$; bvFTD = behavioural variant of frontotemporal dementia; SD = semantic dementia. Error bars represent minimum and maximum scores.

Table 2
Mean performance on the Alternate Uses Task in participant groups (standard deviation in parentheses).

	Controls (n = 20)	bvFTD (n = 15)	SD (n = 10)	Group effect (*p* value)	Posthoc (Direction of Effect)
Fluency	30.45 (7.44)	15.27 (7.50)	7.20 (6.70)	$p < .001$	Controls > bvFTD > SD
Originality	2.03 (0.23)	1.61 (0.33)	1.48 (0.44)	$p < .001$	Controls > bvFTD, SD
Flexibility	8.45 (1.36)	5.07 (1.10)	2.70 (1.95)	$p < .001$	Controls > bvFTD, SD

Note: Fluency = total number of ideas produced across all trials; Flexibility = total number of categories the generated ideas fell under; Originality = average rating for ideas produced.

.19).

3.4. Correlations with neuropsychological measures

Next, we examined potential associations between the AUT scores and performance on neuropsychological tests of interest in the two patient groups. For SD patients, AUT Fluency was strongly associated with performance on the semantic association subtest of the SYDBAT ($r = .81$, $p < .01$), while AUT Originality correlated with the naming ($r = .784$, $p = .01$) and comprehension ($r = .686$, $p < .05$) subtests of the SYDBAT. No other significant associations were evident in SD (all $r < 0.5$, all *p*-values $> .1$). For bvFTD patients, AUT Fluency and Flexibility were not found to correlate with performance on any neuropsychological measures (all $r < 0.5$, all *p*-values $> .09$). AUT Originality correlated with letter fluency performance ($r = .52$, $p < .05$) and response inhibition on the Hayling test ($r = .679$, $p = .01$), with no other significant associations found (all $r < 0.5$, all *p*-values $> .06$). Controls did not complete the comprehensive neuropsychological test battery administered to patients. When we explored potential associations between AUT performance and subscales of the ACE-III screening tool in controls, no significant correlations were found (all $r < 0.5$, all *p*-values $>.06$).

3.5. Voxel-based morphometry analyses

3.5.1. Patterns of atrophy

Relative to controls, patient groups displayed patterns of atrophy consistent with their clinical diagnoses (see Supplementary Materials Fig. 1 and Table 3). Briefly, bvFTD patients showed decreased grey matter intensity in the right frontoinsular cortex, putamen and temporal pole as well as in the left middle and superior frontal gyri. In contrast, SD patients showed characteristic atrophy predominantly in the anterior temporal lobe bilaterally, extending to the medial temporal lobe including the anterior and posterior parts of the hippocampus, as well as

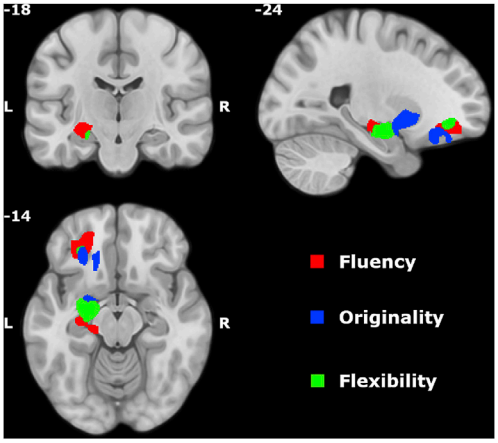

Fig. 2. Convergence across AUT scores: overlapping voxel-wise correlations between grey matter intensity and Fluency, Originality, and Flexibility measures. Separate models exploring correlations between each AUT measure and grey matter intensity were run across all participants (n = 39). Coloured regions show significant clusters extracted using a statistical threshold of $p_{uncorrected} < .001$ with a cluster size extent of 500 voxels (in MNI space).

the insula, basal ganglia, and orbitofrontal cortex. Although bilateral, the burden of atrophy exhibited a left > right predominance, in keeping with previous studies (Irish et al., 2014; Nestor et al., 2006). Direct comparison of the patient groups revealed disproportionate atrophy in SD relative to bvFTD patients in the bilateral anterior temporal lobe, medial temporal lobe including anterior hippocampus, parahippocampal gyrus and amygdala, as well as insula, basal ganglia and orbitofrontal cortex, more pronounced in the left than right hemisphere. The reverse contrast failed to reveal any significant clusters (i.e., bvFTD relative to SD; see Supplementary Materials Fig. 2 and Table 3).

3.5.2. Neural correlates of divergent thinking performance

Voxel-wise whole-brain correlations across the entire sample were conducted to explore associations between grey matter intensity and the three AUT measures (Fluency, Originality, Flexibility; see Supplementary Materials Fig. 3 and Table 4). Fluency of responses was associated with a left medial temporal cluster comprising the anterior hippocampus and parahippocampal gyrus, as well as a left middle frontal gyrus cluster. Flexibility of responses correlated with the left anterior hippocampus, the amygdala, and the left middle frontal gyrus. Finally, Originality of responses correlated with the amygdala, putamen, pallidum, and the same left middle frontal gyrus cluster.

As such, two main clusters were implicated across the AUT measures: (i) a left medial temporal cluster including the anterior hippocampus, parahippocampal gyrus, and amygdala, and (ii) the left middle frontal gyrus (Fig. 2).

3.5.3. Within-group region of interest correlations

Focusing on AUT Fluency as the primary measure of interest, we next explored within-group correlations between grey matter intensity in the left medial temporal and left middle frontal gyrus clusters and AUT Fluency in the bvFTD and SD groups separately (Table 3). In bvFTD, the left middle frontal gyrus cluster was significantly associated with AUT Fluency, while an association with the left medial temporal lobe cluster failed to survive conservative Bonferroni correction. In SD, the left medial temporal cluster was correlated with AUT Fluency and no significant associations emerged with the left middle frontal gyrus. Post hoc power calculations were run using G*Power 3.1 and revealed an achieved power of 0.77 in bvFTD and 0.81 in SD.

4. Discussion

The objective of this study was to explore the capacity for divergent thinking, and its neural substrates, in a well-characterised cohort of patients with semantic dementia (SD) to provide unique insights into the contribution of semantic processing to acts of creative cognition. Our main finding was that, relative to controls, SD patients and a disease control group of behavioural-variant FTD patients showed marked impairments on the AUT, generating significantly fewer responses and uses that lacked originality and diversity. Voxel-based morphometry analyses based on structural MRI enabled us to elucidate the neural bases of these impairments, revealing a central role for medial temporal and prefrontal brain regions in divergent thinking. Here, we discuss our findings in relation to the extant functional neuroimaging literature on creativity, and emphasise the importance of lesion studies in advancing our fundamental understanding of creative cognition.

The most striking finding from this study is our observation of profound impairments in divergent thinking in SD, manifesting in a paucity of responses on the AUT and the provision of responses which were less original and less diverse relative to controls. Looking at the potential underlying cognitive mechanisms, the Fluency of responses in SD correlated robustly with an independent measure of semantic association, which measures the ability to make links between semantic concepts (Savage et al., 2013). Originality of responses in SD was associated with measures of semantic naming and comprehension (Savage et al., 2013). These findings are consistent with the idea that degeneration of the semantic knowledge base results in a narrowed repository from which AUT responses can be configured (Hass, 2017; Kenett and Faust, 2019; Volle, 2018). By this view, the limited store of conceptual knowledge in SD may result in a less flexible semantic memory structure that further hinders declarative search processes (Kenett et al., 2016; Kenett et al., 2018); Leon et al., 2014).

Divergent thinking performance in bvFTD was also found to be significantly compromised across all AUT subscales relative to controls, converging with previous studies (Ruggiero et al., 2019). This marked incapacity to generate uses that differ from the canonical exemplar of an item dovetails with well-documented difficulties in set-shifting, taking the perspectives of others, and disengaging from the immediate sensorium in this syndrome (O'Callaghan et al., 2019), ultimately resulting in an increasingly rigid and inflexible style of interacting with the world. In terms of cognitive mechanisms, the originality of the responses generated by bvFTD patients correlated with letter fluency and response inhibition, suggestive of difficulties with disengagement. Previous studies have established the role of the prefrontal cortex in exerting top-down control to guide the creative process (Benedek and Fink, 2019; Chrysikou, 2019; Gonen-Yaacovi et al., 2013). The degeneration of the prefrontal cortex in this population may disrupt a number of executive processes that support the strategic retrieval of information from memory, the capacity to disengage from the exemplar item, and the ability to override or inhibit prepotent responses when required to generate creative solutions (Chrysikou, 2019).

Our voxel-based morphometry analyses revealed important insights regarding the neural bases of divergent thinking deficits in SD and bvFTD. Of note, we found two clusters that were predominantly implicated in the Fluency of ideas generated on the AUT; namely a left medial temporal lobe cluster centred on the left anterior hippocampus, and a left middle frontal gyrus cluster. Current theories on the neural mechanisms that relate to the creative process posit a frontal function that mediates flexibility and exertion of cognitive control (Benedek and Fink, 2019), and a temporal function that supports semantic integration and insight (Shen et al., 2017). The left middle frontal gyrus cluster correlated strongly with AUT performance in bvFTD, resonating with a large body of work implicating the frontal lobes in the creative process (Beaty et al., 2016, 2017, 2019; Benedek and Fink, 2019; Gonen-Yaacovi et al., 2013) and supporting the associations we found on the behavioural level between divergent thinking performance and neuropsychological indices of frontal lobe function.

In contrast, the left medial temporal cluster was found to correlate robustly with AUT performance in the SD group. Our finding of a predominantly left anterior hippocampal contribution to total Fluency of responses in SD resonates strongly with the proposal that the hippocampus plays a critical role in creative and flexible forms of cognition (Beaty et al., 2018; Madore et al., 2019; Rubin et al., 2014). Patients with hippocampal lesions have been shown to perform poorly across figural and verbal creativity tasks (Duff et al., 2013), and are unable to imagine new experiences (Hassabis et al., 2007). Notably, the anterior hippocampus has been suggested to support coarse global information (i.e., event gist) versus the fine-grained representation of perceptual details in posterior subregions (i.e., specific event details; Brunec et al., 2018). In the context of divergent thinking, anterior hippocampal atrophy may disrupt the capacity to invoke abstracted features that generalise across different settings (Irish and Vatansever, 2020). Looking at the nature of items generated on the AUT, SD patients often defaulted to the canonical exemplar of the test item (e.g., for brick: 'building'), and some displayed a marked inability to deviate or move from the specific item category (e.g., 'you just use bricks to build all sorts of things like houses, apartment buildings and shopping centres'). This was also evident to a lesser extent in the bvFTD group, aligning with their characteristic perseverative tendencies. Importantly, however, SD patients relied heavily on their own previous experiences with the cue item (e.g., 'what I find great that you can do is just turn bricks into steps') resonating strongly with recent studies suggesting a role for episodic memory in creative thinking (Beaty et al., 2018; Madore et al., 2016, 2019). This converges with findings on

Table 3
Correlations between grey matter intensity and AUT Fluency performance.

		Voxel-wise analysis: across group correlations					Region-based analysis: within group correlations			
		size in mm3	t-value	Coordinates (x, y, z)			bvFTD		SD	
							r	***p***	***r***	***p***
Left Medial Temporal Lobe	AUT Fluency	1478	5.39	−26	−18	−9	.54	.05	**.80**	**.006**
Left Middle Frontal Gyrus	AUT Fluency	2700	4.77	−31	36	−13	**.69**	**.007**	.58	.08

Note – Left column: voxel-wise correlations across groups between grey matter intensity and AUT Fluency, using a statistical threshold of $p_{uncorrected} < .001$ with a cluster extent size of 500 voxels (in MNI space). *t*-values refer to the maximal *t*-values of the clusters. Right column: within-group Pearson's correlations in bvFTD and SD groups between the mean grey matter intensity (corrected for age, sex, total intracranial volume) and AUT Fluency. r = Pearson's correlation coefficient. Bold values indicate correlations that survive Bonferroni correction for multiple comparisons (corrected threshold: $p = .0125$).

future simulation tasks, whereby SD patients recapitulate or "recast" past episodic experiences in their entirety and appear unable to construct novel or new experiences from scratch (Irish et al., 2012a, 2012b). As event-driven representations come to dominate the mental landscape of SD, we therefore see an increase in concrete, experience-dependent information on any open-ended cognitive task in which the transfer of knowledge is required (see Irish and Vatansever, 2020). Here we demonstrate that this preference for the familiar and concrete, driven by intact recent episodic memory, extends to the arena of creative thinking and suggests a domain-general mechanism by which SD patients compensate for their prominent semantic impairments (reviewed by Irish, 2020; Irish and Vatansever, 2020).

As the undifferentiated repository of conceptual knowledge, semantic memory can be harnessed at many different levels of abstraction and applied across contexts resulting in a flexible system that is highly conducive to creative thought (Abraham, 2014; Irish, 2020; Kenett and Faust, 2019). For this system to be efficient, elements from episodic and semantic memory need to be extracted and recombined into a flexible representation that can be deployed across multiple contexts (Addis, 2018). The hippocampus has a well-established role in supporting the binding of arbitrary relations between elements into representations that can be flexibly deployed across different contexts (Rubin et al., 2014). In this light, hippocampal atrophy in SD may disrupt the relational binding of content derived from recent episodic experiences and residual semantic concepts, resulting in increasingly inflexible and rigid forms of thought (Irish and Vatansever, 2020). We suggest that the degeneration of the semantic knowledge base in SD not only disrupts access to relevant conceptual information but also the capacity to make appropriate associative links *between* concepts, a cognitive process that is essential for arriving upon unique and creative responses (Kenett, 2018; Kenett and Faust, 2019; Mednick, 1962; Volle, 2018). It will be important for future studies to systematically test how the degradation of conceptual knowledge versus the disruption of relational binding relates to divergent thinking impairments in SD.

Several methodological issues warrant consideration in the current context. Our neuropsychological test battery was constrained due to the nature of these syndromes and the need to minimise the risk of patient fatigue over what was already a lengthy testing session. Future studies might consider exploring the role of disengagement in divergent thinking further, by including measures such as the Wisconsin Card Sorting Test (Heaton et al., 1993). Similarly, it would be interesting to continue to explore how disruption to the binding of concepts influences divergent thinking by including tests such as the Similarities subtest of the WAIS-IV (Wechsler, 2008) or Raven's Progressive Matrices (Raven and Raven, 2003). In addition, it will be important for future studies to consider using non-verbal divergent thinking tasks to complement the outcomes on the AUT, given variable profiles of loss and sparing observed in SD when verbal versus non-verbal cognitive tasks are employed (Irish, 2020; Rankin et al., 2007).

Given the rarity of the SD syndrome, we combined left- and right-SD cases in the current sample to maximise power. Although all of the SD cases showed bilateral anterior temporal lobe atrophy at the time of this study, it remains unclear whether the lateralisation of anterior temporal lobe damage observed in the early stages of the disease trajectory plays a modulating role in divergent thinking disruption (see Supplementary Materials Table 2 for individual SD patient scores). This will be important to address given reports of increased rigidity and behavioural disturbances in the less prevalent right-sided presentation of SD (Kamminga et al., 2015). From a clinical perspective, understanding how rigidity of thought relates to behavioural changes will prove particularly informative for carers, given observations of increasingly rigid behaviours in SD and bvFTD, including strict adherence to routines, fixed food preferences, and stereotypical and inflexible behaviours (Bozeat et al., 2000a; Kamminga et al., 2014). To equip carers to deal with these behavioural changes, longitudinal studies will be essential to chart how cognitive inflexibility potentially relates to behavioural disturbances, and the temporal unfolding of these symptoms.

In summary, this study is the first, to our knowledge, to systematically explore the cognitive and neural mechanisms underlying compromised divergent thinking capacity in SD and bvFTD patients. Using SD as a lesion model for semantic memory, our findings underscore the importance of the conceptual knowledge base for creative cognition. Notably, the progressive deterioration of semantic knowledge in SD not only precludes access to appropriate semantic constructs, but impairs the capacity to draw novel associations between concepts in the service of divergent thinking. Future studies exploring the neurocognitive mechanisms of semantic association will be important to refine our understanding of the mechanisms by which humans arrive upon unique and creative ideas.

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Appendix A. Supplementary data

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