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Unveiling the mystery of déjà vu: The structural anatomy of déjà vu

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ABSTRACT

Déjà vu (DV) is a widespread, fascinating and mysterious human experience. It occurs both in health and in disease, notably as an aura of temporal lobe epilepsy. This feeling of inappropriate familiarity has attracted interest from psychologists and neuroscientists for over a century, but still there is no widely agreed explanation for the phenomenon of non-pathological DV. Here we investigated differences in brain morphology between healthy subjects with and without DV using a novel multivariate neuroimaging technique, Source-Based Morphometry. The analysis revealed a set of cortical (predominantly mesiotemporal) and subcortical regions in which there was significantly less gray matter in subjects reporting DV. In these regions gray matter volume was inversely correlated with the frequency of DV. Our results demonstrate a structural correlate of DV in healthy individuals for the first time and support a neurological explanation for the phenomenon. We hypothesis that the observed local gray matter decrease in subjects experiencing DV reflects an alteration of hippocampal function and postnatal neurogenesis with resulting changes of volume in remote brain regions.

Déjà vu (DV) is an eerie experience in which we recognize that a situation is familiar, sometimes intensely so, while we are concurrently aware that this sense of familiarity is inappropriate (Brown, 2003; O'Connor and Moulin, 2010). Occasional DV is reported by 60–80% of healthy respondents (Adachi et al., 2003; Probst and Jansen, 1991; Sno et al., 1994), implying that the experience is widespread. On the other hand, it also occurs in clinical contexts as a manifestation of brain disease, particularly as an aura of temporal lobe epilepsy (Maudsley, 1889; Penfield, 1955; Stevens, 1990). Suggested explanations for DV in healthy individuals include (i) the activation of a neural system involved in the detection of

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familiarity independently of a – normally closely coupled – system involved in recollection; (ii) the related idea that the current experience is indeed familiar but the source of familiarity is inaccessible; (iii) the theory that a disruption of attention or perception leads to anomalous 'dual' processing of sensory information. An extensive recent review favours explanations in terms of memory (ii) or attention (iii) to the neurological (i) hypothesis (see Adachi et al., 2003).

Studies of DV in patients with epilepsy have implicated a neural network centered on mesiotemporal regions (Bancaud et al., 1994; Bartolomei et al., 2004; Guedj et al., 2010; Halgren et al., 1978; Kovacs et al., 2009; Vignal et al., 2007). We hypothesized that a similar network would be involved in non-pathological DV, and that there would be functional and perhaps even morphological differences in this network between healthy people who do and do not experience DV. We investigated potential differences in brain morphology with a novel multivariate technique – Source-Based Morphometry (SBM) – which is more sensitive to subtle differences in local gray matter volume (GMV) than previously used univariate parametric methods (Kasparek et al., 2010; Xu et al., 2009).

One hundred and thirteen healthy subjects without any neurological or psychiatric condition participated in the study. All subjects underwent magnetic resonance imaging (MRI) of the brain using a 1.5 T scanner and completed the Inventory for Déjà Vu Experiences Assessment (IDEA), a questionnaire used widely in previous DV research (Sno et al., 1994). Subsequently subjects were divided into two groups according to their answer to the critical question A1: 'Have you ever had the feeling of having experienced a sensation or situation before in exactly the same way when in fact you are experiencing it for the first time?' Respondents answering 'yes' were categorized as DV subjects ($N = 87$; 45M; mean age 24.8; SD = 4.17), respondents answering 'never' as non-DV subjects ($N = 26$; 13M; mean age 26.0; SD = 6.64). The individual MRI data were segmented into gray matter images and analyzed using SBM, in which independent component analysis is used to identify naturally grouping, maximally independent sources of local GMV variability with common covariation among subjects, with subsequent analysis of group differences (Xu et al., 2009). The initial analysis was blind to group membership. We then interrogated the data to establish whether there were significant differences in local GMV between DV and non-DV subjects, and whether there was any relationship between local GMV and the frequency of DV experiences (as indicated by subjects in the questionnaire; for details see Supplementary Methods).

Using SBM, eight components (extracted by the Minimum Description Length algorithm) were automatically extracted from gray segment images. Among these one component showed a significant effect of group (Man-Whitney U test, $Z = 2.81$, $p < .05$, Bonferroni corrected for 8 tests). This component involved a set of regions in which there was significantly less gray matter in DV subjects compared to non-DV subjects: bilateral mesiotemporal regions (with maximal effect within hippocampi and parahippocampal gyri), insular cortices, superior temporal sulci, basal ganglia and thalami (Fig. 1A, Table 1). No clear-cut lateralization was observed in our data, though left hemisphere involvement was more extensive (Supporting Online Fig). In keeping with our primary result, further analysis revealed an inverse correlation between GMV (within depicted regions) and the frequency of DV experiences (Kruskal-Wallis ANOVA, 4 groups with 26/24/52/11 subjects, $H = 8.48$, $p < .05$) (Fig. 1B). There were no regions where DV subjects had significantly more gray matter.

The set of brain regions distinguishing DV and non-DV subjects in this analysis mirrors the recently identified distribution of GMV reduction in subjects with mesial temporal lobe epilepsy (MTLE) involving hippocampal and parahippocampal regions, entorhinal and perirhinal cortices, amygdala, lateral temporal neocortex, thalamic and striatal nuclei, cingulate gyrus, insula, and cerebellum (Brazdil et al., 2009; Keller and Roberts, 2008; Pail et al., 2010). These structures belong to a clinically relevant limbic-temporal network, which plays a crucial role in the pathogenesis of MTLE. We note that the widespread GMV abnormalities described in MTLE have been demonstrated using voxel-based morphometry (VBM), a univariate parametric method with lower power to detect subtle morphological differences than the multivariate technique employed in this study. Recently published comparative studies applying both SBM and VBM in a cohort of schizophrenic patients showed that SBM allows detection of local

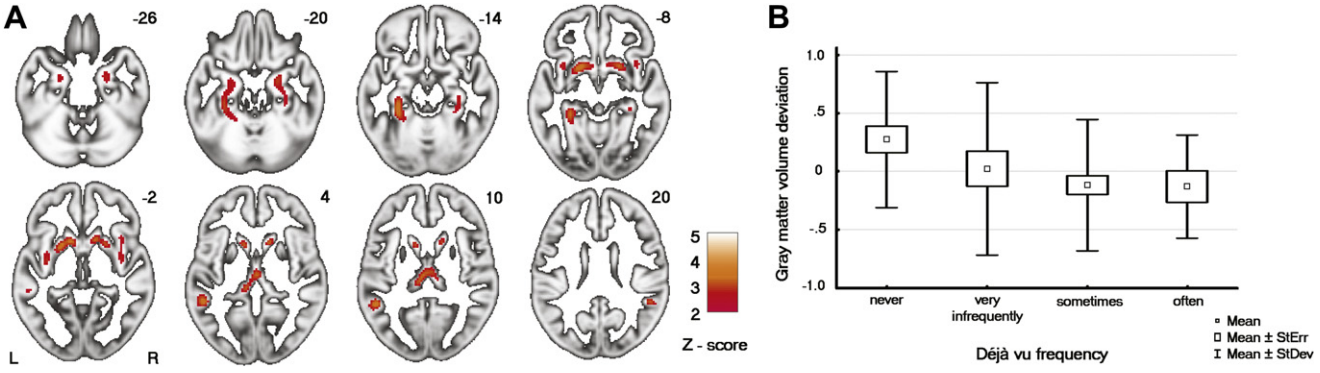

Fig. 1 – A) Brain regions with GMV decrease in subjects with DV experiences. Spatial map of component with significant effect of groups (normalized to unit standard deviation thresholded by $|Z| > 2.5$ and extent threshold 60 voxels). B) GMV within involved set of regions decreases significantly with increasing DV frequency (deviations from mean of the investigated population).

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Table 1 – Differences in GMV detected by SBM (DV < non-DV).

ROI	MNI coordinates	Number of voxels	Z-score in maximum
L Putamen/Caudatum	−20, 10, −6	331	3.89
L Superior temporal sulcus	−52, −46, 8	217	3.80
L Parahippocampal Gyrus/Hippocampus/Fusiform Gyrus/Amygdala	−30, −34, −14	487	3.67
L/R Thalamus	0,−16, 6	242	3.65
R Putamen/Caudatum	22, 10, −6	264	3.47
R Inferior parietal lobule/Superior temporal sulcus	50, −44, 20	69	3.28
R Parahippocampal Gyrus/Hippocampus/Amygdala	22, −6, −22	238	3.11
L Insula	−36, −4, −2	94	2.89
R Insula	38, 14, −6	104	2.88

ROI, regions of interest; L, left,; R, right; MNI coordinates, coordinates in MNI stereotactic space (x, y, z); Number of voxels, cluster size in which there is significant GMV difference between the groups; voxel size, 1.5 × 1.5 × 1.5 mm.

GMV differences which are not detected by VBM (Kasparek et al., 2010; Xu et al., 2009). The GMV differences between DV and non-DV subjects reported here are likely to be quantitatively subtle by comparison with those apparent in MTLE.

The most extensive volume changes in both MTLE and in our study are observed in mesial temporal/hippocampal regions. In this study, within the medial temporal lobes, the most pronounced differences in GMV between healthy subjects with and without DV experiences were found in the parahippocampal regions, where electrical stimulation in patients with epilepsy is most likely to lead to DV (Bartolomei et al., 2004), and which has been associated in healthy subjects with familiarity judgements or the 'feeling of knowing' (Aggleton and Brown, 1999). However, in both epileptic and non-pathological DV, there appears to be a widespread alteration of neural structures and networks. These volume changes seen in the insular, lateral temporal and subcortical regions (incl. caudate and putamen) are most likely to represent secondary consequences of altered anatomical connectivity within the primarily involved hippocampal formation (Crofts et al., 2011). It is noteworthy that DV has been elicited during deep brain stimulation in a hemidystonic patient, indicating the functional significance of the subcortical part of this network, and emphasising the functional relationship between the hippocampus and basal ganglia in the genesis of DV (Kovacs et al., 2009).

The qualitative similarity of the experience of DV in pathological and non-pathological instances suggests a common underlying process (Adachi et al., 2010). Our results point to similarities in the anatomical structures involved. It remains an open question how closely the physiological basis of non-pathological DV resembles an ictal event, as hypothesized by Wilder Penfield almost fifty years ago (Penfield, 1955). The hippocampal formation is especially plastic – as it must be given its crucial role in memory acquisition – and is exceptionally vulnerable to the effects of a variety of insults, including seizures, ischemia or inflammation, as well as environmental and physiological influences, such as early life psychosocial stress or sleep deprivation. These factors, especially when occurring early in development, have been linked to hippocampal atrophy, alterations of postnatal neurogenesis in the dentate gyrus, and neuronal hyperexcitability (McEwen, 1999; Novati et al., 2011). Given our anatomical findings, the paroxysmal character of DV and the possible impact of environmental and molecular factors on hippocampal neurogenesis and excitability, the role of 'small seizures' in the genesis of non-pathological DV experiences deserves consideration. Future work is required to clarify whether the common anatomical basis of epileptic and non-epileptic DV, revealed by this study, truly reflects a common physiology.

Conflict of interest statement

The authors declare that they have no competing financial interests.

Author contributions

M.B., R.M., T.U., T.K. and I.R. designed the study and discussed analyses and results; R.M. and M.M. acquired imaging and questionnaire data acquisition; R.M. performed the analyses; M.B. and A.Z. wrote the paper with input from all authors.

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Supplementary material

Supplementary data related to this article can be found online at doi:10.1016/j.cortex.2012.03.004.

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