Title: Insights into déjà vu: Associations between the frequency of experience and amplitudes of low-frequency oscillations in resting-state fMRI.

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Significance statement

This study examines the neurophysiological underpinnings of déjà vu (DV) experience by assessing a metric of brain activity from resting-state neuroimaging data. In doing so, we have revealed differences in brain function between individuals who have experienced DV and those who have not in brain regions implicated in DV and those comprising the default mode network (DMN). We interpret our findings to suggest that the DMN and other cortico-subcortical circuitry are disrupted in individuals who experience DV, which leads ultimately to the erroneous feeling of familiarity. These findings enrich current understanding of DV and provide a neuropsychological model that should guide future research.

Abstract

The phenomenon of déjà vu (DV) has intrigued scientists for decades, yet its neurophysiological underpinnings remain elusive. Brain regions have been identified in which morphometry differs between healthy individuals according to the frequency of their DV experiences. This study built upon these findings by assessing if and how neural activity in these and other brain regions also differ with respect to DV experience. Resting-state fMRI was performed on 68 healthy volunteers, 44 of whom reported DV experiences (DV group) and 24 who did not (NDV group). Using multivariate analyses, we then assessed the (fractional) amplitude of low-frequency fluctuations (fALFF/ALFF), a metric that is believed to index brain tissue excitability, for 5 discrete frequency bands within sets of brain regions implicated in DV and those comprising the default mode network (DMN). Analyses revealed significantly lower values of fALFF/ALFF for specific frequency bands in the DV relative to the NDV group, particularly within mesiotemporal structures, bilateral putamina, right caudatum, bilateral superior frontal cortices, left lateral parietal cortex, dorsal and ventral medial prefrontal cortex, and the posterior cingulate cortex. The pattern of differences in fALFF/ALFF measures between the brains of individuals who have experienced DV and those who have not provides new neurophysiological insights into this phenomenon, including the potential role of the DMN. We suggest that the erroneous feeling of familiarity arises from a temporary disruption of cortico-subcortical circuitry together with the upregulation of cortical excitability.

Keywords: Deja vu, ALFF, fALFF, resting-State fMRI, Default Mode Network.

1. Introduction

Déjà vu (DV) is an intriguing phenomenon that has attracted the attention of scientists for decades. From a psychological perspective, DV is a spontaneous metacognitive state combining conflicting mental evaluations – specifically, a subjective feeling of familiarity coupled with an awareness that this feeling is experienced inappropriately (Brown, 2004; Metcalfe and Schwartz, 2016). This fleeting feeling of erroneous familiarity is reported in up to 76% of the healthy population (Adachi et al., 2003), and is generally believed to reflect non-pathological irregularities in brain function among memory-related structures within the mesial temporal lobes (Illman et al., 2012). The phenomena of DV is also reported frequently as a type of aura in temporal lobe epilepsy, however, and in psychiatric conditions such as anxiety and depression (Illman et al., 2012; Richardson and Winokur, 1967). Earlier brain stimulation studies performed by Bartolomei et al. (2012) revealed that this pathological form of DV can be elicited through a specific pattern of neural signaling within a medial temporal lobe network, with indirect involvement of the lateral temporal cortex. Although the experience appears to be qualitatively similar whether it occurs as a non-pathological phenomenon or a pathological manifestation in epilepsy (Warren-Gash and Zeman, 2014), these two forms of DV appear to be associated with distinct neuroanatomical substrates (Brázdil and Zeman, 2013; Labate et al., 2015). It remains to be seen, then, whether the same neurophysiological mechanism underlies non-pathological.

Unfortunately, the unpredictable and fleeting nature of DV makes it very difficult to elucidate its neurophysiological substrates while the phenomenon is occurring. In recent years, several studies have attempted to elicit analogues of DV experimentally (Brown and Marsh, 2009; Cleary et al., 2012; Cleary and Reyes, 2009; O'Connor et al., 2008; Urquhart et al., 2018). Cleary (2012), for example, engineered partial familiarity for experimental stimuli without subjects' conscious recollection. Similarly, Urquhart and colleagues succeeded in generating a mnemonic conflict whereby participants experienced familiarity with stimuli and a concomitant awareness of the implausibility of this familiarity feeling using a modified Deese-Roedriger-McDermott false memory procedure (Roediger and McDermott, 1995; Urquhart et al., 2018). However, it remains to be seen whether these analogues of DV are suitable for neuroimaging investigations of the phenomenon.

As an alternative, several neuroscientific investigations have identified morphological differences between the brains of healthy individuals who report having the experience of DV and those who do not, particularly within mesiotemporal structures, insular cortices, superior temporal sulci, basal ganglia and thalami (Brázdil et al., 2012; Labate et al., 2015; Peslova et

al., 2018). One study built upon the knowledge that grey-matter volume covaries among brain structures that co-activate consistently as nodes of functional networks (Evans, 2013); Shaw et al. (2015) observed patterns of increasing and decreasing grey-matter volume covariance among many of the aforementioned brain structures with higher frequencies of self-reported DV experience, interpreting this to reveal two neural "networks" associated with the phenomenon. Metrics of brain structure can only ever provide a crude proxy of brain function, however, and offer limited insight into the patterns of neural signaling that underpin DV.

A more accurate measurement of brain function can be achieved with resting-state functional magnetic resonance imaging (fMRI). Covariance in the spontaneous low-frequency fluctuations (0.01-1.0Hz) of blood oxygenation level-dependent signal captured by fMRI is believed to reflect functional networks of intrinsic brain activity (Biswal et al., 1995; Zou et al., 2008). Indeed, it has been shown repeatedly that low-frequency fluctuations of the resting-state fMRI signal are physiologically meaningful and reflect spontaneous neuronal activity (Anderson, 2008; Biswal et al., 1995; Hu et al., 2015; Liu et al., 2014; Lowe et al., 1998; Yang et al., 2019). Further, studies have shown a positive relationship between low-frequency fluctuations and resting-state fluorodeoxyglucose metabolism (Aiello et al., 2015), functional activation and neuroanatomical connectivity (Di et al., 2013; Zhang et al., 2014). Metrics of the resting-state fMRI signal have been developed to estimate spontaneous brain excitability within nodes of functional networks. One such index is the amplitude of low-frequency fluctuations (ALFF; Zang et al., 2007), which is defined as the square root of the power spectrum within a low-frequency range. Another index that appears less susceptible to physiological noise is the fractional ALFF (fALFF) – the ratio of power spectrum of low-frequency fluctuations to that of the entire frequency range (Zou et al., 2008). The latter has gained in popularity, and has been used to demonstrate altered functional connectivity in patients with neurodegenerative diseases (e.g., Hu et al., 2015; Liu et al., 2014; Yang et al., 2019) and temporal lobe epilepsy (Zhang et al., 2010).

Using both ALFF and fALFF metrics of resting-state fMRI, the present study explored differences in brain excitability between healthy individuals who report DV experiences and those who do not. We hypothesized that the former group would show greater spontaneous neural activity in brain structures implicated previously in DV compared to individuals who report no experience of the phenomenon. Additionally, we decided to study DV-related changes in ALFF/fALFF throughout a set of brain regions comprising the so-called default mode network (DMN) – an interconnected group of brain structures that demonstrate intrinsically elevated and covarying ALFF values (Fransson, 2006; Yang et al., 2007; Zou et al., 2008), and

exhibit covarying decreases in activity during attention-demanding, goal-directed tasks. Recently, disrupted excitability and reduced functional connectivity within the DMN has been demonstrated in idiopathic generalised epilepsy (Parsons et al., 2020). Since DV is experienced frequently as an epilepsy aura (Illman et al., 2012), this condition can provide a useful model for pathological DV. We hypothesised, therefore, that ALFF/fALFF measures throughout the DMN will be reduced in those experiencing DV compared with those who do not.

2. Material and methods

2.1. Subjects

Eighty-eight healthy individuals volunteered for the study, all aged between 18 and 33 years and reporting no neurological or psychiatric condition. All volunteers completed the Inventory for Déjà vu Experiences Assessment (IDEA) – a questionnaire used commonly in DV research (Sno et al., 1994). Question A1 of this instrument asks, "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?" Individuals answering 'yes' to this question were asked to describe their typical DV experience in their own words, and their definitions of the phenomenon were verified by two trained independent psychologists (K.M. and L.S.) before including them in the final sample. Each participant was then asked to complete a battery of psychological questionnaires to screen for any unrecognized psychiatric conditions: The nine-item Patient Health Questionnaire (Kroenke et al., 2001), the seven-item Generalized Anxiety Disorder Questionnaire (Spitzer et al., 2006), and the ten-item Perceived Stress Scale (Cohen et al., 1983). Eleven volunteers were excluded on the basis of these pre-screening measures; 10 were identified as suffering potentially from a neurological or psychiatric condition, and one provided an unclear description of their DV experience. Of the volunteers who were included in the study, a further 9 were omitted from any analyses due to poor data quality.

The final sample therefore included 68 participants (38 males; mean age = 25.95 years [SD = 3.66]), comprising 44 individuals who reported experiences of DV (DV group) and 24 participants who did not (NDV group). The latter consisted of individuals who reported to have never experienced this phenomenon (n=17) and those unable to answer question A1 because they could not imagine the experience (n=7). With regards to the frequency of self-reported DV experience, six participants reported having infrequent experience of the phenomenon (less than once a year), 31 experienced DV several times a year, and seven claimed to experience it frequently (several times a month).

The study was approved by the Research Ethics Committee of Masaryk University, and all participants provided written informed consent.

2.2. MRI acquisition

Both structural and functional imaging protocols were performed in a single session, with a 3T Siemens Magnetom Prisma scanner and 64-channel head-neck coil. Structural data were acquired with a T1-weighted high-resolution protocol using an MPRAGE sequence with the following parameters: TR = 2300 ms, TE = 2.33 ms, TI = 900 ms, FA = 8°; 240 sagittal slices with 1 mm isotropic voxels and an in-plane FOV of 224x224 mm; and GRAPPA with a PAT factor = 2. Functional data were acquired with echo-planar imaging and simultaneous multi-slice option (CMRR MB-EPI) during a period of 8 minutes and 33 seconds, in which participants rested with their eyes-closed. The parameters of BOLD signal measurement were guided by recommendations from the Human Connectome Project (Glasser et al. 2013, Smith et al. 2013), but with minor changes; for instance, the usage of standard anterior-posterior (AP) phase encoding direction rather than the combination of a balanced number of volumes with left-right and right-left. Time-series consisted of 700 volumes, with TR = 720 ms, TE = 33 ms, 72 axial slices with in-plane FOV = 180x208 mm, an acquisition matrix of 90x104, 2mm isotropic voxels, pixel bandwidth = 2290 Hz, FA = 26°, MB factor = 8, and AP phase encoding direction.

2.3. MRI data processing

All MRI data were processed in SPM12, build 6225 (Wellcome Trust Centre for Neuroimaging at University College London, UK; http://www.fil.ion.ucl.ac.uk/spm/), running under Matlab 8.4. R2014b. Functional images were processed as follows: the time-series were realigned to the first volume to correct for head motion, transformed into standard stereotactic space (MNI), and spatially smoothed with a Gaussian filter (FWHM = 5 mm). The voxel size was 2x2x2 mm isotropic. The T1-weighted anatomical high-resolution data were registered to the mean functional image of each subject and spatially normalized into MNI space.

2.4. ALFF and fALFF calculation

The low frequency range was subdivided to 4 bands as defined previously (Zuo et al., 2010): slow-5 (0.01 - 0.027 Hz), slow-4 (0.027 - 0.073 Hz), slow-3 (0.073 - 0.198 Hz) and slow-2 (0.198 - 0.25 Hz). Due to the relatively high sampling rate we were able to achieve (TR = 0.72 s), we also added a slow-1 band (0.3 Hz – 0.5 Hz) in an attempt to evaluate BOLD fluctuations

in higher frequencies (see Penttonen and Buzsáki, 2003). Maps of ALFF and fALFF values were then computed from the preprocessed BOLD time-series as follows: Only grey matter voxels were selected using *a priori* tissue probability maps from SPM12, using a benevolent threshold of 0.2 combined with individual subject assessment of in-brain voxels (thereby avoiding noise or out-of-brain data, but also leaving as many grey matter voxels as possible for the subsequent analyses). Time-series in each valid voxel were detrended (removal of the mean and linear drift) and high-pass filtered with a cut-off of 200 s, implemented in SPM12; and signals relating to white matter or cerebrospinal fluid, calculated as the first principle component extracted from representative brain regions, were used as nuisance signals and removed by GLM-based filtering. Fast Fourier transform was then applied to the clean time-series. Finally, ALFF values were calculated in each individual frequency band as the square root of power integrated over a specific frequency band, and fALFF values were calculated as a ratio of power spectrum within a specific frequency band to that of entire frequency range. To control for the possible effect of local grey matter volume, the resulting values were corrected as established in previous studies (Han et al., 2011).

2.5. Statistical analysis

2.5.1. Déjà vu regions of interest (DV-ROIs)

To examine relationships between resting-state fMRI data and self-reported DV experience, we interrogated the brain regions defined by Shaw et al. (2015); that is, regions emerging from a delineation of the findings of (Brázdil et al., 2012) in which grey-matter volume differed between healthy individuals according to their experience of DV frequency. Regions of interest (ROIs) were generated as spheres with a radius of 5 mm centered on these brain regions. An illustration of these ROIs is given in Figure 1, and more detailed information is provided in Supplementary Table S1.

2.5.2. Default mode network regions of interest (DMN-ROIs)

A clear consensus on the delineation of the DMN is not yet available. Therefore, in this study we decided to implement the resting state DMN localization provided by Lin et al.'s (2017) extensive brain mapping study. Again, ROIs were generated as spheres with a radius of 5 mm centered on these localisations. These ROIs are illustrated in Figure 1, and their MNI coordinates are presented in Supplementary Table S2.

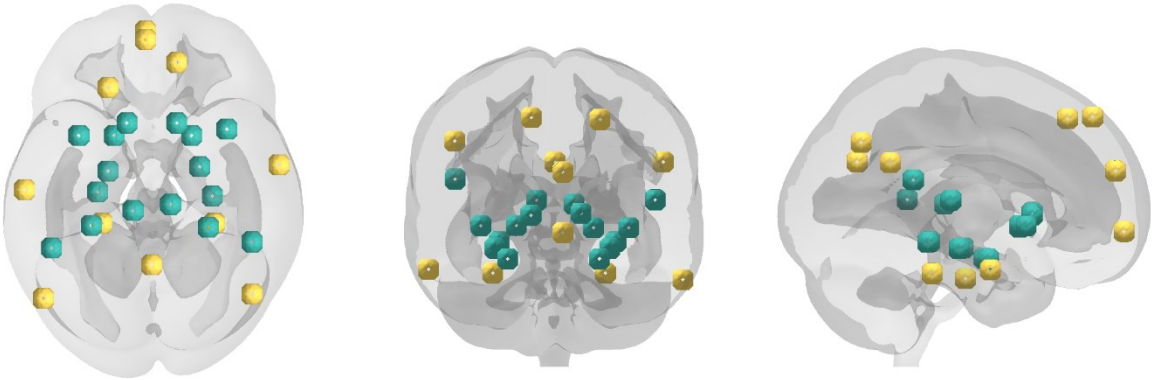

Figure 1. An illustration of DV-ROIs (*green*) and DMN-ROIs (*yellow*).

Partial Least Squares (PLS)

Mean values of ALFF and fALFF were extracted from both DV-ROIs and DMN-ROIs. Subsequently, mean-centered Partial Least Squares (PLS; Krishnan et al., 2011; McIntosh and Lobaugh, 2004; http://pls.rotman-baycrest.on.ca/source) analyses were implemented to evaluate differences between DV and NDV subjects in ALFF or fALFF values across all ROIs in each set. This multivariate technique allowed us to identify latent variables that captured reliable patterns of difference in ALFF or fALFF values between the DV and NDV groups across all 16 brain regions comprising the DV-ROIs, or all 11 DMN-ROIs, simultaneously, negating the need for multiple-comparison correction when assessing group differences among each set of ROIs. This PLS analysis was performed separately for each ALFF and fALFF values, and for each frequency band. The reliability of group differences identified in each PLS analysis was determined with 5000 permutations and 1000 bootstraps.

To assess the specific influence of déjà vu frequency, we calculated post-hoc Kruskal-Wallis ANOVA tests on the three subgroups reporting some experience of the phenomenon where PLS identified significant differences in ALFF or fALFF values between the DV and NDV subjects.

3. Results

3.1. DV-ROIs

PLS analyses conducted on revealed that both ALFF and fALFF values showed non-significant trends towards slightly higher values for the DV compared with the NDV group in the slow-1 and slow-2 frequency bands. Conversely, values for both metrics were slightly greater for the NDV relative to the DV group in slow-3, slow-4 and slow-5, but these comparisons did not reach statistical significance. These results are presented in Supplementary Materials.

Significant differences were found in the slow-3 frequency band, however, with the NDV group showing higher fALFF values. As shown in Table 1 and Figure 2, the most pronounced differences in this direction were observed in the right caudate, thalamus and putamen, and bilateral amygdala.

Table 1. Comparisons of ALFF and fALFF values within DV-ROIs, in the slow-3 frequency band.

ROIs		**fALFF**	**ALFF**
Caudate	L	-1.07	-0.04
	R	-2.94*	0.02
Putamen	L	-1.63	-0.19
	R	-2.13*	0.52
Insula	L	-1.61	0.64
	R	-0.87	0.83
Amygdala	L	-1.98*	1.46
	R	-2.36*	1.91
Hippocampus	L	-0.46	0.57
	R	-0.79	1.25
Parahippocampal gyrus	L	-0.93	1.37
	R	-1.78	1.27
Thalamus	L	-1.87	0.11
	R	-3.32*	0.89
Superior temporal sulcus	L	-1.13	1.53
	R	-0.76	0.77
PLS p-value		**0.029***	**0.146**

Note: The table presents the results of PLS analyses; specifically, the vector of saliences expressed as *z*-scores (stability across subjects of the measure extracted from each brain region), with negative values representing NDV>DV, and the *p*-value of the latent variable obtained from permutation testing. Asterisks indicate *p*-values with $\alpha<0.05$ and *z*-scores >1.96. *Abbreviations*: L/R = left/right.

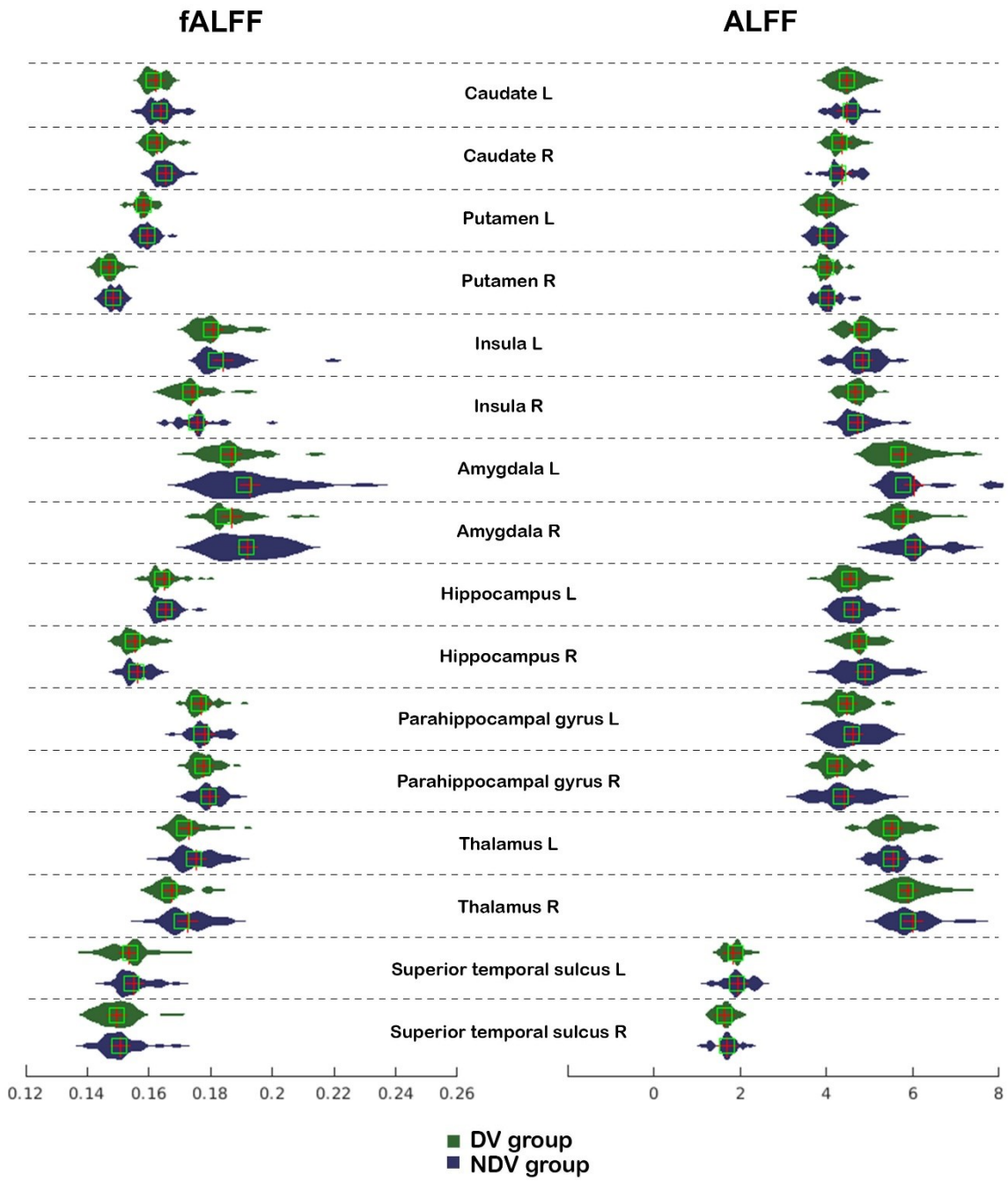

Figure 2. Violin plots depicting the distribution of ALFF and fALFF values across the DV and NDV group within DV-ROIs for the slow-3 frequency band. *Abbreviations*: L/R = left/right.

3.2. DMN-ROIs

An opposing trend was observed in brain regions comprising the DMN-ROIs: ALFF and fALFF values were higher for the DV relative to the NDV group in the slow-5 frequency band, and the NDV group showed higher values in the slow-1, slow-2, slow-3, and slow-4 bands. The majority of analyses did not reach statistical significance, however, indicating that these differences were insufficiently reliable. These results are presented in the Supplementary Materials. Statistically significant differences were again found within DMN-ROIs in the slow-3 band between the DV and NDV groups for ALFF, with the higher amplitudes in the NDV group. Significantly higher amplitudes in NDV were found in the left posterior cingulate cortex, bilateral parahippocampal gyri, left parietal cortex and right superior frontal cortex.

Table 2. Differences in fALFF and ALFF values within DMN-ROIs in the slow-3 frequency band.

Label		**fALFF**	**ALFF**
PCC	bilateral	2.38	-0.61
Dorso-medial PFC	bilateral	1.22	-0.31
Ventro-medial PFC	bilateral	1.21	-0.91
Parahippocampal gyrus	L	2.23	-2.17*
	R	2.11	-1.41
Lateral parietal cortex	L	2.05	-1.93
	R	0.87	-0.41
Superior frontal cortex	L	0.91	-0.38
	R	2.25	-2.64*
Inferior temporal cortex	L	1.12	-1.40
	R	0.88	-0.55
PLS *p*-value		**0.10**	**0.048***

Note: The table presents the results of PLS analyses; specifically, the vector of saliences expressed as *z*-scores (stability across subjects of the measure extracted from each brain region), with negative values representing NDV>DV, and the *p*-value of the latent variable obtained from permutation testing. Asterisks indicate *p*-values with $\alpha<0.05$ and *z*-scores >1.96. *Abbreviations*: L/R = left/right, PCC = posterior cingulate cortex, PFC = prefrontal cortex.

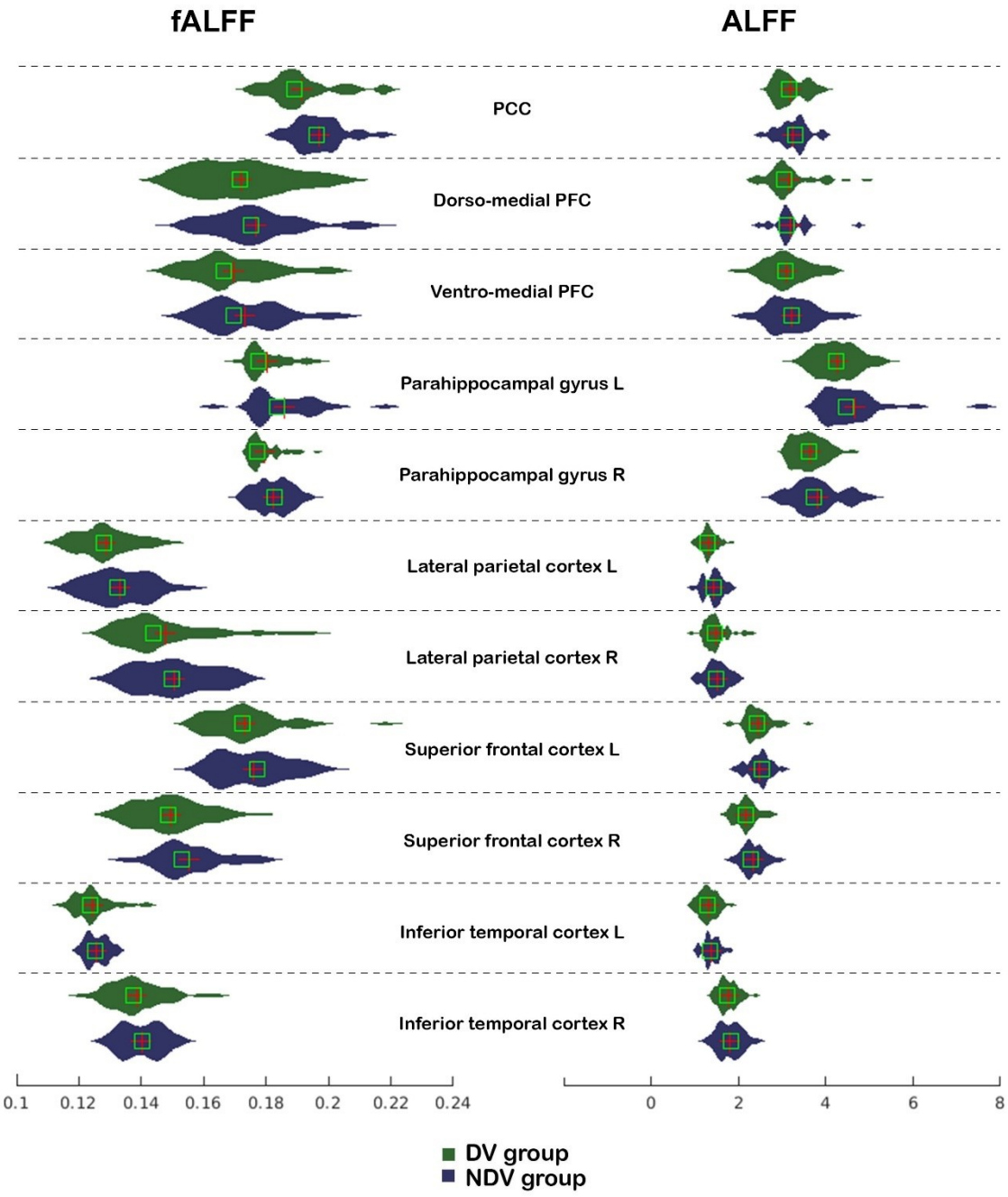

Figure 3. Violin plots illustrating the distribution of ALFF and fALFF values in the slow-3 frequency band within DMN-ROIs. *Abbreviations*: L/R = left/right, PCC = posterior cingulate cortex, PFC = prefrontal cortex.

3.3. *DV frequency analyses*

To examine whether the self-reported frequency of déjà vu experiences corresponded to the fALFF and/or ALFF indices of brain activity in the slow-3 band within ROIs revealed by the PLS analyses, a non-parametric analysis was conducted on the three DV subgroups; subjects reporting the phenomenon less than once a year, those reporting it several times a year, and those reporting it several times a month. As illustrated in Supplementary Figures S5-8, several of the DV- and DMN-ROIs showed apparent trends of linear associations between (f)ALFF values and the frequency of déjà vu experience reported by DV subgroups. None of these apparent trends reached statistical significance, however, likely reflecting the insufficient power resulting from these small subgroup sizes.

4. Discussion

By assessing the amplitude of low frequency oscillations in resting-state hemodynamics as an indirect measure of neural signals, this study evaluated brain activity associated with déjà vu (DV) experience. This revealed reduced amplitudes of low-frequency fluctuations (fALFF/ALFF) in the .073-.198 Hz (slow-3 frequency band) in individuals who report some experience of this phenomenon compared with those who do not, both within brain regions implicated previously in DV (DV-ROIs) and those comprising the default mode network (DMN-ROIs).

Alterations in neural signaling within mesiotemporal circuits has been demonstrated directly in pathological DV (Bartolomei et al., 2012), and indirectly on the basis of neuroanatomical data in non-pathological DV (Shaw et al., 2015). In addition to these structures, the present study demonstrates the involvement of the bilateral putamina, right caudate, bilateral superior frontal cortices, left lateral parietal cortex, dorsal and ventral medial prefrontal cortex, and posterior cingulate cortex. Interestingly, changes in the medial prefrontal cortex and lateral parietal cortex were also observed in functional imaging data acquired during the experimental elicitation of a DV analogue performed by Urquhart et al.(2018). The medial prefrontal region is known to be involved in cognitive control, monitoring and conflict resolution (Ridderinkhof et al., 2004). As suggested by Urguhart et al., this region may therefore signal the mismatch in mnemonic information from various sources experienced phenomenologically as DV. This research team also hypothesise that such mnemonic conflict is not sufficient, however; DV experience also requires the (correct) evaluation of the eliciting stimulus as new (Urquhart et al., 2018). This hypothesis is supported partly by our findings of

more pronounced activity in the superior frontal cortex, the anterior part of which seems to be responsible for recognition between a current scene and episodic memory, and error detection, while the posterior part of the superior frontal gyrus is associated consistently with decision-making processes (Achim and Lepage, 2005; Dobbins et al., 2003; Navarro-Cebrian et al., 2016; Schacter and Slotnick, 2004). Further, more pronounced activity within the superior frontal cortex has been observed during an episodic memory task in the brains of individuals who report no experience of DV (Nigro et al., 2019). Our findings also converge with those of Nigro et al. (2019) in revealing reduced brain responses in individuals who have experienced DV relative to those who have not within the right parahippocampal gyrus, and bilateral hippocampi, thalami and caudate. The present study extends these findings even further by showing this pattern not only in task-dependent activation, but also in terms of intrinsic neuronal activity expressed during resting state.

To interpret our results in terms of neuronal excitability, we need to look closely at the ALFF/fALFF studies in a disease scrutinized most extensively in the context of DV; namely, epilepsy. In focal epilepsies, higher ALFF and fALFF values are reported in the supposed epileptogenic foci with moderate to high sensitivity and specificity (Chen et al., 2015; Zhang et al., 2010). It is suggested that this reflects either local neuronal hyperexcitability or hypersynchrony. Zhang et al. (2010) also notes, however, that in some brain regions overlapping with the default mode network, his sample of focal epilepsy patients showed decreased ALFF values in agreement with our findings. Studies of idiopathic generalized epilepsies (IGE) report different findings; Liao et al. (2013), for instance, observed no significant difference in ALFF values in IGE, and McGill er al. (2014) found lower values of ALFF and fALFF in the prefrontal cortex and thalamus (structures shown previously to be essential for the initiation and propagation of epileptiform activity in IGE). These regional differences correspond to those found in our cohort of individuals who reportedly experienced DV. Wang et al. (2014) explored fALFF in IGE across a range of frequency bands and found a rather complicated pattern of results: The thalamus showed increased fALFF in a range corresponding to the slow-4 band assessed in the current study, and decreased values in slow-2. Conversely, fALFF values decreased in slow-5 and increased in slow-2 within the medial prefrontal cortex. These results align closely with the trends observed in the present study in the DV group. In other words, the brains of patients with IGE, presenting focal epilepsies outside the epileptogenic foci, and the brains of individuals reporting DV experience appear to share similar characteristics of lower ALFF/fALFF value distribution. The mechanism(s) driving this similarity remains to be ascertained, however. McGill et al. (2014) propose that a

decrease in ALFF in the IGE brain within the thalamic region reflects dysregulated thalamo-cortical circuitry within the frontal lobe. Wang et al. (2014) arrive at the same conclusion, suggesting a potential impairment of the brains default function in IGE. It is plausible that the same principles can be applied to the brains of individuals experiencing DV – that is, the erroneous discrimination of familiarity reflects a disruption of the default mode network and/or another cortico-subcortical circuitry. More subtle disruptions might lead to the phenomenon of non-pathological DV, while greater aberrations might result in idiopathic generalized epilepsy and seizures.

Low frequency oscillations are believed to reflect cyclic intrinsic modulation of gross cortical excitability and long distance neuronal synchronization (Buzsáki and Draguhn, 2004; Vanhatalo et al., 2004). Alterations in low frequency oscillation amplitudes (ALFF/fALFF measures) observed in our sample of individuals who reported DV experiences might reflect the upregulation of focal cortical excitability, possibly resulting in DV occurrence. Support for this hypothesis comes from earlier studies that managed to elicit DV experiences through the stimulation of specific brain regions: Halgren et al. (1978) produced the feeling of DV by stimulating the hippocampus and amygdala, Bancaud et al. (1994) elicited it when stimulating temporal neocortex, Bartolomei (2004) was able to generate DV by stimulating the entorhinal and perirhinal cortices, and Kovacs et al. (2009) reported induced DV experiences through stimulation of the left internal globus pallidus.

In the current study, the low frequency range was subdivided into 4 constituent bands defined previously as slow-5 (0.01 - 0.027 Hz), slow-4 (0.027 - 0.073 Hz), slow-3 (0.073 - 0.198 Hz) and slow-2 (0.198 - 0.25 Hz; Zuo et al., 2010). Previous studies have focused predominantly on the slow-4 and slow-5 frequency bands, neglecting slow-3 and slow-2 (Chen et al., 2015; Egorova et al., 2017; Han et al., 2011; Liu et al., 2014). Some studies selected even narrower spectrum of frequencies within the slow-4 band (Hoptman et al., 2010). This is likely because Zuo et al. (2010) categorized slow-4 and slow-5 as related most closely to gray matter signal, and therefore most useful in identifying the neural correlates of functional processing and disorders. For instance, slow-4 neuronal fluctuations are suggested to reflect the spontaneous intrinsic activity of the basal ganglia (Kalcher et al., 2014; Wang et al., 2016), and therefore present useful metrics for investigating the neural correlates of movement disorders. Since the brain regions we have interrogated in the present study fall outside of basal ganglia region, it is unsurprising that the signals emerging from this region were not detected in our analyses. In contrast, the slow-2 band and, to a lesser extent, the slow-3 band are suggested to reflect not only gray matter signal but also white matter and other (cardiac or respiratory)

signals (Zuo et al., 2010). Since the mesiotemporal structures implicated in DV and encompassed by the DMN are a unique mixture of grey and white matter, the slow-3 and slow-2 frequency bands therefore present useful indices for brain activity within these structures implicated in DV experience (Wang et al., 2014). To control for possible cardiac and respiratory effects, we employed normalization to whole brain values. The potential influence of other signals (e.g., adjacency of a vessel) on slow-2 and slow-3 bands remains a limitation of this study, however, and demands further refinements in metric of low-frequency fluctuations.

Lastly, while the findings of the present study advance our neuroscientific understanding of the functional anatomy of déjà vu, further research is needed to explore other factors that might influence experiences of the phenomenon through their known effects on brain function. The present study did not attempt to match individuals reporting DV and those who did not on body mass index and cigarette smoking, for example, which have been shown to impact upon fractional amplitude of low-frequency fluctuation in several brain regions (Chao et al., 2018; Wen et al., 2021). Future research should examine the influence of such factors on the frequency of DV experience, thereby facilitating more accurate neuropsychological models of this phenomenon.

Conclusion

This is the first study to examine the potential neural activity underpinning the experience of déjà vu by assessing the amplitude of low frequency oscillations in resting-state functional brain imaging data. In doing so, we have revealed differences in brain function between individuals who have experienced déjà vu and those who have not; specifically, we have observed significant differences in ALFF and fALFF measures between these groups in brain regions implicated previously in déjà vu experience and those comprising the default mode network that have not yet been investigated in this context. Such differences within the default mode network suggest that these groups differ in the brains resting state. We interpret these findings to indicate that, in parallel with idiopathic generalized epilepsies, the default mode network and other cortico-subcortical circuitry are disrupted in individuals who experience déjà vu, which leads ultimately to the erroneous feeling of familiarity.

Conflict of interest

Authors report no conflict of interest.

Author Contributions

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Conceptualization, M.B., M.M., E.Z.; Methodology, M.M., E.Z., M.K.; Investigation, L.S., K.M., M.K.; Formal Analysis, M.M.; Resources, M.M., R.M.; Writing - Original Draft, E.Z., M.K., K.M., B.S.; Writing - Review & Editing, E.Z., D.J.S., B.S.; Visualization, M.M., R.M., D.J.S.; Supervision - M.B.; Project Administration, K.M., M.K., L.S., E.Z.; Funding Acquisition, L.S., M.B.

Data accessibility statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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