MAGNETIC RESONANCE IMAGING DETERMINANTS OF INTRAINDIVIDUAL VARIABILITY IN THE ELDERLY: COMBINED ANALYSIS OF GREY AND WHITE MATTER

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Abstract—Elderly individuals display a rapid age-related increase in intraindividual variability (IVV) of their performances. This phenomenon could reflect subtle changes in frontal lobe integrity. However, structural studies in this field are still missing. To address this issue, we computed an IVV index for a simple reaction time (RT) task and performed magnetic resonance imaging (MRI) including voxel based morphometry (VBM) and the tract based spatial statistics (TBSS) analysis of diffusion tensor imaging (DTI) in 61 adults aged from 22 to 88 years. The age-related IVV increase was associated with decreased fractional anisotropy (FA) as well as increased radial (RD) and mean (MD) diffusion in the main white matter (WM) fiber tracts. In contrast, axial diffusion (AD) and grey matter (GM) densities did not show any significant correlation with IVV. In multivariate models, only FA has an age-independent effect on IVV. These results revealed that WM but not GM changes partly mediated the age-related increase of IVV. They also revealed that the association between WM and IVV could not be only attributed to the damage of frontal lobe circuits but concerned the majority of interhemispheric and intrahemispheric corticocortical connections.

The notion of intraindividual variability (IVV) refers to the variability in performance across trials (or occasions) of one individual (Li et al., 2001; Hultsch and MacDonald, 2004). It has been long thought that the use of mean values based on single measures in large groups is an appropriate experimental strategy to control for the variability of cognitive performances within persons (for review see MacDonald et al., 2009). Several recent contributions challenged this viewpoint and postulated that IVV represents a major source of systematic errors when assessing cognitive functions (Nesselroade, 2002; Hultsch and MacDonald, 2004; Lindenberger and von Oertzen, 2006; Hultsch et al., 2008). This is particularly true for elderly individuals who display a rapid age-related increase in IVV that correspond to as much as several decades of between-person age differences (Hultsch et al., 2000; Nesselroade and Salthouse, 2004). The increased IVV in old age was first attributed to the fluctuations of biomarkers of aging, including sensory acuity, forced expiratory volume and grip strength (Li et al., 2001; Strauss et al., 2002; Anstey et al., 2005). More recently, MacDonald et al. (2006) defended the idea that IVV is a cognitive marker of central nervous system integrity. The rapid changes of IVV in a cognitive task may thus reflect altered grey matter (Murtha et al., 2002; West et al., 2002; Stuss et al., 2003) and/or white matter (Anstey et al., 2007).

The structural substrates of the IVV are still poorly defined. The most widely accepted idea concerns the association between this variable and frontal lobe integrity (West et al., 2002). In fact, two early studies reported that lesions of frontal grey matter (GM) are accompanied by increased IVV (Murtha et al., 2002; Stuss et al., 2003). Indeed, Murtha et al. (2002) found that persons with frontotemporal dementia were more variable than those with Alzheimer’s disease for a similar level of disease severity, implying differential involvement of frontal versus medial temporal regions to the increase of IVV. Moreover, Stuss et al. (2003) compared 25 patients with frontal lesions (due to various acute conditions including infarction, hemorrhage and trauma) with 11 patients with non-frontal lesions and 12 control participants on reaction time (RT) tasks. Consistent with their initial hypothesis, they found that patients with frontal lesions were more variable than those with non-frontal lesions or controls. In particular, patients with lesions in dorsolateral prefrontal cortex and/or in the superior medial frontal cortex showed the highest variability. The impact of white matter (WM) changes in IVV was rarely explored. Anstey et al. (2007) found that there was an association between the corpus callosum area (traced on
the mid-sagittal slice) and the IIV in mild cognitive impaired patients but not in controls. To date, no study examined the relationship between IIV, GM and WM changes in a life-span perspective. For instance, although the age-related decrease in cognitive performances may be at least partly due to subtle structural changes in frontal lobe subdivisions (for review see Giorgio et al., 2010), the concomitant impact of frontal GM and WM changes on IIV in healthy aging has not been studied. In order to address these issues, we computed an IIV index for a simple RT task and performed magnetic resonance imaging (MRI) including voxel based morphometry (VBM) and the tract based spatial statistics (TBSS) analysis of diffusion tensor imaging (DTI) parameters (i.e. fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD) and mean diffusivity (MD)) in 61 adults aged from 22 to 88 years.

**EXPERIMENTAL PROCEDURES**

**Participants**

There were 15 individuals between 20 and 34 years old, 15 between 35 and 49 years old, 17 between 50 and 64 years old, and 14 older than 64 years (Table 1). All participants were French native speakers and had at least 4 years of formal education. Exclusion criteria included history or neurological evidence of stroke, past head injury with loss of consciousness, history of severe medical illnesses (i.e. metastatic brain cancer), and hearing, vision, or motor impairment that precluded cognitive testing. We administered an MMSE (Folstein et al., 1975) to all participants as well as a standard neuropsychological battery to participants over 60 years old only in order to rule out incident dementia and Mild Cognitive Impairment (MCI). This battery included the Letter-Number Sequencing subtest of the Wechsler Memory Scale III for working memory (Wechsler, 1997), the Cued Recall (CR48) items test (Ivanou et al., 2005) and the CERAD Word List Memory (Welsh et al., 1994) for episodic memory as well as the Hayling test (Burgess and Shallice, 1996), the French version of the standard Stroop colour-word interference task (Stroop, 1935) and Consonant Updating Test (Morris and Jones, 1990) for executive functions. The participants with an MMSE score below 28 were also not included in this study. Moreover, the participants fulfilling the MCI criteria described by Peterson and Negash (2008) were also discarded. In particular, a score below 1.5 standard deviations from the normative mean in at least one neuropsychological test was eliminatory. Young and older adults were recruited from the community via local advert. All participants gave written informed consent to participate in the study after the procedures had been explained. The local Ethics Committee has approved the present study.

**Intraindividual variability (IIV)**

The IIV was derived from a simple RT task (de Ribaupierre et al., 2006). This computerised task was presented on a PC (screen of 17-inch) using E-prime software (Psychology Software Tools Inc., Pittsburgh, PA, USA). Participants faced the computer screen at a distance of approximately 50 cm. A button box, placed in front of them, was used to measure manual reaction time. Participants had to press a button with the index finger of his dominant hand as quickly as possible when a signal stimulus (a cross) appeared on the computer screen. This signal stimulus was preceded by a warning stimulus (a point in the centre of the screen). The signal stimulus stayed on the screen until the participant pressed the button. The instructions emphasised the fact that the participant had to respond as fast as possible without anticipation of the signal stimulus. Five inter-stimulus intervals could separate the warning stimulus from the signal stimulus (500, 800, 1100, 1400, 1700 ms). The order of these inter-stimulus intervals across trials was pseudo-random. A given inter-stimulus interval could not be used twice in succession. Moreover, the number of use of each inter-stimulus interval was equal. The signal stimulus always appeared on an imaginary circle (diameter: 10 cm) centred on the warning signal at five different screen locations: above the warning stimulus (top location), at 72° (right location), at 144° (bottom-right location), at 216° (bottom-left location) and at 288° (left location) from the vertical axe crossing the warning stimulus. The number of use of each location was equal and no single location could be used twice in succession. Reaction times were measured in milliseconds. This simple reaction time task included a practice (six trials) and a test session (120 trials). The 120 RTs were used to compute the IIV. Although the intraindividual standard deviation (ISD) computed on raw RTs is the simplest way to evaluate the IIV, it does not take into account the systematic change of RTs over trials associated with practice. Moreover, an increase of the ISD on raw RTs may simply reflect the aging process (Hultsch et al., 2002). To address these issues, we controlled for the effects of age, trial and their interaction on the RTs before computing ISDs (see Hultsch et al., 2002). Briefly, age and trial were entered in a regression analysis as predictors of RTs. Then, residual scores were computed by subtracting the RTs predicted by the model from the measured RTs. Finally, ISDs were computed on these residual scores.

**MR imaging**

All MRI scanning was performed on a 3T Scanner (Magnetom Trio, Siemens, Erlangen, Germany). 3D T1 MPRAGE: sagittal acquisition, 192 slices, matrix 250×256, 0.9×0.9×0.9 mm³, TE 3 ms, TR 2500 ms, one average, TI 1100 ms, flip angle 9°. DTI: 12 diffusion directions isotropically distributed on a sphere and b=1000, 1 B0 image without diffusion weighting, 128×128×49 matrix, 1.8×1.8×3.0 mm³ voxel size, echo time TE 74 ms, repetition time TR 5300 ms, two averages.

**Plan of the data analyses**

The data analyses could be divided into two steps. First, the whole and the mask restricted brain VBM analyses as well as the TBSS analysis were used to define regions of interest (ROIs) associated with IIV after accounting for education and gender. Then, the relevant parameters of each ROI were fed into forward regression analyses to examine whether WM changes mediate the age effect on IIV.

**GM VBM analysis of T1 data**

VBM analysis was performed by using the FSL software package (http://www.fmrib.ox.ac.uk/fsl/, Version 4.1) developed by the FM-RIB Center (Oxford University, United Kingdom). Standard steps were used to analyse the data (Smith et al., 2006, 2007). The mandatory steps included: (1) brain-extraction using BET (brain extraction tool, part of FSL); (2) tissue-type segmentation using FAST4 (part of FSL); (3) non-linear transformation of the native...
Fig. 1. On the left side: coronal (top left), sagittal (top right) and transversal (bottom left) view of the skeletonised white matter tracts and the grey matter. Green voxels show the skeletonised fiber tracts, yellow and red voxels show a significant negative correlation between FA and IIV, once controlled for education and sex, after TFCE-correction. Copper colour area shows the anterior GM mask used in the VBM analysis. On the right side: 3D coronal (top left), sagittal (top right) and transversal view (bottom left) of the voxels showing a significant negative correlation (P<0.05) between FA and IIV, once controlled for education and sex, after TFCE-correction. Radiological conventions (left to right).

GM images into MNI (Montreal Neurological Institute) reference space; (4) creation of a study-specific GM template; (5) non-linear re-registration of the native GM images into the study-specific GM template; (6) smoothing of the modulated segmented images with an isotropic Gaussian kernel and a sigma of 3 mm. Ultimately, voxel-wise general linear model (GLM) was applied using permutation-based non-parametric testing (RANDOMISE, part of FSL), correcting for multiple comparisons implementing threshold-free clustered enhancement (TFCE) (Smith and Nichols, 2009). Fully corrected P-values <0.05 are considered as significant. IIV was used as explanatory regressor in our analyses with level of education and gender used as additional non-explanatory co-regressors. The entire GM template included 235,506 voxels. In order to specifically assess the association between IIV and structural changes within the frontal lobe, the VBM analysis was repeated with a restricted anterior GM mask. The anterior GM mask included the whole frontal lobe (see Fig. 1, left part). To create this mask, the frontal lobe image of the MNI structural Atlas implemented in FSL was first superposed on the study specific GM template. Then, the voxels belonging both to the study specific GM template and the frontal lobe image were included in this mask. In addition to the frontal lobe image, the central gyrus and the upper part of the temporal lobes were used as landmarks in the sagittal view of the study specific GM template to orient the selection of voxels. This anterior GM mask consisted of 73,061 voxels including prefrontal cortex (Murtha et al., 2002), dorsolateral prefrontal cortex and the superior frontal cortex (Stuss et al., 2003). The regions showing a significant correlation between IIV and GM through the whole brain and/or the mask restricted VBM analyses were used to determine ROIs for subsequent regression analysis.

WM TBSS analysis of DTI data

The TBSS analysis of the DTI data was also performed by means of the FSL software package (https://www.fmrib.ox.ac.uk/fsl/, Version 4.1) developed by the FMRIB Center (Oxford University, United Kingdom) according to the standard procedure (Smith et al., 2006). In summary, TBSS projects all subjects’ FA data onto a mean FA tract skeleton using non-linear registration. The tract skeleton is the basis for voxel-wise cross-subject statistics and reduces potential misregistrations. The TBSS skeleton mask included 121,723 voxels. The other DTI derived parameters axial (AD), radial (RD) and mean (MD) diffusivity were analysed in the same way by re-using the spatial transformation parameters that were estimated in the initial FA analysis. Voxel-wise statistical analysis was performed with TFCE-correction (Smith and Nichols, 2009) for multiple comparisons, considering fully corrected P-values <0.05 as significant. IIV was used as explanatory regressor in the analyses with level of education, gender and age as non-explanatory co-regressors. The regions showing a significant correlation between IIV and FA through the WM TBSS analysis were subsequently used as ROIs to compute a FA index. More precisely, the FA index was the average of all the FA values associated with the voxels within the ROIs. The same procedure was used to compute the AD, RD and MD indexes. These indexes were then used in subsequent forward regression analyses.

Correlation and regression analysis

We checked the normality of the continuous variables by carrying out skewness and kurtosis tests, and carried out standard transformations to normalise non-Gaussian variables. The relationships between RT, IIV and age were assessed using Spearman rho correlation coefficients (r). Age and the relevant parameters of the ROIs were entered in univariate analyses as predictor of IIV. In order to explore whether brain changes partly explained the association between age and IIV, significant variables in the univariate analyses were then fed into forward regression models with age systematically entered as first predictor followed by the relevant parameters of the ROIs. The likelihood-ratio test was used to compare two significant competing models’ degree of fit. Statistical analyses were performed with SPSS software version 15 and Stata software version 9.2.1.

RESULTS

Behavioural analysis

The variable of age, IIV and TR were normally distributed. In agreement with previous reports (Anstey, 1999; Hultsch et al., 2000, 2002; Nesselroade and Salhthouse, 2004), we observed a strong age-related IIV increase as well as a strong age-related RT increase. In fact, age showed a

significant positive correlation with RT ($r_g=0.52, P<0.001$) and IIV ($r_g=0.50, P<0.001$). A positive correlation also existed between RT and IIV ($r_g=0.62, P<0.001$).

**GM VBM analysis of T1 data**

When the entire GM was considered, there was no TFCE corrected supra-threshold negative correlation between IIV and GM densities. This was also the case when restricting the analysis to the frontal cortex. Moreover, there was no TFCE corrected supra-threshold positive correlation between IIV and GM densities. Thus, no GM volume was extracted to feed subsequent analysis.

**WM TBSS analysis of DTI data**

After controlling for the effect of gender and education, IIV was still negatively related to the FA within the main white matter fiber tracts (corpus callosum; forceps major and minor; superior longitudinal fasciculus; inferior fronto-occipital fasciculus; cortico-spinal tract; anterior thalamic radiation) after TFCE-correction (see Fig. 1, Table 2). Similarly, RD and MD were still positively related to the IIV within the main fiber tracts after TFCE-correction. Moreover, the spatial distributions of the significant voxels for FA, RD and MD were similar (Table 2). Conversely, IIV was not related to AD after controlling for gender and education. When age was entered as third non-explanatory co-regressor in the voxel-based analysis, the associations between RD as well as FA and IIV did not persist. However, a significant relationship was still found between FA and IIV in the left and right part of the splenium and in some posterior, middle and anterior parts of the left inferior fronto-occipital fasciculus.

**Regression analysis in ROI-based data**

Since FA, RD and MD correlated with IIV within most of the skeletonised white matter tracts once removed the effect of gender and education, we computed the average FA, RD and MD within the skeletonised white matter tracts and used them as indexes to feed subsequent regression analyses. The FA, RD and MD indexes were normally distributed. Univariate and multiple regressions are summarised in Table 3. In agreement with the WM TBSS analysis, univariate regression models showed that age, FA, RD and MD indexes predicted IIV (Table 3, left part). In order to avoid multi-collinearity between the three DTI indexes, three different forward multiple regressions were computed with age as first predictor and one DTI index (different in each model) as second predictors of IIV (Table 3, right part). The explained variance of FA index in the forward multiple regression (model 1) was much lower in multivariate compared to univariate regression models (19% vs. 5%). However, adding FA index (model 1) still brought a significant contribution to the model including age only ($\chi^2=8.95, P=0.003$). The association between RD index and IIV (model 2) as well as the association between MD index and IIV (model 3) previously found in the univariate regressions did not persist after the initial introduction of age in multivariate models.

**DISCUSSION**

Our data document, for the first time to our knowledge, that WM but not GM changes partly mediated the age-related increase of IIV. They also reveal that this association cannot be only attributed to the damage of frontal lobe circuits but rather concerns interhemispheric and intrahemispheric

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**Table 2. Significant clusters for the WM TBSS analysis of the correlation between IIV and the different DTI parameters**

<table>
<thead>
<tr>
<th>DTI parameter</th>
<th>Cluster index</th>
<th>Cluster size in mm$^3$</th>
<th>Z-max$^{a}$</th>
<th>Z-MAX</th>
<th>Z-MAX</th>
<th>Z-MAX</th>
<th>COG X$^c$</th>
<th>COG Y$^c$</th>
<th>COG Z$^c$</th>
<th>Side</th>
<th>Anatomic regions</th>
</tr>
</thead>
<tbody>
<tr>
<td>FA</td>
<td>1</td>
<td>39,134</td>
<td>0.999</td>
<td>53</td>
<td>76</td>
<td>63</td>
<td>-0.05</td>
<td>-12.86</td>
<td>16.88</td>
<td>Bilat$^d$</td>
<td>Genu of CC$^e$, forceps major and minor, SLF$^f$, IFOF$^g$, cortico-spinal tract, anterior thalamic radiation.</td>
</tr>
<tr>
<td>RD</td>
<td>1</td>
<td>70,853</td>
<td>0.999</td>
<td>51</td>
<td>-122</td>
<td>46</td>
<td>0.95</td>
<td>-17.55</td>
<td>17.68</td>
<td>Bilat$^d$</td>
<td></td>
</tr>
<tr>
<td>MD</td>
<td>1</td>
<td>57,151</td>
<td>0.999</td>
<td>132</td>
<td>111</td>
<td>56</td>
<td>1.81</td>
<td>-14.86</td>
<td>18.62</td>
<td>Bilat$^d$</td>
<td></td>
</tr>
</tbody>
</table>

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**Table 3. Univariate and forward multiple regressions**

<table>
<thead>
<tr>
<th>Factors</th>
<th>b</th>
<th>95% CI$^a$</th>
<th>P</th>
<th>Adj$^b$ R$^2$</th>
<th>Factors</th>
<th>b</th>
<th>95% CI</th>
<th>P</th>
<th>Adj$^b$ R$^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.46</td>
<td>[0.25; 0.66]</td>
<td>&lt;0.0001</td>
<td>0.24</td>
<td>Model 1</td>
<td>Age</td>
<td>0.34</td>
<td>[0.11; 0.57]</td>
<td>0.005</td>
</tr>
<tr>
<td>FA index</td>
<td>-294.4</td>
<td>[-446; -142]</td>
<td>0.0003</td>
<td>0.19</td>
<td>FA index</td>
<td>-177.5</td>
<td>[-341; -13.5]</td>
<td>0.034</td>
<td>0.05</td>
</tr>
<tr>
<td>RD index</td>
<td>189’119</td>
<td>[93’021; 267’018]</td>
<td>0.0001</td>
<td>0.21</td>
<td>RD index</td>
<td>93’828</td>
<td>[-23’186; 210’843]</td>
<td>0.037</td>
<td>0.24</td>
</tr>
<tr>
<td>MD index</td>
<td>159’242</td>
<td>[68’691; 249’793]</td>
<td>0.0008</td>
<td>0.16</td>
<td>MD index</td>
<td>55’875</td>
<td>[-61’072; 172’822]</td>
<td>0.011</td>
<td>0.24</td>
</tr>
</tbody>
</table>

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$^a$ 95% confidence interval, $^b$ adjusted $R^2$. 

corticocortical connections as well as extracortical projecting fibre tracts.

There have been two previous studies in patients with frontal lobe pathologies suggesting that GM changes in frontal lobe may be related to IIV. In their study, Murtha et al. (2002) found a higher variability among persons with frontotemporal dementia compared to those with Alzheimer’s disease for a similar level of disease severity. In the same line, Stuss et al. (2003) examined the IIV among patients with frontal and non-frontal lesions and reported that those with circumscribed frontal lesions were more variable in their performances compared to those with non-frontal lesions or controls. Individuals with lesions in right and left dorsolateral prefrontal cortex or in the superior medial frontal cortex exhibited the most pronounced variability. In the present study, the GM density did not correlate with the IIV. This was true even when the analysis was restricted to the frontal lobe. It is thus likely that the conclusions drawn by the study of selected populations of patients with neurological deficits are not valid when assessing the determinants of IIV in brain aging.

Our main experimental finding concerns the association between three DTI parameters and IIV. The FA decrease in white fiber tracts (corpus callosum; forceps major and minor; superior longitudinal fasciculus; inferior fronto-occipital fasciculus; cortico-spinal tract, anterior thalamic radiation) was associated with increased IIV. Importantly, this decrease concerned both homogeneously distributed fibers with high (such as the long interhemispheric connections in the corpus callosum) and intermediate (such as intrahemispheric connections) anisotropy. The parallel increase of RD and MD observed within the same tracts in the absence of an AD increase supports further the idea that myelin shrinkage and/or axonal loss may represent key pathological substrates of IIV in brain aging (Song et al., 2002, 2003; Adler et al., 2004). In the only conceptually close DTI study, Anstey et al. (2007) also reported a relationship between FA decrease in anterior cingulate cortex and IIV in adults aged from 60 to 64 years old with mild cognitive impairment.

However, both the TBSS data with age as co-regressor and regression analysis with age as first explanatory variable of IIV demonstrate that the age effect on IIV cannot be explained by WM microstructural changes alone. In fact, the association between RD, MD indexes and IIV in TBSS analyses did not persist after controlling for age. In the same line, the introduction of these DTI parameters as second explanatory variables (after age) in forward regression models did not explain an additional percentage of IIV variability. Only FA had also an age-independent effect on IIV. In fact, when age was introduced before the FA index in the model, the association between FA index and IIV was still statistically significant. This dissociation between FA and the other DTI parameters, already found in studies comparing MCI and healthy controls as well as stable and progressive MCI (Bosch et al., in press; Haller et al., 2010), would support the idea that IIV may be partly due to reduced fiber tract coherence (leading to FA changes only) possibly in the left and right part of the splenium and in some posterior, middle and anterior parts of the left inferior fronto-occipital fasciculus rather than myelin loss (Adler et al., 2004). Since the inclusion of age not only overshadowed the association between diffusion parameter indexes (RD, MD) and IIV but also provoked a drastic weakening of the association between FA index and IIV, the role of additional structural and functional parameters such as changes in age-related synaptic densities, neurotransmitter systems, functional network and cerebrovascular reactivity should be considered for explaining the IIV decrease in old age (Backman et al., 2006; Kelly et al., 2008; MacDonald et al., 2008).

Strengths of the present study include the combined analysis of GM and WM changes in the same sample of healthy individuals across a wide age range and use of both VBM and ROI methods for GM. Moreover, we assessed automatically WM integrity with DTI-TBSS. This method avoids certain limitations of classic ROI analyses, notably the operator dependency, the time-consuming manual ROI selection, and the difficulty to delineate the ROI borders unequivocally. Moreover, the analysis includes the entire brain and is not restricted to a priori defined areas. Several limitations should also be considered when interpreting the present results. First, the sample size was relatively small. Second, we cannot formally exclude that MCI individuals younger than 60 years old took part in this study as the full neuropsychological battery was not administrated to participants under 60 years old. However, this is an unlikely scenario since all of our cases had an MMSE score higher than 28. Third, the relationship between MRI data and IIV was established on the basis of a unique cognitive task. The simple reaction time task used in this study could possibly favour the WM association with IIV in detriment of the GM one. In this respect, Stuss et al. (2003) reported that lesion in the frontal lobe increased the IIV mainly in the complex RT tasks. In the same line, the results of Haier et al. (2005) supported this view as they found a correlation between RTs and WM but no correlation between RTs and GM in a simple RT task whereas they found a correlation between RTs and GM in a task implying memory. Thus, IIV computed from an RT task of higher complexity or implying higher cognition (memory, language) could possibly relate to GM data. Third, the cross-sectional nature of our study prevented us from examining the concomitant evolution of IIV and WM. Future longitudinal studies on a large number of participants with repeated MRI measures and thorough neuropsychological examination are clearly needed to further explore these issues.

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