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Christian Stephan-Otto, Sara Siddi, Carl Senior, Jorge Cuevas-Esteban, Maria Rosa Cambra-Martí, Susana Ochoa, Gildas Brébion

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**Remembering verbally-presented items as pictures:
Brain activity underlying visual mental images in schizophrenia patients with
visual hallucinations**

Christian STEPHAN-OTTO^{a,b,c}, Sara SIDDI^{b,c,d,e}, Carl SENIOR^f,
Jorge CUEVAS-ESTEBAN^b, Maria Rosa CAMBRA-MARTÍ^b,
Susana OCHOA^{a,b,c}, Gildas BRÉBION^{a,b,c*}

^a Institut de Recerca Sant Joan de Déu, Esplugues de Llobregat, Spain

^b Parc Sanitari Sant Joan de Déu, Sant Boi de Llobregat, Spain

^c Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Madrid, Spain

^d Section of Clinical Psychology, Department of Education, Psychology, and Philosophy, University of Cagliari, Italy

^e Facultat de Medicina, Universitat de Barcelona, Spain

^f School of Life & Health Sciences, Aston University, Birmingham, UK

* Corresponding author:

Gildas Brébion, Research and Development Unit - Parc Sanitari Sant Joan de Déu

Dr. Antoni Pujadas, 42, 08830 - Sant Boi de Llobregat, Barcelona, Spain

E-mail address: gildas.brebion@pssjd.org

Abstract

Background: Previous research suggests that visual hallucinations in schizophrenia consist of mental images mistaken for percepts due to failure of the reality-monitoring processes. However, the neural substrates that underpin such dysfunction are currently unknown. We conducted a brain imaging study to investigate the role of visual mental imagery in visual hallucinations. **Method:** Twenty-three patients with schizophrenia and 26 healthy participants were administered a reality-monitoring task whilst undergoing an fMRI protocol. At the encoding phase, a mixture of pictures of common items and **labels** designating common items were presented. **On the memory test,** participants were requested to remember whether a picture of the item had been presented or merely its **label**. **Results:** Visual hallucination scores were associated with a liberal response bias reflecting propensity to erroneously remember pictures of the items that had in fact been presented as words. At encoding, patients with visual hallucinations differentially activated the **right** fusiform gyrus when processing the words they later remembered as pictures, which suggests the formation of visual mental images. **On the memory test,** the whole patient group activated the anterior cingulate and medial superior frontal gyrus when falsely remembering pictures. However, no differential activation was observed in patients with visual hallucinations, whereas in the healthy sample, the production of visual mental images at encoding led to greater activation of a fronto-parietal decisional network on the **memory test**. **Conclusions:** Visual hallucinations are associated with enhanced visual imagery and **possibly** with a failure of the reality-monitoring processes that enable discrimination between imagined and perceived events.

Key words: schizophrenia, visual hallucinations, reality-monitoring, fusiform gyrus, neuroimaging

Remembering verbally-presented items as pictures:**Brain activity underlying visual mental images in schizophrenia patients with
visual hallucinations****1. Introduction**

Visual hallucinations occur in schizophrenia with a lower prevalence than do auditory hallucinations, and hence they have been the object of much scantier investigation (van Ommen et al., 2016; Waters et al., 2014). Visual hallucinations appear to be associated with activity in the visual cortex (Zmigrod, Garrison, Carr, & Simons, 2016). The brain imaging study of a schizophrenia patient with visual hallucinations evinced brain activity in higher visual areas corresponding to the content of the hallucinations, as well as in the hippocampus, involved in memory retrieval (Oertel et al., 2007). Visual hallucinations might consist of reactivation of mental images retrieved from visual memory and misinterpreted as perceptions (Barnes, 2015; Bentall, 1990). To explore this theory at a cognitive level, Brébion, Ohlsen, Pilowsky, and David (2008) presented a mixture of pictures and **labels** of common items to a sample of patients with schizophrenia, and required the participants to remember afterwards whether a picture of the item had been presented. The patients with visual hallucinations were found to demonstrate greater propensity than the other patients to erroneously remember pictures when only the label of the items had been presented. This suggests that the visual mental images they had formed on the basis of the word-stimuli were later mistaken for real pictures. Such confusion may stem from excessive visual imagery production, or alternatively, from defective reality monitoring processes **by which mental images would be readily accepted as perception independent of**

their abundance or vividness.

Several studies have attempted to determine the neural bases of confusion between imagined and perceived pictures in the general population. Gonsalves et al. (2004) reported that their participants activated the precuneus, the inferior parietal cortex, and the anterior cingulate during the encoding of words they later remembered as pictures. These authors argued that false memories of pictures were induced by the activation of brain areas that are involved in visual imagery. Kensinger and Schacter (2005) obtained different but compatible results. In their study, the encoding of neutral items later remembered as pictures was associated with activation of the parahippocampal and fusiform gyri, and these brain regions were also assumed to be involved in visual imagery. Other studies have focused on the brain areas activated during the **memory test**, when participants have to use reality-monitoring processes to judge whether pictures have been seen or only imagined –a decision partly made on evaluation of the contextual features of these pictures (Johnson, Hashtroudi, & Lindsay, 1993). Okado and Stark (2003) reported that false memories of pictures were associated with activation of the right anterior cingulate gyrus. They concluded that this activation was driven by the high level of conflict and effort required in judging the status of the imagined pictures. Indeed, the anterior cingulate has been identified as involved in conflictual decision making (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Brown, 2013; Chudasama et al., 2013; Walton, Crosson, Behrens, Kennerley, & Rushworth, 2007; Whitman, Metzack, Lavigne, & Woodward, 2013). In Kensinger and Schacter's (2006) study, the pictorial misattribution of word stimuli during the **memory test** was associated with activation of the left middle frontal gyrus.

No brain imaging study, as far as we know, has related false memories of pictures to ratings of visual hallucinations or visual imagery. We conducted an fMRI study of schizophrenia patients and healthy individuals, using the same paradigm as in Brébion et al. (2008), to investigate the brain areas associated with the mistaking of imagined pictures for real ones in patients with visual hallucinations and in non-clinical individuals with high visual imagery abilities. The results obtained in the healthy sample have been reported in another manuscript (Stephan-Otto et al., 2017). A subgroup of healthy individuals **with high abilities in generating visual imagery mentally** was found to activate the left inferior occipital gyrus –an area involved in visual perception– when processing the words they later remembered as pictures. In the **memory test**, these **individuals** did not make more picture misattributions overall than did their counterparts **with lower visual imagery abilities**. However, they took longer to respond that they remembered seeing pictures when there was none, and they differentially activated the left middle frontal gyrus as well as the inferior and superior parietal lobes while making these false judgments. We assumed that these brain areas were involved in the reality-monitoring process that enables the participants to evaluate whether the imagined pictures that came to mind had actually been perceived. The activation of the left middle frontal gyrus corroborates Kensinger and Schacter’s (2006) observation. With regard to the parietal lobe, it has been proposed as being involved in the retrieval of contextual information (Kensinger & Schacter, 2006; King & Miller, 2014; Kurkela & Dennis, 2016; Leiker & Johnson, 2015; Mitchell & Johnson, 2009).

In the current report we present the results derived from the schizophrenia sample. In agreement with previous behavioral findings (Brébion et al., 2008), we expected the visual hallucination scores to be associated with increased rates of false

memories of pictures. At the brain level, we hypothesized that the patients with visual hallucinations, similarly to the visual imagery-prone healthy individuals, activated visual areas when processing the words they later remembered as pictures. Following the above-mentioned studies of healthy individuals, we expected the anterior cingulate (Okado & Stark, 2003) and middle frontal gyrus (Kensinger & Schacter, 2006) to be involved in the false remembering of pictures during the **memory test**. Whether a fronto-parietal network is specifically implicated in patients with visual hallucinations, as it is in the healthy visual imagery-prone individuals, and whether longer judgment times are similarly required for false memories in these patients, was investigated. Verbal hallucinations were studied as well to determine the specificity of the expected associations with visual hallucinations.

2. Method

2.1. Participants

Twenty-six healthy participants (10 females) were recruited from the general population by means of announcements: age: $m = 37.3$, $sd = 9.1$; education level¹: $m = 5.9$; estimated verbal IQ²: $m = 104$. The inclusion criteria were age between 18 and 60 years and fluency in Spanish. The exclusion criteria were neurological or mental disease, intellectual disability, head injury, alcohol or drug abuse in the past six months, and current severe physical disease, as well as the standard exclusion criteria for participation in fMRI procedures, namely claustrophobia and metallic implants including fitted pacemaker and cochlea implants.

¹ The scale used was: 1 = no studies; 2 = uncompleted primary studies; 3 = completed primary studies; 4 = high school uncompleted; 5 = high school completed; 6 = undergraduate studies; 7 = bachelor's or master's degree; 8 = doctorate

² Corresponding estimated IQs for the *Test de Acentuación de Palabras* scores (Gomar et al., 2011).

Twenty-three patients with schizophrenia (DSM-IV criteria, 11 females) were recruited from the Parc Sanitari Sant Joan de Déu network of mental health services in Barcelona, Spain: age: $m = 42.4$, $sd = 9.2$; education level¹: $m = 4.9$; estimated verbal IQ²: $m = 100$; illness duration (number of years elapsed since the first psychiatric hospitalization): $m = 14.2$, $sd = 9.8$. The inclusion criteria were the same as for healthy participants with the additional criterion of being able to provide informed consent. The exclusion criteria were also the same except that the exclusion of mental disease only applied to organic mental disorders and dementia.

The two groups were equivalent for sex distribution and verbal IQ. However, the healthy controls tended to be younger than the patients ($t(47) = 1.96$, $p < .06$), and they presented a significantly higher education level ($t(47) = 2.3$, $p < .025$). All of the procedures were approved by the Parc Sanitari Sant Joan de Déu ethics committee, and all participants provided informed consent before taking part in the study.

2.2. Clinical rating scales

Clinical assessment in patients was conducted shortly after the completion of the task by a trained clinical psychologist who was blind to the experimental hypotheses. Positive and negative symptoms were assessed using the Spanish version of the Scale for the Assessment of Positive Symptoms (SAPS; $m = 15.3$, $sd = 16.3$) and the Scale for the Assessment of Negative Symptoms (SANS; $m = 5.9$, $sd = 7.8$) (Peralta & Cuesta, 1999). A verbal hallucination score was computed by adding up the scores obtained on the 2nd and 3rd items of the hallucination scale ('voices commenting' and 'voices conversing') ($m = 2.0$, $sd = 3.6$, range 0-10). Given the low prevalence of current visual hallucinations, the score for current or past visual hallucinations was tallied ($m = 2.1$, sd

= 1.8, range 0-5). **The verbal and visual hallucination scores were significantly intercorrelated ($r = .48, p < .025$).**

2.3. Material

Ninety items were selected, including 72 common objects (*saw, apron, envelope...*) and 18 vegetables (*carrot, cauliflower, onion...*). Participants were presented with either the mere **label** of the item or the picture of the item along with its **label**. Half of the items were presented as single words and the other half were presented as word/picture pairs. Two versions of the stimuli were prepared: the 45 stimuli that were presented as words in one version were presented as word/picture pairs in the other. The use of each version was counterbalanced among subjects. All material was presented to participants throughout via Presentation software (<http://www.neurobs.com/>). Before both the encoding and the **memory test** phases, participants were given a few practice trials to ensure familiarity with the task.

2.4. Procedure

Prior to the experimental protocol, participants were provided with an opportunity to ask any questions they had.

Encoding:

All items were presented one by one in pseudo-random order with each slide (word or word/picture pair) being presented for 3.5 seconds, separated by fixation-crosses. The duration of the fixation cross presentations varied across trials from 2 to 5.5 seconds according to an exponential distribution with mean = 3.18 seconds. The encoding of the items was **incidental** as the task was described as a classification task: participants were required to indicate whether the presented items were vegetables or

not, and to give their response by pressing one of two buttons ('vegetable' or 'other'). They were not informed of the subsequent **memory test**. The computer registered correct and incorrect responses, as well as misses (i.e., no response during the stimulus or subsequent fixation cross presentation), and the response times for each type of response.

Memory test:

The presentation of the stimuli was followed by a 6-minute delay during which a structural MRI scan was acquired for each participant. Then the participants were informed that they would be presented with all the labels of the previous stimuli, and that they would have to remember whether a picture accompanied the word when it was displayed at the encoding phase. Each of the labels was presented one at a time during a 3.5 second period, in a pseudo-random order different from that used in the encoding phase, but with interstimulus fixation cross durations that varied according to a similar exponential distribution. After the appearance of each label the participants were asked to provide their response by pressing one of two buttons ('with picture' or 'without picture'). The correct responses, i.e., presented words remembered as words (WW) and presented pictures remembered as pictures (PP), were recorded, as were the incorrect responses: the omissions, i.e., presented pictures remembered as words (PW) and the false memories, i.e., presented words remembered as pictures (WP). Again, missed trials were recorded, as were the response times for each type of response. The rates of correct and false memories were combined (Corwin, 1994) to compute a discrimination index Pr , reflecting the ability to discriminate words from pictures (**rates of correct memories of pictures – rates of false memories of pictures**), and a response bias

index Br, reflecting the propensity to report words as pictures in case of uncertainty (rates of false memories of pictures/(1-Pr)).

2.5. fMRI data acquisition

Functional MRI data were acquired using a General Electric 1.5 Tesla Signa HD scanner at the Parc Sanitari Sant Joan de Déu. A T2*-weighted functional echoplanar imaging sequence depicting BOLD contrast was obtained using a standard head coil. In total, 270 volumes were collected with the axial plane parallel to the AC-PC axis, using the following scanning parameters: 26 slices, 4 mm thickness, 1 mm gap, TR = 2000 ms, TE = 40 ms, 24 cm FOV, 64 × 64 acquisition matrix, flip angle = 90°. The first four volumes in each run were discarded to allow for magnetic saturation effects. Visual stimuli were presented on a rear projection screen and viewed through a mirror mounted on the head coil, and all responses were collected with an MR-compatible response box (FORP, Current Designs, Inc., USA; www.curdes.com).

2.6. fMRI data preprocessing

Imaging data were analyzed using SPM8 (Wellcome Department of Imaging Neuroscience, London; www.fil.ion.ucl.ac.uk/spm) running under MATLAB (Release 2009a, The MathWorks, Inc., Natick, Massachusetts). All of the volumes from each participant were spatially realigned to the first image in each series, in order to correct for small head movements and to generate a mean image per functional run. Motion parameters were examined for each subject to ensure no movements larger than the voxel size were present (no runs were discarded). The resulting series were warped into SRI24 space (Rohlfing, Zahr, Sullivan, Pfefferbaum, & Manuscript, 2010) using isotropic voxels ($3 \times 3 \times 3 \text{ mm}^3$), with a standard EPI template as deformation target,

and then spatially smoothed using a Gaussian kernel of 8 mm full-width-at-half-maximum.

2.7. fMRI data analysis

The preprocessed fMRI data were analyzed with an event-related model. In order to assess random effects at the individual level, the activity associated with the experimental conditions was modelled with a hemodynamic response function (HRF) and its time derivative. Displacement and rotation motion parameters were included as confounds in the individual model. A 200s high-pass filter cut-off was used to remove low frequency noise, together with an AR(1) model to correct for temporal autocorrelation. For both tasks, four event types were determined by the response in the **memory test**: WW, PP, PW, and WP. To compare each event, linear contrasts were constructed to test experimental effects of interest. These contrasts were entered into a second level analysis in which subjects were treated as a random effect. One-sample and two-sample t-tests were used to assess within-group and between-subgroup activations, respectively. The resulting statistical parametric maps were generated using an uncorrected threshold³ at voxel level defined by $p < 0.001$ and a cluster extent threshold defined by a family-wise-error (FWE) corrected $p < 0.05$. Activation peaks were labelled according to the SRI24/TZO cortical parcellation map (Rohlfing et al., 2010) based on the template described by Tzourio-Mazoyer et al. (2002).

³ A slightly different cluster-defining threshold ($p < 0.003$) was used for the fMRI analyses conducted in the healthy sample, as reported in Stephan-Otto et al. (2017).

2.8. Plan of analysis

Perception processes of the presented pictures (P) and words (W) were studied with the contrasts $P > W$ and $W > P$. During the encoding phase, the items that were subsequently correctly remembered as pictures (PP) or as words (WW) were studied with the contrasts $PP > PW$ and $WW > WP$. The words later erroneously remembered as pictures (WP) were studied with the contrasts $WP > WW$ and $WP > PP$. During the **memory test**, the items correctly remembered as pictures or as words were studied with the contrasts $PP > PW$ and $WW > WP$, while the words erroneously remembered as pictures were studied with the contrasts $WP > WW$ and $WP > PP$. Missed responses were not modeled because there were extremely few of them.

Due to machine errors, a few fMRI data from the healthy control group were missing (see Stephan-Otto et al., 2017). Likewise, one patient's data had to be discarded from fMRI analyses because they were corrupted. **Preliminary analyses were conducted in the remaining 22 patients to identify the socio-demographic and clinical factors that might have confounded any obtained cerebral activity. Education level and verbal IQ did not have any significant effect in any of the above contrasts and they were not considered in the fMRI analyses. On the other hand, age, sex, and illness duration presented significant effects and were therefore controlled for in all the following fMRI analyses conducted in patients.**

The contrasts of interest were first conducted in the group of 22 patients, using age, sex, and illness duration as covariates. Then, three comparisons of subgroups of patients were conducted using these covariates. The patients with significant current or past visual hallucinations (score ≥ 3 , $n = 10$) were compared to those who had never experienced visual hallucinations (score = 0, $n = 8$). Two patients scoring 1 and two patients scoring 2 on the visual hallucination score were excluded

from these subgroup comparisons. Then the patients with verbal hallucinations (score ≥ 2 , $n = 6$) were compared to those without verbal hallucinations (score = 0, $n = 16$). **In order to control for the overlap between verbal and visual hallucinations, the verbal hallucination score was added to the covariates when contrasting patients with vs. without visual hallucinations, while the visual hallucination score was added to the covariates when contrasting patients with vs. without verbal hallucinations.** Lastly, to study the neural mechanisms of false memories of pictures independently from hallucinations, we compared the patients with the most liberal response bias ($Br \geq .42$, $n = 8$) to those with the most conservative response bias ($Br \leq .23$, $n = 9$). Five patients with intermediate Br values were excluded from these comparisons. **The Pr index was added to the covariates to control for the potential impact of memory efficiency on the rate of false remembering of pictures.** Similar subgroup comparisons of participants with liberal ($Br \geq .42$, $n = 10$) vs. conservative ($Br \leq .23$, $n = 10$ for encoding, and $n = 9$ for **memory test**) response bias were conducted in the healthy control group, controlling for **age, sex,** and Pr .

3. Results

3.1. Behavioural performance

The response bias index Br , reflecting propensity to remember word-items as pictures, was equivalent in the patient and healthy control groups ($m = .33$, $sd = .17$ vs. $m = .33$, $sd = .19$). A regression analysis was conducted on this index in the 23 patients, including Pr , education level, verbal IQ, verbal hallucination score, and visual hallucination score as predictors. The visual hallucination score was significantly associated with Br ($\beta = .67$, $p < .05$), indicating that higher ratings of visual hallucinations were associated with increased rates of false memories of pictures, as

expected. On the other hand, the verbal hallucination score was unrelated to Br (β near zero). Then a regression analysis was conducted on the response times for the false memories of pictures, including age, education level, verbal IQ, verbal hallucination score, and visual hallucination score as predictors. The visual hallucination score was not significantly associated with increased response times ($\beta = .34, p = .21$).

3.2. *fMRI results*

3.2.1. Perception and encoding

The activations observed in 25 healthy control participants are presented in Table 1. Visual areas were activated for both perception ($P > W$) and encoding ($PP > PW$) of the pictures, and the right supramarginal gyrus and superior parietal lobe were activated during the encoding of the words later remembered as pictures ($WP > PP$).⁴ In the patient group, only the contrast $P > W$, reflecting picture perception, yielded significant activation, and this was observed in the same visual areas as in the healthy sample: the bilateral lingual (**MNI coordinates: 0, -89, 2**) and left and right fusiform gyrus (**MNI: -30, -68, -7 and 35, -52, -11**), cluster size = **1276**, cluster level significance: $p_{FWE} < 0.001$. A trend toward activation was observed in the right middle occipital gyrus (**MNI: 33, -78, 21**; cluster size = **51**; cluster level significance: $p_{FWE} < 0.098$)⁵.

When the patients with vs. without visual hallucinations were compared to each other, significant activation was observed only for the contrast $WP > WW$, reflecting the encoding of words later remembered as pictures. As expected, the patients with visual

⁴ This information was previously reported in Stephan-Otto et al. (2017).

⁵ The results relative to picture perception in 20 of the patients were described and discussed in another manuscript (Stephan-Otto et al., 2016).

hallucinations differentially activated a visual area, namely the right fusiform gyrus, during the presentation of these words (MNI: 33, -78, 21; cluster size = 88; cluster-level significance: $p_{FWE} < 0.002$). **In this contrast, age, sex, and verbal hallucination score were not associated with any significant brain activity. However, illness duration was significantly associated with decreased activity in the fusiform gyrus bilaterally, and in the left lingual gyrus.** When the patients with verbal hallucinations were compared to those without them, **no differential brain activation was observed for any of the contrasts studied. Likewise,** comparisons of participants with high vs. low Br did not reveal any differential activation in either the patient or the healthy sample.

3.2.2. Memory test

The activations observed in 24 healthy participants⁴ and in the 22 patients are presented in Table 2 and Table 3, respectively. The healthy participants activated various brain areas, including visual areas, when correctly remembering pictures (PP > PW), while the patients only activated the left caudate and amygdala. When falsely remembering pictures (WP > WW), the patients were found to bilaterally activate the anterior cingulate and medial superior frontal gyrus (see Figure 1), while no significant activation was observed in the healthy sample.

No significant differential activation was observed for any of the contrasts studied when the patients with visual hallucinations were compared to the other patients. **The patients with verbal hallucinations presented increased bilateral activation in the thalamus (MNI: 5, -30, -2) and in the precuneus (MNI: 23, -45, 10) (cluster size = 317; cluster-level significance: $p_{FWE} < 0.001$) relative to the other**

patients when correctly remembering pictures (PP > PW). When the patients with high vs. low Br were compared to each other, those with high Br demonstrated differential activation of the **left superior temporal gyrus (MNI: -58, -43, 11; cluster size = 47) when erroneously remembering pictures (WP > WW), although this was only observed at a trend level of significance (cluster-level significance $p_{FWE} < .07$).** No differential activation emerged in any of the contrasts studied when the healthy participants with high Br were compared to those with low Br.

4. Discussion

The current paradigm, which examined the mechanisms behind reality monitoring and visual hallucinations, required the participants to remember whether previously encoded items referring to common objects had been presented as pictures or as **labels**. As expected, higher ratings of visual hallucinations were associated with increased rates of false memories of non-presented pictures, which replicates a previous behavioural study (Brébion et al., 2008). This bias was, on the other hand, entirely unrelated to verbal hallucinations. At the cortical level, the patients that presented current or past visual hallucinations differentially activated a visual brain area, namely the right fusiform gyrus, when they encoded words they later remembered as pictures. This finding is compatible with Kensinger and Schacter's (2005) study of healthy individuals, which similarly revealed activation of the fusiform gyrus during the encoding of neutral words later remembered as pictures. These authors encouraged their participants to use visual imagery at encoding, which may explain the significant activation of the fusiform gyrus in their whole non-clinical sample, while in our schizophrenia sample, only patients with spontaneous use of visual imagery might have activated it. In our study, the fusiform gyrus –which is involved in the recognition of

objects (Kassuba et al., 2011; Konen, Behrmann, Nishimura, & Kastner, 2011)— was also activated by the entirety of the patient and healthy groups during the presentation of the picture stimuli. The implication of this visual brain region in both picture perception and the formation of imagined pictures corroborates studies that evinced common neural bases for visual perception and visual imagery (Cichy, Heinzle, & Haynes, 2012; Lee, Kravitz, & Baker, 2012). **The activation of a visual area during this encoding process seems to be specific to the patients with visual hallucinations. Indeed, those with a greater tendency to remember the words as pictures—as reflected by their more liberal response bias irrespective of their visual hallucinatory status— did not demonstrate any differential activation when encoding the words they later remembered as pictures; they seem to have reached a high rate of false memories of pictures by means of a mechanism other than the spontaneous formation of visual mental images at encoding.**

Thus, in patients with visual hallucinations, the mere presentation of the **label** of common items led to the same visual area activation as did the presentation of pictures of these items. This observation confirms our assumption that visual hallucinations in schizophrenia are associated with abundant visual imagery. In a previous study of verbal memory in schizophrenia, patients with visual hallucinations were found to make little use of the typical verbal strategies of serial and semantic clustering when learning lists of familiar words (Brébion, Ohlsen, Pilowsky, & David, 2011). It was suggested that these patients used visual imagery of the target words as a mnemonic strategy in preference to the verbal strategies implemented by the other patients. A link between visual hallucinations and strength of visual mental imagery was recently reported in patients with Parkinson's disease (Shine et al., 2015). **In similar manner, verbal hallucinations, which were not associated with visual imagery in our study, might**

be associated with strong auditory imagery (Moseley, Smailes, Ellison, & Fernyhough, 2016).

The **memory test** involved reality-monitoring processes insofar as imagined pictures that potentially came to mind had to be distinguished from pictures actually presented at the encoding phase (Johnson et al., 1993). **It should be noted that if no visual mental image had been formed during the presentation of the label, the task, rather, involved the external source monitoring process of remembering whether a word or a picture had been presented on the screen.** The entire group of patients activated the anterior cingulate when erroneously remembering pictures, in agreement with a study that used an analogous paradigm in healthy participants (Okado & Stark, 2003). A study of face recognition in healthy participants similarly revealed activity of the anterior cingulate cortex during false memories of faces; this activity, moreover, correlated with increased response time for these erroneous responses (Iidaka, Harada, Kawaguchi, & Sadato, 2012). Functional abnormalities in the anterior cingulate have also been associated with the external misattribution of self-generated speech in patients with auditory-verbal hallucinations (Allen et al., 2007). Event-related studies of patients with schizophrenia have suggested that disruption in the anterior cingulate is associated with deficits in the monitoring of conflicts and errors (Alain, McNeely, He, Christensen, & West, 2002; Mathalon et al., 2002).

When falsely remembering pictures, our patients as a group also bilaterally activated the medial superior frontal gyrus. **This brain area might be associated with external source monitoring of the presented stimuli. Indeed, reality-monitoring processes, notably the evaluation of internally-generated information, have been shown to involve the medial prefrontal cortex** (Buda, Fornito, Bergström, & Simons,

2011; Metzak, Lavigne, & Woodward, 2015; Mitchell & Johnson, 2009). **Meanwhile, a subgroup of our healthy participants –those with high visual imagery abilities– activated another section of the frontal gyrus, namely the left middle frontal gyrus, when falsely remembering pictures** (Stephan-Otto et al., 2017). Kensinger and Schacter (2006) similarly reported that the left middle frontal gyrus was involved in pictorial misattribution in their healthy sample. **Activity in the left middle frontal gyrus was also found to be associated with the spatial source monitoring of visual shapes** (Slotnick, Moo, Segal, & Hart, 2003). Frontal lobe and anterior cingulate cortex might be critically involved in the process of false remembering in both schizophrenia patients and healthy participants, **and the left middle frontal gyrus may possibly have a specific role in the source monitoring of visual information.**

The fact that healthy participants with high visual imagery abilities differentially activated a fronto-parietal network when erroneously remembering pictures presumably reveals their difficulty in distinguishing their abundant mental images from the target pictures. This difficulty is also reflected by their increased response time when judging the status of the imagined pictures. Visual imagery proneness in the healthy sample, however, was not associated with higher rates of false memories of pictures, a probable consequence of efficient reality-monitoring processes in these individuals. The patients with visual hallucinations, in contrast, did not demonstrate any distinct activation pattern relative to the other patients during the erroneous **remembering** of pictures, nor any increased response time when making this false judgment, but visual hallucination scores were associated with increased rates of false memories of pictures. These divergences from the healthy **visual imagery-prone** subsample point to reality-monitoring dysfunction in patients with visual hallucinations

since they seem to accept their mental images as real without implementing the expected extra-decisional processes. Alternatively, **the reality-monitoring processes might be intact in patients with visual hallucinations, but the visual mental images formed in the presentation phase might be more vivid than they are** in visual imagery-prone healthy individuals, and therefore these patients might be less likely to question their reality. **They would simply regard these images as percepts without engaging in a reality-monitoring test.**

A limitation of our study is that small-sized subsamples of patients were included in the subgroup comparisons. Due to the difficulty of patient recruitment, clinical samples usually involve a limited number of participants. This is especially true when a symptom of low prevalence such as visual hallucinations is studied. In addition, a few of the patients included in our visual hallucination subgroup had suffered visual hallucinations in the past but were not currently hallucinating. Results might be stronger if only patients with current visual hallucinations were included. **Further, we cannot rule out the possibility that the effects observed in patients with visual hallucinations were to some extent influenced by the coexistence of other psychiatric symptoms. Notably, both depressive and obsessive-compulsive disorders have been associated with strong mental imagery (Klein & Moritz, 2014).** Our findings **therefore call for replication in larger samples with better control of the potentially confounding factors.** The study nonetheless provides neural evidence for the involvement of visual imagery in the formation of visual hallucinations in schizophrenia patients. **Whether excessive visual imagery alone accounts for the hallucinatory phenomenon, or whether it has to be coupled with deficient reality-monitoring processes for visual hallucinations to occur, remains to be determined.**

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Legend for figure

Figure 1: Activation cluster associated with the contrast $WP > WW$ during **the memory test** in the whole patient group. Top: section of the cluster pertaining to the medial superior frontal gyrus. Bottom: sagittal plane illustrating the extent of the cluster, which also encompasses the anterior cingulate. The $z = 35$ and $x = -6$ planes of the SRI24 structural template are shown for illustration purposes only.

Figure 1. Brain activity associated with false remembering of non-presented pictures in 22 schizophrenia patients.

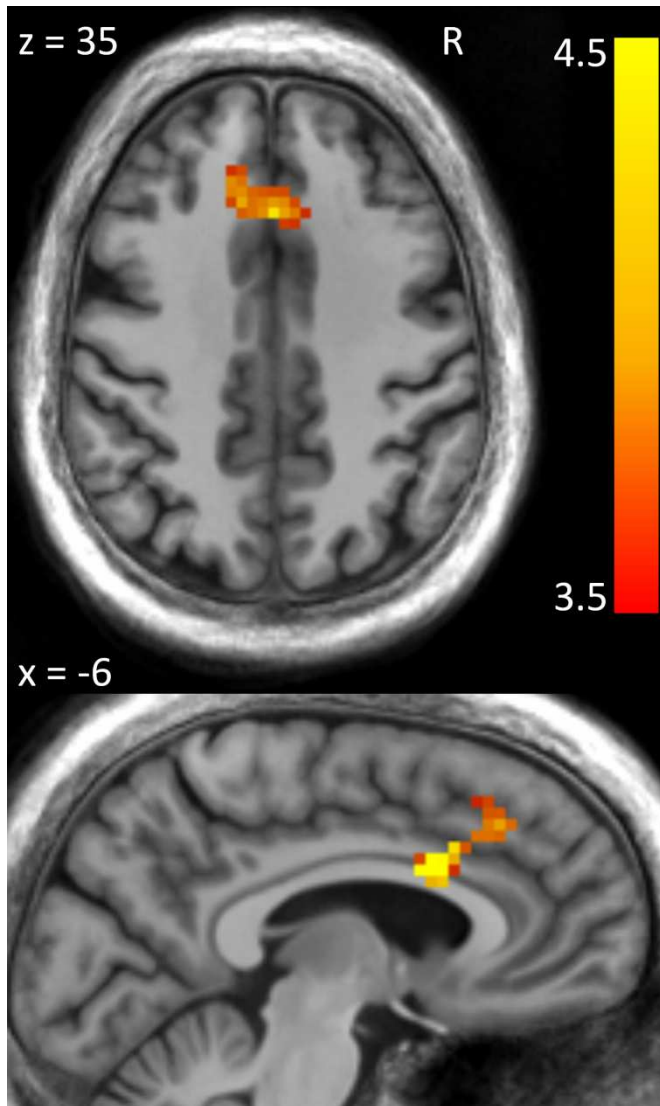


Table 1. Brain activation areas during perception and encoding in 25 healthy participants, after controlling for sex and verbal IQ.

		Contrast	Cluster size and corrected significance p_{FWE}	Cluster peak coordinates (MNI)	Region
Perception		P > W	338 (0.001)	-30, -73, -6	Fusiform L
		(voxel-level	639 (0.001)	28, -72, -6	Fusiform R
		$p_{FWE} < 0.05$)	111 (0.001)	-4, -89, -6	Lingual R / L
			73 (0.001)	-37, -82, 11	Middle occipital gyrus L
		W > P	265 (0.002)	62, -40, 45 49, -41, 59	Supramarginal gyrus R + Inferior parietal lobe R
Encoding	Correct subsequent memories	PP > PW	203 (0.006)	-43, -66, -4	Lateral occipital complex L
			101 (0.107)	38, -66, -3	Lateral occipital complex R
		WW > WP	N. S.	-	-
	False subsequent memories of pictures	WP > WW	N. S.	-	-
WP > PP		184 (0.010)	63, -41, 41 39, -57, 60	Supramarginal gyrus R + Superior parietal lobe R	

MNI = MNI stereotactic coordinates; p_{FWE} = family-wise error corrected p-value.

Table 2. Brain activation areas during the memory test in 24 healthy participants, after controlling for sex and verbal IQ.

		Contrast	Cluster size and corrected significance p_{FWE}	Cluster peak coordinates (MNI)	Region
Memory test	Correct memories	PP > PW (T = 3.90)	91 (0.008)	-7, -91, -1	Calcarine L + Lingual L
			94 (0.007)	7, 14, -5	Caudate R
		89 (0.009)	-10, 6, 4	Caudate L	
		57 (0.038)	-7, -73, 41	Precuneus L	
		69 (0.022)	-46, -59, 52	Inferior parietal lobe L + angular gyrus L	
			-43, -61, 38		
		WW > WP	N. S.		-
False memories of pictures	WP > WW	N. S.			-
	WP > PP	N. S.			-

MNI = MNI stereotactic coordinates; p_{FWE} = family-wise error corrected p-value.

Table 3. Brain activation areas during the memory test in 22 patients, after controlling for age, sex, and illness duration.

		Contrast	Cluster size and corrected significance p_{FWE}	Cluster peak coordinates (MNI)	Region
Memory test	Correct memories	PP > PW	95 (0.013)	-13, 11, -4	Caudate L+ amygdala L
		WW > WP	N.S.	-	-
	False memories of pictures	WP > WW	95 (0.020)	-6, 16, 24 -8, 35, 36	Ant. cingulate R+L + Medial sup frontal gyrus R+L
		WP > PP	N.S.	-	-

MNI = MNI stereotactic coordinates; p_{FWE} = family-wise error corrected p-value.