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ORIGINAL PAPER

Disturbances of Agency and Ownership in Schizophrenia: An Auditory Verbal Event Related Potentials Study

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Abstract A 'sense of self' is essentially the ability to distinguish between self-generated and external stimuli. It consists of at least two very basic senses: a sense of agency and a sense of ownership. Disturbances seem to provide a basic deficit in many psychiatric diseases. The aim of our study was to manipulate those qualities separately in 28 patients with schizophrenia (14 auditory hallucinators and 14 non-hallucinators) and 28 healthy controls (HC) and to investigate the effects on the topographies and the power of the event-related potential (ERP). We performed a 76-channel EEG while the participants performed the task as in our previous paper. We computed ERPs and difference maps for the conditions and compared the amount of agency and ownership between the HC and the patients. Furthermore, we compared the global field power and the topographies of these effects. Our data showed effects of agency and ownership in the healthy controls and the hallucinator group and to a lesser degree in the non-hallucinator group. We found a reduction of the N100 during the presence of agency, and a bilateral temporal negativity related to the presence of ownership. For the agency effects, we found significant differences between HC and the patients. Contrary to the expectations, our findings were more pronounced in non-hallucinators, suggesting a more profoundly disturbed sense of agency compared to hallucinators. A contemporary increase of global field power in both patient groups indicates a compensatory recruitment of other mechanisms not normally associated with the processing of agency and ownership.

Keywords Auditory evoked potential · Agency · Ownership · Schizophrenia · Auditory verbal hallucination · Self-monitoring · N100

Introduction

"Here are my legs, my hands, I can also feel my head, but cannot find it again. I hear my voice when I speak, but the voice seems to originate from some other place." For this schizophrenic patient (Parnas and Handest 2003) it was not obvious who the initiator of his action was. In the last 150 years, more and more complex theories about how people distinguish between self-generated and external stimuli, the so-called 'self-monitoring', were developed. The research in psychiatric disorders is inseparably connected to the research in 'self-monitoring'—as deviations from the normal function as seen in especially psychotic disorders provide a basis in understanding the normal function.

Models essentially go back to the year 1866, when the German physicist Hermann von Helmholtz questioned: "When an image moves across the retina, how do we know whether the world or our eyes are moving?" He postulated that the difference must lie in the motor command in active movements. With information provided by this motor command, sensory consequences of the eye movements become predictable. Sperry (1950) and Von Holst (1954) followed the ideas of Helmholtz and suggested an efference copy mechanism towards sensory brain areas, which

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allows distinguishing between incoming sensory feedback and internal representation. When there is a match between this "efference copy", later termed "corollary discharge", and the sensory consequences, the changes will be considered as self-generated.

Blakemore et al. (1998) examined the neural responses to either self-produced or externally produced tactile stimuli using functional magnetic resonance imaging (fMRI). They found an increased activity in the somatosensory cortex in externally produced stimuli. However, in the anterior cerebellar cortex less activity was noted during movement that generated tactile stimuli than during movement that did not. They suggested that the cerebellum predicts the sensory consequences of movement and provides the signal to weaken the sensory response in the somatosensory cortex. These experiments provide an anatomic correlate to the comparator model.

Feinberg (1978) and Frith (1992) largely extended the model. Feinberg hypothesized that the mechanism of the model does also occur in thinking. He further hypothesized that a deficient comparator mechanism may provide an explanation for first rank symptoms like auditory hallucinations and thought broadcasting in schizophrenia.

According to Feinberg and Frith, the comparators serve as an evaluation function whether actions are externally or internally caused. It may underlie our sense of agency, the awareness that I am the one who is causing or generating an action. The American philosopher Gallagher defined agency as the sense that I am the one who is causing or generating an action, building what he called a 'minimal self' (Gallagher 2000). From the phenomenological point of view, many symptoms of schizophrenia such as auditory hallucinations, thought insertion or delusions of control seem to be due to a disturbed sense of agency. Importantly, the auditory-verbal domain seems to be frequently affected. Therefore, this system, and its association to auditory verbal hallucinations, was of particular interest in further research.

The empirical counterpart to these philosophical and phenomenological considerations has shown that there are indeed biologically well characterized mechanisms that seem to implement the perception of agency, in particular also in the domain of processing of self-generated sounds. Heinks-Maldonado et al. (2005) examined the auditory N100 component of event-related brain potential elicited during speech production. They observed that an unaltered voice feedback generated a dampened auditory N100 response compared to the N100 evoked by an alien auditory feedback. They suggested a precise forward model in the auditory cortical response that allows to immediately distinct self and externally generated auditory stimuli. A reduction of the N100 response is also observed when subjects vocalize simple syllables, compared to a condition where subject listen to such vocalizations after a cue (Oestreich et al. 2015).

In an own experiment, we experimentally manipulated two aspects of the self-monitoring process, namely agency as being the cause of an event, and ownership, as recognizing features of the action (i.e. the particular voice) to be one's one (Hubl et al. 2014). Event-related potentials (ERP) recorded in healthy individuals showed that these two processes were related to rather different, and seemingly quite independent patterns of activation. In addition, it confirmed effects of earlier papers (Ford et al. 2001a, b; or Heinks-Maldonado et al. 2005) where the N100 suppression was attributed to agency effects.

In the present paper, we aimed to investigate these effects in schizophrenic patients compared with healthy controls. Furthermore, we compared the effects between auditory hallucinators (AH) and non-hallucinators (NH) and examined whether there is an association between the severity of the schizophrenic symptoms, measured with the PANSS, and disturbances in their senses of agency or ownership.

Materials and Methods

Subjects

28 patients with schizophrenia or schizoaffective psychosis (ICD-10 F20 or F25) and 28 healthy adult comparison subjects (HC) participated in the study (Table 1). The group of HC included the 13 subjects from our previously published paper (Hubl et al. 2014). For HC, medical and psychiatric disorders served as exclusion criteria. None of them reported any history of auditory, visual, psychiatric, or neurological disorders. Among the patients, 14 experienced auditory verbal hallucinations (AH) and 14 did not experience AH in their recent medical history (NH). Patients were defined as hallucinators if they reported frequent and present hallucinations. Non-hallucinators were defined by not reporting any hallucinations for at least 2 weeks. Most of the non-hallucinators had never reported hallucinations ($n = 9$).

All study procedures were done at the Department of Psychiatric Neurophysiology of the University Hospital of Psychiatry, Bern. Subjects provided written informed consent and the study was conducted in agreement with the Declaration of Helsinki as well as approved by the local ethics committee of the Canton of Bern.

All subjects were screened with the Whispered-Voice Test (Macphee et al. 1988) to detect hearing impairments. General psychopathology was assessed by the PANSS in all patients (Kay et al. 1987). The specific hallucinatory symptomatology was measure by application of the

Table 1 Characteristics of study participants; none of the differences were significant [means (SD)]

	Normal controls	Hallucinators	Non-hallucinators
Age	37.8 (14.4)	42.1 (10.1)	41.1 (10.7)
Gender (males/females)	14/14	8/6	9/5
Neuroleptic dosage (chlorpromazine equivalents)[a] (mg)	–	537.8 (547.4)	504.5 (420.0)
PANSS (total score)	–	71.1 (18.6)	70.1 (17.2)
Positive symptoms PANSS	–	16.3 (4.7)	15.3 (3.6)
Negative symptoms PANSS	–	18.5 (8.6)	20.0 (8.9)
General psychopathology PANSS	–	32.7 (8.8)	30.5 (9.1)
Suicidal items PANSS	–	4.6 (2.2)	4.3 (1.7)
Auditory hallucination rating scale	–	21.7 (9.6)	0.0 (0.0)
PSYRATS	–	31.5 (13.7)	10.0 (7.0)

[a] Chlorpromazine equivalents were calculated according to Leucht et al. (2003, 2014), PANSS positive and negative symptom score (Kay et al. 1987), auditory hallucinations rating scale (Hoffman et al. 2003), PSYRATS psychotic symptom rating scale (Haddock et al. 1999)

auditory hallucination rating scale (AHRS, Hoffman et al. 2003) and the PSYRATS (Haddock et al. 1999).

Experimental Design and Stimulus Material

Our experimental design (Table 2) allowed separating the effects of agency and ownership in an auditory perception paradigm by eliminating the effects of speech production. In brief, the reader was presented a word that he had to read immediately aloud. However, in the different conditions, either the visual or the auditory component or both were modified. Therefore, the experiment consisted of the following six conditions: (a) subjects saw a word, read it aloud, and heard it immediately in their own voice (normal); (b) subjects saw a word, read it aloud, and immediately heard it spoken by another, unfamiliar voice (unfamiliar); (c) the subject heard him/herself speaking a word [playback of the previously recorded word during condition (a)] without having seen or read a word (feedback-only); (d) subjects heard an unfamiliar voice speaking a word without having seen or read a word (feedback-unfamiliar); (e) subjects saw a word, read it aloud, and heard it with a delay of 200 ms in their own voice (delay); and (f) subjects saw a word and read it aloud, but received no auditory feedback (read-aloud-only). The identical unfamiliar voice was used in conditions (b) and (d). The aim of the last condition was to eliminate speech-related artefacts of the normal, unfamiliar and delay condition. Data from a separate behavioral study that is still under analysis indicates that controls and patients were highly accurate (98 % correct) in distinguishing their own voice from the unfamiliar voice.

During the experiment, the subjects sat in a comfortable resting position in front of computer screen (distance 70 cm) and a microphone in a slightly darkened room. The subjects wore headphones (Sennheiser HME 110) which effectively dampen external auditory input. Prior to the experiment, we individually adjusted the volume of a pink

Table 2 The stimulation conditions: Overview and brief description of the six conditions

Name	Description	Agency	Ownership
Normal	Subjects saw a word, read it aloud, and immediately heard it in their own voice	+	+
Unfamiliar	Subjects saw a word, read it aloud, and immediately heard it, but spoken with an unfamiliar voice	+	−
Feedback-only	Without seeing and reading a word, the subject heard him/herself speaking a word	−	+
Unfamiliar-only	Without seeing and reading a word, subjects heard an unfamiliar voice speaking a word	−	−
Delay	Subjects saw a word, read it aloud, and heard the word in their own voice, but with a delay of 200 ms	±	+
Read-aloud-only	Subjects saw a word and read it aloud, but received no auditory feedback. This condition was used to control for speech-related artefact	−	−

Agency and ownership effects are indicated for each condition with + for the presence of the respective effect and − for the absence. In the delay condition, the presence of a distorted the agency effect is indicated with ±

(1/f) noise to mask bone conductions when subjects were speaking at regular volume levels, wearing the headphones. For this purpose, participants were asked to count loudly, while the pink noise volume level was increased gradually, and to indicate when they lost auditory comprehension of their own voice (content). During the experiment, the noise was constantly played in the background through the headphone. In the experimental conditions, in which the subjects heard their own or an unfamiliar voice, the loudness of the presented word was set to 20 dB above the individual pink noise level.

The words and their concreteness ratings were selected from a word list from Wirth et al. (2008, 2011) and consisted of 270 German, two-syllable, concrete, and neutral nouns. During the experiment, the words were presented in the center of the screen. When no word was presented, a fixation cross was shown instead. In the three conditions that included a word presentation, the word was shown for 1 s (visual angle of a 5-letter word was 4.9 degrees). There were a total of 90 trials in each of the six conditions, in total 540 trials. Therefore, the 270 words were presented twice in the same condition, except of the words from the normal and feedback-only condition where 90 different words appeared in the two conditions, but where identical for both conditions. To present the unfamiliar voice, the subject's voice onset was detected through the microphone, which triggered immediately the playback of the visually presented word read by an unfamiliar speaker. The triggering was precise enough to make subject experience that the sound onset was undelayed. These unfamiliar word stimuli were previously recorded and were spoken by a local speaker of the same sex as the subject. In the Unfamiliar condition, there was no delay.

Each trial consisted of a 1-s pre-stimulus period with only the fixation cross shown, followed by the presentation of a visual stimulus and/or an auditory feedback. The trials were presented in a pseudo-random order over the duration of the experiment. The trials were separated by 3 s. Furthermore, 10 short breaks were given during the experiment. The duration of the entire experiment was about 35 min. To analyze the behavioral data, the delays between the stimulus and the onset of the voice were individually collected in the normal and the unfamiliar conditions. They were then averaged within the subjects and afterwards across groups.

Electrophysiological Recordings

The electroencephalogram (EEG) was recorded using silver/silver chloride electrodes. Attachment to the scalp based on the international extended ten-twenty system at 74 regularly spaced standard positions. For artefact monitoring, two additional EOG electrodes were placed below each eye. The impedances were kept below 20 kΩ. Recording references were provided by F3 and F4. Buffer amplifiers separated these two electrodes electrically. A 4-min resting state EEG preceded the experiment for clinical evaluation. The EEG was continuously digitized during the entire experiment (bandpass filter 0.016–150, 500 Hz sampling rate) and stored for offline analysis using a Nihon Kohden Neurofax EEG 1100G system. In the EEG, the onset of the visually and acoustically presented stimuli was displayed by markers.

Data Pre-processing

An ICA-based correction of eye-movements was performed in all EEG data (Jung et al. 2000). The EEG was recomputed to average reference, and periods with visually detectable remaining artefacts (muscle activity and electrode artefacts) were marked and eliminated by an EEG expert. Channels containing excessive artefacts (namely electrode artefacts) were interpolated using spherical splines. Now, all signals were bandpass filtered between 1.5 and 30 Hz. The continuous EEG recordings were segmented into 1.200-ms epochs, beginning 200 ms before voice/sound onset to 1.000 ms after the onset, based on the markers given by the stimulation programme. EEG segments were averaged within each stimulus condition and subject. Mean number of included trials (SD) per condition was 79.5 (11.0), range 33–90 for the HC (one participant did not finish the experiment); 76.5 (19.9), range 8–90 for AH, (excessive muscle artefacts in one participant) and 80.5 (7.0), range 57–90 for the NH. With EEG findings consistent with the other patients and similar mean numbers of included trials between the groups, we decided not to exclude this patient. The individual mean ERP of the Read-Aloud-Only stimulus condition was subtracted from the individual ERPs of the Normal, Unfamiliar, and Delay conditions to correct for speech-related artefacts.

The grand mean ERP was computed across all conditions (feedback-only, unfamiliar-only, normal, unfamiliar, delay) and subjects. As in the preceding study (Hubl et al. 2014), the ERP was divided into temporal components based on spatial similarity assessed by the correlation coefficient of grand mean of the five conditions. The peaks of this curve indicated start, respectively end point, of a particular time window corresponding to separable, stable, and mathematically defined ERP components (Michel et al. 2009). Similar to the previous study, we identified a N100 time window from 116 to 170 ms, and a "late component", from 172 to 356 ms. The ERP maps were averaged subject- and condition-wise across time within each of these two temporal components.

Statistical Analysis

The statistical analysis pursued several goals, using particular, and quite different methods. These goals and the rationales for the choice of the particular methods are briefly presented in the following paragraphs. The computational details for each method are then presented in the remainder of the methods section.

- We aimed to replicate previous results obtained in similar experiments. Namely we were interested in previously reported effects of a precise forward model modulating the auditory cortical response (Ford et al. 2001a, b; Heinks-Maldonado et al. 2005) and in the so called speech induced suppression (SIS) reported e.g. by Oestreich et al. (2015) in the N100 waveshape.
- We wanted to quantify and compare among groups the amount of activity in the ERP that can be attributed to those processes in the brain that account for the perception of agency and ownership in healthy controls. This type of question calls for spatial filtering procedures that we have implemented in the so called template based analysis.
- We speculated that group differences in the perception of agency and ownership may not only arise in different amounts of activation of those processes identified in the healthy controls (as assessed in the template based analysis), but also because functionally different processes were activated. This implies a different spatial distribution of the associated brain activity, which can be assessed using topographical comparisons of the normalized ERP scalp maps. This line of comparisons was implemented using topographic analyses of variance (TANOVAs) as implemented in the Ragu software (Koenig et al. 2011).
- Finally, we wanted to know if the overall amount of activation in the ERPs, independent of the spatial distribution of activity, was sensitive to differences between groups and/or conditions. This line of comparisons was thus based on the quantification and comparison of the global field power (GFP). This may account for effects that may have been eliminated by the normalization step in the TANOVAs.

The replication of previous N100 waveshape findings was based on the condition with the subjects talking and hearing the own voice [condition (a)] and the condition where subjects just listened to their own voice [condition (c)]. However, note that contrary to the SIS type of setup, the listen only condition had no cue. Since the statistical analysis of this effect is contained in the template based analyses and the TANOVAs, no further statistics were computed.

In order obtain the spatial filters for the template-based analysis, we computed the ERP signatures of agency and ownership, as defined by the GFP-normalized grand-mean difference maps of conditions (a) and (b) against conditions (c) and (d) for the agency effect, and as conditions (a) and (c) against conditions (b) and (d) for the ownership effect. These maps correspond to the forward solution of those sources that accounted for the perception of agency and ownership in the group of healthy controls. These two mean difference map series were averaged within the previously identified analysis windows and used as basis unto which the individual ERPs were projected (Brandeis et al. 1992). This projection thus estimated, in a single number per time point, the amount of variance of the ERP that could be attributed to the activity of those sources defining the processing of agency and ownership in the healthy controls in all the ERPs included in the analysis. The individual quantifiers of agency and ownership were thus computed in each subject and averaged across time in the corresponding analysis windows.

Please note that these indices of agency and ownership were based on a priori different spatial templates. Therefore, we refrained from quantifying for interactions in the template-based analysis; this assessment would imply cross-type comparisons. Furthermore, in our first paper we found spatially almost independent effects of agency and ownership in healthy controls (Hubl et al. 2014), such that we had no reasons to expect an interaction.

For the statistical analysis of the obtained mean indices, they were compared between the three groups (AH, NH, HC) and between corresponding conditions using repeated measures ANOVAs. Significant group by condition interactions in the ANOVA were further specified post hoc using Student's t tests. Furthermore, we calculated the correlation coefficient between the PANSS total score as well as the PSYRATS and the agency and ownership values of the patient groups (AH, NH and collapsed patient group).

The statistical comparison of the topography of the ERP component maps was based on a randomization procedure called TANOVA, using randomization statistics to compare multichannel ERPs (Strik et al. 1998). This procedure is implemented in the Ragu program (Koenig et al. 2011). Significant effects of the TANOVA suggest at least partially different sources of the analyzed ERP component maps as the TANOVA considers the entire scalp field as a single entity. The main analysis followed a 2×2 design with the two orthogonal factors agency and ownership and the four conditions normal (agency +/ownership +), feedback-only (agency −/ownership +), unfamiliar (agency +/ownership −), and unfamiliar-only (agency −/ownership −) (see Table 2). Computing these conditions against each other allowed us to assess pure agency and ownership effects.

The analysis of GFP followed the same logic as the TANOVA and compared the four main conditions (agency +/− and ownership +/−) using the 2 × 2 design previously used in the TANOVA. For the analysis of agency, the data were collapsed across all ownership conditions; for the analysis of ownership, all agency conditions were aggregated (aggregated GFP values). We performed two-factorial repeated measures ANOVAs comparing the GFPs of the groups and conditions. Again, significant ANOVA-effects including group and condition were followed up by post hoc Student's *t* tests to further specify the effects.

An additional one-way TANOVA contrasted the Feedback-Only condition against the Normal condition, to investigate previously reported effects of a precise forward model modulating the auditory cortical response (Ford et al. 2001a, b; Heinks-Maldonado et al. 2005). To assess the delay effect, the Delay condition was computed against the Normal condition using a one-way TANOVA.

Results

Behavioural Data

The normal controls showed a mean voice onset of 0.592 ms (SD 0.083 ms) after the onset of stimulus words. The patient group showed a slightly later voice onset of 0.621 ms (SD 0.120 ms) in the hallucinators and 0.617 ms (SD 0.154 ms) in the non-hallucinators. None of the differences was significant.

ERP Waveshapes and Speech Induced Suppression

The results of the computation of the SIS are shown in Fig. 1. Given the spatial distribution of the difference between trials with and without concurrent vocalization of the subject (see Fig. 3a below) that had a maximum anterior to Cz, we chose to show the effect at the electrode Fz. The pattern observed in healthy controls closely resembles the pattern reported by Oestreich et al. (2015). Patients showed as expected an overall reduction of the N100, and a smaller difference between the two marginal means.

Template-Based Analysis

The results of the template based analysis are shown in Fig. 2.

N100 Component

(a) In the N100 component for the agency effect, the overall group by condition interaction was significant in the ANOVA [$F(3,43) = 12.01$, $p < 0.001$]. Post-hoc *t* tests found significant differences in the agency effects between the HC and the patient groups [AH vs HC ($t = 3.097$; $p = 0.005$), NH vs HC ($t = 4.534$; $p < 0.001$)], but not among the patient groups [AH vs NH ($t = 0.289$; $p = 0.775$)].

(b) In the N100 component for the ownership effect, the overall ANOVA showed no significant effects for group [$F(3,43) = 1.26$, $p = 0.299$].

(c) The global PANSS showed no significant correlations to the agency effect in the AH group ($r = 0.382$, $p = 0.177$), and the NH group ($r = -0.309$, $p = 0.282$). Similarly, no significant correlation was found between the PANSS and the ownership effect (AH $r = -0.111$, $p = 0.705$; NH $r = -0.111$, $p = 0.706$).

(d) Neither significant correlations between the PSYRATS and the agency effect (AH $r = 0.184$, $p = 0.529$; NH $r = -0.033$, $p = 0.911$) nor the PSYRATS and the ownership effect (AH $r = 0.161$,

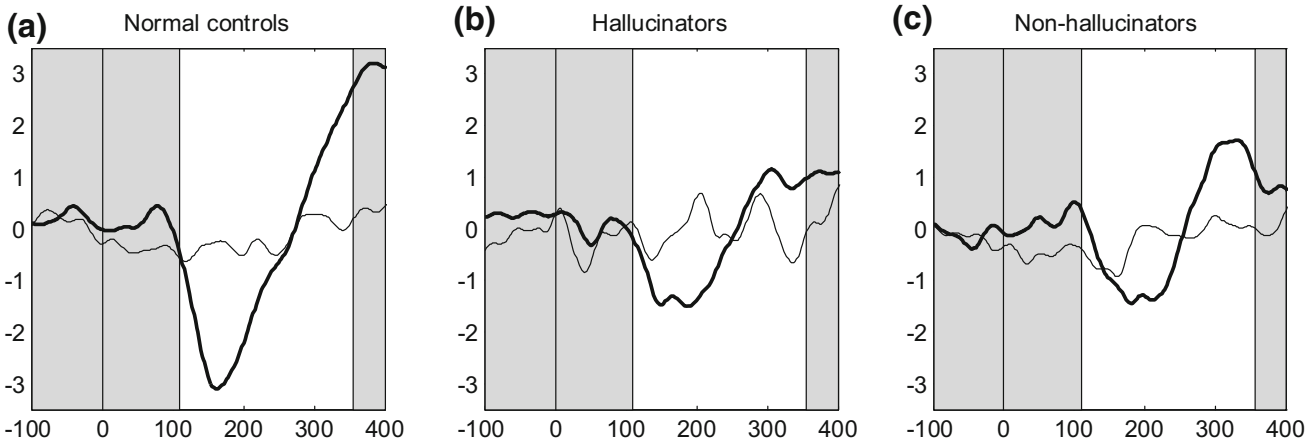

Fig. 1 Auditory event related potentials: speech induced suppression (N100) in normal controls (**a**), schizophrenia patients with auditory hallucinations (**b**) and patients without hallucinations (**c**). *Thick line* subjects listening; *thin line* while talking

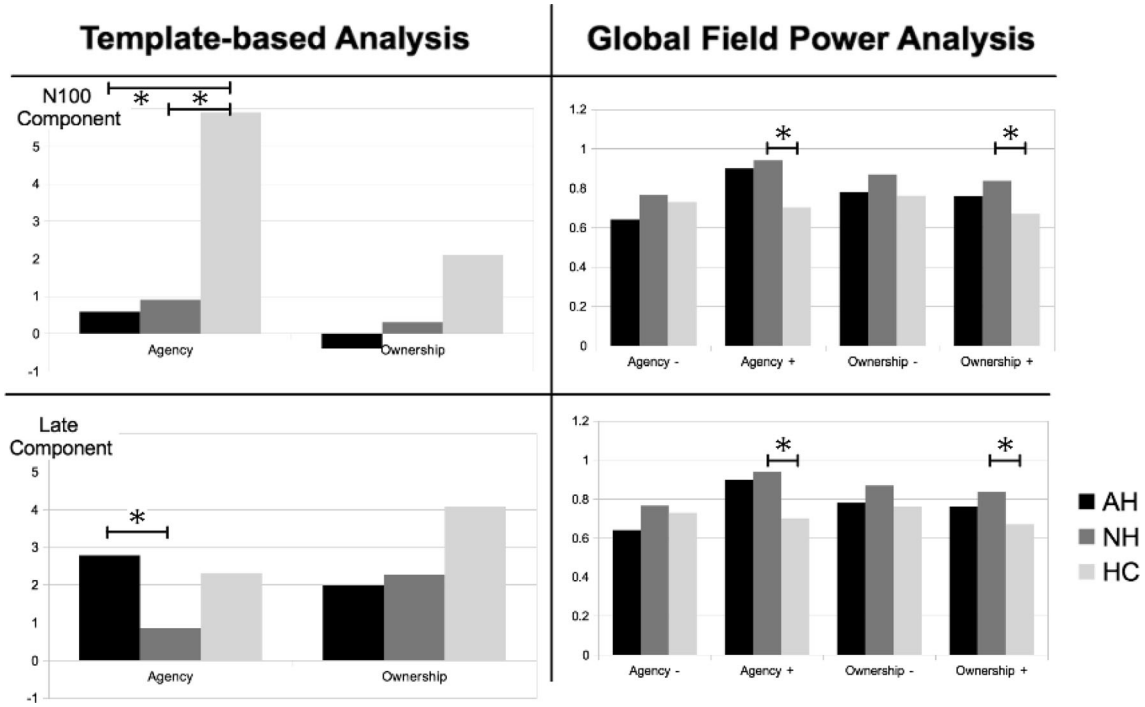

Fig. 2 Template-based analysis and global field power analysis. *AH* auditory hallucination, *NH* no hallucination, *HC* healthy controls

$p = 0.581$; NH r $= -0.187$, $p = 0.522$) were found among the patient groups.

Late Component

(a) In the late component for the agency effect, a two-factorial ANOVA (Group x Condition) showed no group by condition effect [$F(3,43) = 0.588$, $p = 0.63$]. However, when only the two patient groups were compared, the ANOVA showed a significant interaction [$F(3,26) = 5.38$, $p = 0.03$].
(b) There were no significant effects related to ownership in the late component.
(c) In the AH group, the PANSS indicated a nearly significant negative correlation with the agency effect (r $= -0.522$, $p = 0.060$), but not for the NH group (r $= 0.104$, $p = 0.723$).

In contrast, the PANSS showed a trend for a positive correlation for the ownership effect in the AH group (r $= 0.470$, $p = 0.090$), but not so for the NH group (r $= -0.220$, $p = 0.450$).

TANOVA Effect

N100 Component

Overall, the N100 showed the typical central negativity with the bilateral temporal positivity (Fig. 3).

The topographies of the agency effects showed a pattern of central positivity (Fig. 3a). Further, they differed in all 3 groups from the topographies of the ownership effects. Significant agency effects could be found in the HC ($p < 0.001$) and the AH ($p < 0.001$). The effects in the NH were not significant ($p = 0.080$). The TANOVA indicated neither a significant ownership effect (HC/AH/NH $p = 0.100/0.504/0.221$) nor a significant interaction (HC/AH/NH $p = 0.106/0.147/0.356$) in any group. When the agency effects were compared between groups, the difference between the AH and HC was not significant ($p = 0.637$). A significant differences could however be found between the NH and HC ($p = 0.015$). The differences between AH and NH were not significant ($p = 0.129$).

The t-map of the N100 ownership effect showed a pattern of bilateral centrotemporal negativity, most distinctly in the normal controls (Fig. 3). No significant differences in ownership between the AH and HC ($p = 0.961$), NH and HC ($p = 0.763$) and AH and NH ($p = 0.886$) could be found with the TANOVA.

Late Component

The late component showed a pattern of occipitoparietal negativity and bilateral frontal positivity (Fig. 4). The TANOVA indicated significant main effects of agency for HC ($p = 0.007$) and AH ($p = 0.028$). No significant agency effects could be found in NH ($p = 0.687$).

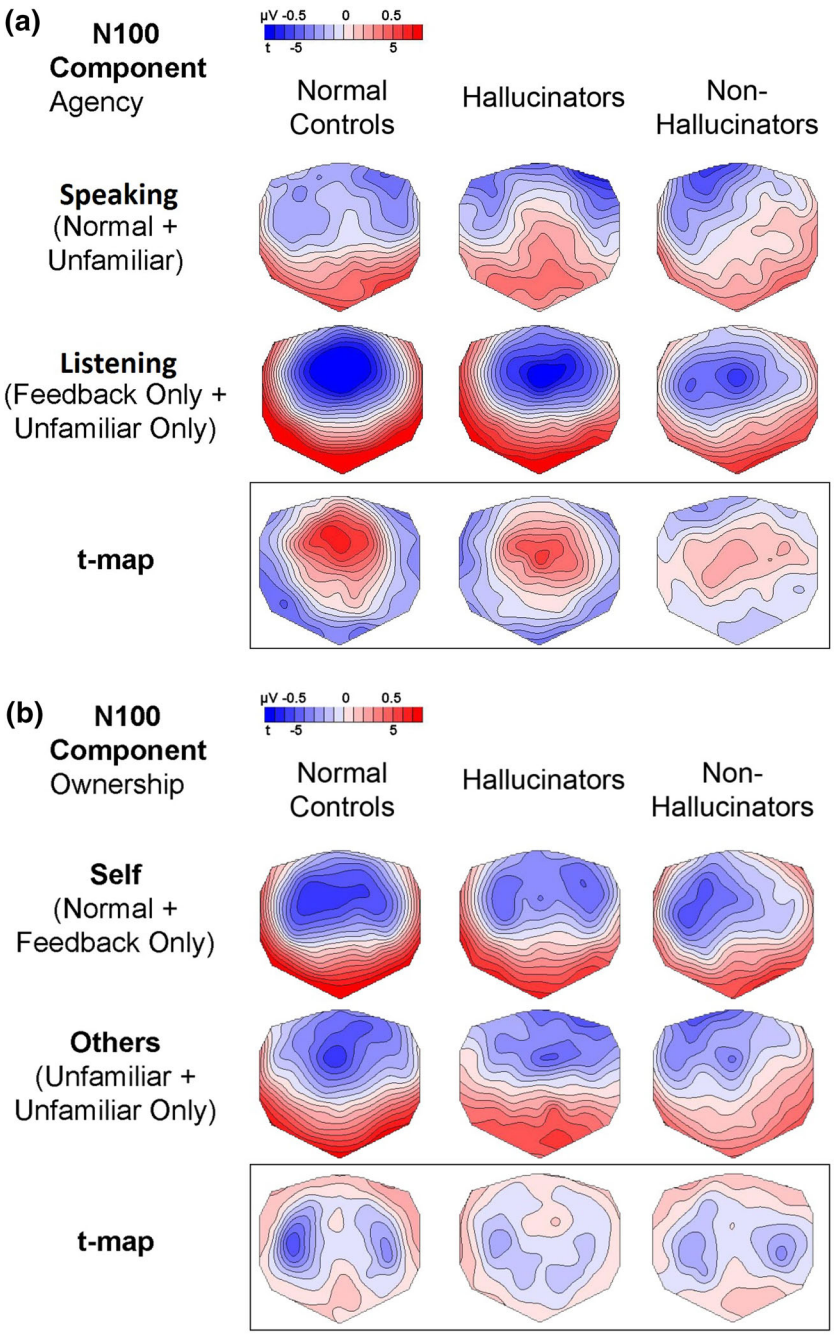

Fig. 3 Main effects of **a** agency and **b** ownership of normal controls, hallucinators and non-hallucinators in the N100 component

The ownership effects were only significant for the HC ($p < 0.001$) and NH ($p = 0.008$), but not for the AH ($p = 0.109$). No significant interaction could be found in any of the three groups (HC/AH/NH $p = 0.194/0.202/0.841$).

Significant differences between the agency patterns could be found between the AH and HC ($p = 0.003$). No statistically significant differences between the other groups could be found (NH–HC $p = 0.181$ and AH–NH $p = 0.114$). No significant differences in ownership between the AH and HC ($p = 0.180$), NH and HC ($p = 0.311$) and AH and NH ($p = 0.897$) could be found.

Global Field Power (GFP) Analysis

N100 Component

In the N100 component, we found GFP values between 0.754 and 1.013 μV over all groups for the agency effect and between 0.817 and 0.966 μV for the ownership effect

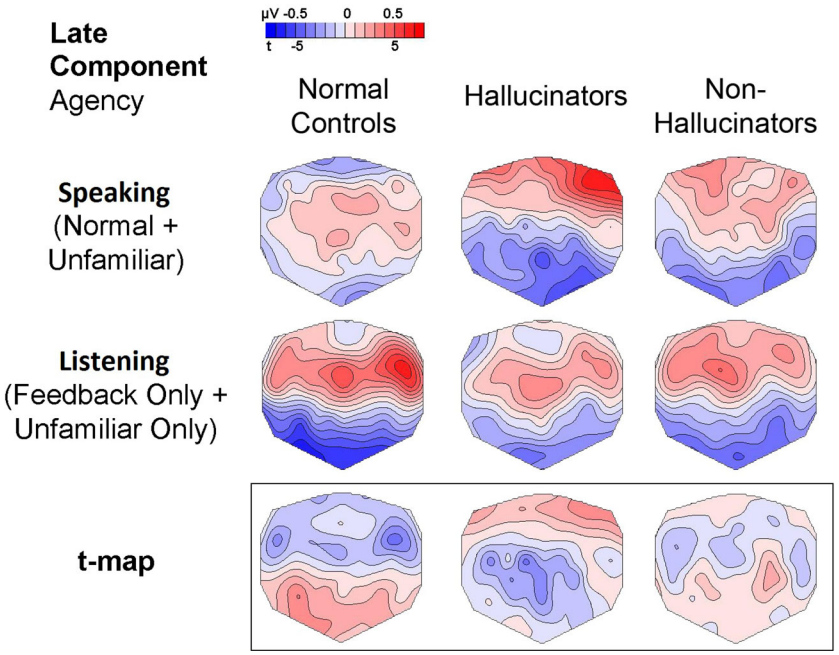

Fig. 4 TANOVA agency effects of normal controls, hallucinators and non-hallucinators in the late component

(Fig. 2). In general, the NH showed a stronger GFP than the AH and the HC. A two-factorial ANOVA (Group × Condition) with the aggregated GFP values showed a significant interaction between group and condition [$F(9129) = 2.61$, $p = 0.008$]. Between the AH and their matched HC, the interaction was not significant [$F(3,78) = 2.291$, $p = 0.085$] but we found an interaction between the NH and matched HC [$F(3,78) = 7.00$, $p < 0.001$]. There was no interaction between the patient groups [$F(3,78) = 0.016$, $p = 0.997$]. The t tests showed differences between the NH and HC in the N100 in the agency + condition [$t = 2.648$; $p = 0.014$; mean GFP (μV) AH = 0.997, NH = 1.013, HC = 0.804] and ownership + condition [$t = 2.178$; $p = 0.039$; mean GFP (μV) AH = 0.934, NH = 0.966, HC = 0.820].

Late Component

The late component showed somewhat weaker GFP between 0.640 and 0.940 μV for the agency effects and between 0.669 and 0.869 μV for the ownership effects (Fig. 2). The NH showed the strongest voltage, particularly in the presence of agency and ownership. The overall ANOVA showed an interaction between the group and the combined condition [$F(9129) = 2.69$, $p = 0.007$]. Between the AH and matched HC, the interaction was significant [$F(3,78) = 5.058$, $p = 0.003$], as well as the interaction between the NH and matched HC [$F(3,78) = 3.851$, $p < 0.013$], but not between the two groups. In the post hoc t tests, we found differences between the NH and the HC in the agency + [$t = 3.510$; $p = 0.002$; mean GFP (μV) AH = 0.899, NH = 0.940, HC = 0.701] and the ownership + condition [$t = 2.652$; $p = 0.013$; mean GFP (μV) AH = 0.760, NH = 0.837, HC = 0.669], and a tendency for more GFP in the agency + condition in the AH group compared to their controls ($t = 1.85$, $p = .076$). There were no significant differences in the GFP between the other groups in the late component.

Delay Effect

To assess the delay effect, we computed the delay against the normal condition. For the HC, this showed significant TANOVA results only in the N100 component (N100 $p = 0.038$). For the AH group, significant TANOVA results were to find in both components (N100 $p = 0.019$, late $p = 0.002$). The NH showed no significant TANOVA effects (N100 $p = 0.497$, late $p = 0.439$).

We found no significant differences in the TANOVA among the three groups (AH vs HC $p = 0.521$, NH vs HC $p = 0.405$, AH vs NH $p = 0.294$).

Discussion

Sense of agency and ownership and their function in the distinction between internal and external stimuli are important parts of an intact ‘sense of self’. A disturbed sense of self is thought to be a causal factor in the psychopathology of psychosis.

From a purely topographical perspective, our data showed the expected effects (of agency and ownership) in the healthy controls and the hallucinator group and to a lesser degree in the non-hallucinator group. Namely, we found a reduction of the central N100 during the presence of agency, and the bilateral temporal negativity related to the presence of ownership as reported in previous papers (Hubl et al. 2014). While this confirmation is only partial for the control group (13 of the 28 controls were part of the previous study) the basic similarity of the results in the patient group indicates that the experiment is replicable in a clinical population.

However, there were considerable differences in the amount of activation that could be attributed to these topographic effects, as assessed by the template-based analysis: In the N100 component, the amount of activation that showed the expected agency and ownership related changes was strongly reduced in both patient groups as compared to the healthy controls.

Interestingly, the overall amount of activation, as assessed by the GFP analysis yielded a very different pattern: The highest GFP was found in the non-hallucinators, reaching significance against controls in the agency (+) and the ownership (+) condition.

Since the differences in the amount of activation have already been represented in the template based and GFP analyses, the TANOVAs measured the purely topographic effects, using normalized data. In the agency condition, we found significant differences between the topographies of the non-hallucinators and the healthy controls in the N100 component. In contrast, the hallucinators showed topographies closer to the healthy controls.

Summarizing, our data suggest that in the N100 period, which is crucial for the processing of auditory-verbal selfmonitoring (Ford et al. 2001b, Ford et al. 2005), the overall stimulus related activity (as measured by the GFP) is quite unaffected in the patient groups. However, processes that normally represent agency and ownership (as quantified by the template based analysis and the TANOVAs) were strongly reduced and inconsistent in the patients. Interestingly, and contrary to the prior expectation, this inconsistency was more pronounced in the non-hallucinators. We note that compared to the hallucinators, the inhomogeneity of the non-hallucinators may be related to inclusion criteria that favors inhomogeneity in the psychopathology and neurobiology. One might thus expect that taking the psychopathology ratings into account would partially disentangle this heterogeneity. This was the case in the non-hallucinators, where the agency related activation decreased with increasing PANSS scores, but the hallucinators showed an opposite pattern. However, the PANSS integrates many dimensions of psychopathology that are unrelated to hallucinations, and we did not find an inverse relation between the severity of hallucinations and the suppression of the N100 to self-generated sounds as previously reported (Heinks-Maldonado et al. 2007).

In the late component, we found a pattern of differences within and between groups that differed from the N100 findings. The template-based analysis indicated a clear agency effect in the hallucinator group but only little effects in the non-hallucinators. Thus, disturbed agency processing seemed to continue in the non-hallucinators in this component. The ownership effect was equally decreased in both patient groups.

To assess whether those findings were attributed to different topographies or differences in the global power, we performed a GFP analysis and TANOVAs. The GFP analysis showed a similar pattern as in the N100 component, with the highest GFP in the non-hallucinators in the agency (+) and the ownership (+) condition. Regarding the topographies, the hallucinators showed a more distinct pattern from the two other groups. The differences in the topographies were statistically significant between the hallucinators and the healthy controls. We suggested in our previous paper that in the late component, agency and ownership of the sense of self might be integrated by a common mechanism (Hubl et al. 2014) and shaped by higher cognitive processing.

Summarizing, the increase of global field power in the patients in both the N100 and the late component might indicate the compensatory recruitment of other mechanisms that are not normally associated with the processing of agency and ownership. On the other side, the topographic pattern of agency processing in the hallucinators was albeit reduced in amplitude, topographically more stable and not significantly different from those of the controls. This may thus be an indicator that hallucinators have, more than non-hallucinators, still intact mechanisms that can represent presence and absence of agency, but the activation is insufficiently linked to the factual presence or absence of agency. A possible anatomical basis of this misattribution of agency may be found in experiments using diffusion tensor imaging (DTI) to measure structural connectivity. In auditory hallucinators, significantly higher white matter directionality in the arcuate fasciculus and the anterior corpus callosum were found, compared to non-hallucinators and normal controls (Hubl et al. 2004), probably resulting in a volumetric increase of the auditory cortex (Hubl et al. 2010).

A limitation of our study might be the masking of potentially interesting effects by residuals of the motor movement artefact, which have been removed by subtracting the "Read-Aloud-Only" condition. However, for all groups, the ERPs displayed similar topographies, and the contrast that may have been affected by such a residual (namely the agency effects) was comparable to other

studies, such that we assume that such residual artefacts have not played a relevant role in our analysis. No statistically significant differences in the mean voice onset suggest an equal compliance in the patients and the normal controls.

Furthermore, our data suggest that apart from dysfunctions of the "corollary discharge" or "efference copy" mechanism which are central to the representation of agency, other processes that require an integration with memory content representing one-self (ownership) might contribute to the underlying fundamental deficits in schizophrenia.

The agency effects of the patients seem to be influenced to some degree by the severity of the symptoms. Our study suggests that neither a disturbed sense of agency nor a disturbed sense of ownership alone is a sufficient explanation for the origin of auditory hallucinations in schizophrenic patients.

Perez et al. (2012) investigated agency effects in earlier disease stages. They found putative evidence for a corollary discharge dysfunction already in the early disease stages. However, it would be interesting whether high cognitive functions such as the sense of ownership are already affected in early disease stages, or whether they are manifestations in the course of the disease. Furthermore, it would be interesting to investigate additional aspects in the psychopathology of schizophrenia, such as the neurotransmitter systems. In previous studies, the influence of glutamate on agency and ownership was investigated using a low-concentrated ketamine-infusion in healthy individuals (Moore et al. 2011). Their data showed that ketamine mimics certain aberrant agency experience that is also found in schizophrenia. It would be interesting for further experiments to investigate with our experimental assembly the role of ketamine in healthy individuals and to compare these results to schizophrenic patients, to investigate whether there is a common disturbance. Another investigation should concern the effects of the antipsychotic medication on the 'sense of self'. The fact that nearly all schizophrenic patients were under antipsychotic treatment with effects on various transmitter systems and that stopping this medication is often unethical, further investigations concerning the effect of these drugs are required. A possible way would be the investigation of patients with other disorders requiring the intake of antipsychotics, such as bipolar disorders or major depressive disorder and comparison of those patients to a control group suffering from the same disorder and not being under antipsychotic treatment. More experimental work with the most recent methods of brain imaging and even to a greater degree innovative new models for agency and ownership are required for further investigations of a disturbed 'sense of self'. It will provide the basic understanding in the comprehension of very fundamental processes of the human brain.

Conclusively our findings suggest that schizophrenia patients have disturbances in the processing of agency and ownership compared to healthy controls. Interestingly, these effects are most pronounced in patients without hallucinations, whereas patients with hallucinations show a reduced, but in its form a more normal effect.

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