Clinical practice of rTMS reveals a functional dissociation between agency and hallucinations in schizophrenia

Renaud Jardri^{a,b,*}, Yvonne Delevoye-Turrell^{c,d}, Bernard Lucas^d, Delphine Pins^a, Virginie Bulot^d, Christine Delmaire^e, Pierre Thomas^{a,d}, Pierre Delion^{a,b}, Jean-Louis Goeb^{a,b}

^a Université Lille Nord de France, CNRS UMR-8160, CHRU de Lille, 59037 Lille, France

^b CHRU de Lille, Service de Psychiatrie de l'enfant et de l'adolescent, Hôpital Fontan, 59037 Lille, France

^c Université Lille Nord de France, EA1059, rue du Barreau, 59653 Villeneuve d'Ascq, France

^d CHRU de Lille, Service de Psychiatrie adulte, Hôpital Fontan, 59037 Lille, France

^e CHRU de Lille, Service de Neuroradiologie, Hôpital Salengro, 59037 Lille, France

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ABSTRACT

We report here the case of a hospitalized 11 year-old boy (YP) with a positive diagnosis of 'Childhood Onset Schizophrenia'. YP experienced verbal-auditory hallucinations, a delusion of alien control and hetero-aggressive behaviour. Antipsychotic drugs were unsuccessful and furthermore provoked severe acute dystonia. fMRI-guided rTMS applied over several cortical regions provided the means to reveal for the first time a functional dissociation between auditory-verbal hallucinations and agency. These results demonstrate the efficacy of rTMS for young patients suffering from drug-resistant hallucinations but they furthermore question the physiopathology of the hallucinatory process by suggesting that agency and hallucinations may be sub-served by different neural networks.

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1. Introduction

Hallucinations can be defined as perceptions with no corresponding source in the outside world. These symptoms remain a particularly challenging psychopathological phenomenon in schizophrenia both in adults and in children (Larøi, Van der Linden, & Goeb, 2006), as they can persist in more than 25% of patients even after adequate medication (Pantelis & Barnes, 1996). A possible underlying neuro-cognitive mechanism for auditory-verbal hallucinations (AVH) is a problem of agency, i.e., misattribution of the self-inner speech as coming from outside (McGuire et al., 1995). Transcranial magnetic stimulation (TMS) is a non-invasive technique which can modulate the neural excitability of the brain-region targeted (Hallett, 2000). This method has been increasingly applied in cognitive neuroscience as a brain-mapping method but also showed, when applied repetitively, significant efficacy in the

treatment of psychiatric disorders such as auditory hallucinations (for a review, see Aleman, Sommer, & Kahn, 2007). More specifically, recent studies have shown that rTMS treatment applied over the left temporal-parietal junction is successful in reducing the intensity of AVH episodes and in addition, has an effect on patients' performances in a self-other discrimination task for source monitoring (Brunelin, Poulet, et al., 2006). However, even if these results support such an hypothesis, it is not possible today to definitely discard the plausible implication of two separate but functionally linked neural networks for AVH and self-agency, respectively. Indeed, to demonstrate a common network for these two dimensions, one should be able to obtain the opposite effect, i.e., an effect on AVH by modulating agency. In this report, we present a clinical-case that demonstrates the effectiveness of rTMS treatment for agency only, which suggests that AVH and agency are two different functions that may in fact be sub-served by different and probably complementary neural networks.

2. Clinical history

YP was an 11 year-old Caucasian child. His perinatal period and infant life was reported to be normal. From age nine, parental inter-

* Corresponding author at: Université Lille 2, Laboratoire de Neurosciences Fonctionnelles et Pathologies, CNRS UMR 8160, Explorations Fonctionnelles de la Vision, Hôpital Roger Salengro, Centre Hospitalier Universitaire, 59037 Lille Cedex, France. Tel.: +33 320 446 281; fax: +33 320 446 732.

E-mail address: r-jardri@chru-lille.fr (R. Jardri).

views made mention of severe withdrawal periods, during which YP remained crawled up in a corner of his room, refusing all types of communication. During the same period, YP experienced at school violent episodes of asocialisation, which were accompanied by massive anxiety attacks. Despite adequate dosage of hydroxyzine treatment, these symptoms persisted and thus, a series of examinations were conducted—EEG, CT-scan, blood-tests, which were all normal. With time, the prostration episodes became more complex with periods of sudden psychic regression, depersonalization, bilateral mydriasis, aggressive behaviour, e.g., biting, and abnormal behaviour, e.g., walking on all fours and grunting. Successive treatment based on antipsychotics remained unsuccessful or needed to be interrupted due to acute dyskinesia.

A first hospitalization period of 6 weeks in our department of Child and Adolescent-Psychiatry was decided in May 2005. Consistent with his medical records, YP showed introverted behaviour, resistance to dialog and revealed oddness with food selection. YP reported auditory-verbal hallucinations (AVH) especially in the evening. A diagnosis of childhood onset schizophrenia (COS) was proposed with a positive Kiddie-SADS (Ambrosini, 2000) and a negative result for the Autism Diagnostic Interview-Revised (Lord, Rutter, & Le Couteur, 1994), respectively. A combination of antipsychotic drugs (olanzapine, 7.5 mg/day) and family psychotherapy were started. YP's symptomatology was maintained under control, at least partially, with this treatment for about 1 year. However, resurgences of the aggressive episodes especially made it difficult to maintain YP in school. Even with an increase of the olanzapine posology (10 mg/day), YP experienced more frequent and severe AVH episodes, which sometimes fused with delusions of alien control. Following this, a second hospitalization was decided in March 2006.

3. Clinical challenge

YP was provided with both pharmacotherapy and institutional psychotherapy (Delion, 2005). He revealed bad tolerance to antipsychotic drugs and thus, olanzapine was stopped; YP was left on a low dosage of hydroxyzine only. We hypothesized that an important part of his abnormal behaviour was the consequence of catatonia. This was evidenced by the efficacy of the zolpidem diagnosis test (Thomas, Rascle, Mastain, Maron, & Vaiva, 1997). Consequently, lorazepam was progressively administrated up to a maximum of 10 mg/day. Lorazepam efficacy was confirmed both by a 65% score-decrease in an adapted-version for children of the Bush-Francis Catatonia Rating Scale (BFCRS) (Cohen et al., 2005) and by significant clinical improvements, with greater accessibility during semi-structured interviews. However, invalidating refractory-AVH and severe self-awareness impairments led us to consider additional treatment. The first possibility was to use clozapine, which presents less extrapyramidal side-effects but is of limited use in children because of possible hematologic and cardiac adverse events (Kranzler et al., 2006). The second therapeutic option was to use rTMS, which has already been validated in adult schizophrenia with drug-resistant hallucinations (Aleman et al., 2007). YP's extremely preoccupied clinical state lead us to select the second option as rTMS has been shown to be well tolerated both in adults and in children (Quintana, 2005) especially in protocols that inhibit rather than activate cortex (Gilbert, 2008). Informed consent was obtained from both of YP's parents.

rTMS was delivered using a MAGSTIM super-rapid* stimulator with a standard figure-of-8 TMS-coil over the temporo-parietal junction (see Section 4). The power of the stimulator was reduced to 45% for YP's safety – which corresponded to 100% of YP's motor

threshold.¹ Stimulation was given at low frequency (1 Hz), for a total of 10 sessions of 1000 pulses each (a total of 10⁴ pulses) displayed over a period of 10 consecutive working days. Following recent data suggesting that rTMS can significantly be improved with fMRI guidance (Jardri, Lucas, et al., 2007; Sommer et al., 2007), we proposed to personalize the rTMS treatment in YP by using functional-maps that evidenced an agency abnormal network in a speech task (Jardri, Pins, et al., 2007). The originality of this task was to assess self-awareness in the same modality as that of YP's hallucinations. Throughout, YP revealed very good tolerance to these sessions. The effectiveness of rTMS in the improvement of self-awareness as well as in the magnitude and the frequency of AVH were evaluated by implementing an objective test battery before and after treatment.

4. Assessment methods and results

Three objective tasks were used to test agency in YP; these are described in detail in the next paragraphs. It is important to notice at this stage that these tasks were implicit, i.e., subjects are not consciously aware of the metacognitive processes that are tested. Second, control groups and familiarization phases were used for all tasks to ensure that the reported changes in performance were attributed to the effects of the rTMS sessions only. A fourth test was used to evaluate the magnitude and the frequency of AVH. For this, we used the auditory hallucination rating scale (AHRS) (Hoffman et al., 2003) and considered a significant improvement to be present when a 20% score increase was observed after 10 sessions of rTMS. Throughout non-parametric tests were used and the significance level was set at 0.05.

4.1. Motor agency

We have recently developed the use of the collision paradigm to probe the working status of the pre-reflective sense of agency, without the need of reflection or of verbal judgment (Bulot, Thomas, & Delevoeye-Turrell, 2007). The subject's task was to use a hand-held object to stop the fall of a pendulum that was either self-released (task S) or externally released by the experimenter (task E). The hand-held object was fitted with a force transducer that provided the means to measure the grip force applied by the subject to avoid object slip at the critical time of impact (Delevoeye-Turrell, Giersch, & Danion, 2003). The subject's capacity to interact efficiently with the pendulum was evaluated on each and every trial by measuring the fractional amount of force by which the grip force exceeded the minimal grip force truly needed at the time of impact to avoid object slip. The smaller the excess, the more efficient the interaction. The objective indicator of the sense of agency was taken as the efficiency difference between tasks S and E. In the present case, subjects performed 18 trials for each task in a pseudo-random order.

Fig. 1-left presents the original results obtained in a group of 15 healthy adults (top) and 15 stabilized adults with schizophrenia (bottom). All subjects were tested twice within a period of 2 weeks to confirm the stability of the findings. Overall, healthy adults use less excessive grip force in self than in experimenter-imposed collisions. Adults with schizophrenia use similar levels of

¹ Several confounding factors may have modified cortical excitability in YP. First, the electrical motor threshold, already known to be increased in children (Garvey et al., 2003), might have been magnified by benzodiazepine administration in YP. Lower motor thresholds are however traditionally described in schizophrenia spectrum disorders. Thus, in order to minimize and control these factors, we personalized the intensity-level of the magnetic beam in reference to YP's motor threshold, measured the first day of each week of treatment.

Fig. 1. The measure of the pre-reflective sense of agency in a group of healthy adults ($N = 15$, top left) and a group of adults with schizophrenia ($N = 15$, bottom left). One can clearly see that in hallucinating adults with schizophrenia there is a significant absence of difference in the efficiency of finger force between self-initiated and externally initiated collisions. On the right side of this figure are the data obtained in a group of healthy children ($N = 4$, mean age of 11.4) and in a child with early onset schizophrenia (YP). Results reveal that the difference in grip efficiency between self-initiated and externally initiated collisions is present in young children and indicates that they have adult-like effects of motor agency on motor performance. The key result in YP was that the pattern of results before rTMS was similar to that observed in adults with schizophrenia. However, after rTMS treatment the pattern of results in YP was similar to that observed in the groups of healthy adults and children, indicating a significantly improved sense of agency at the pre-reflective level of function.

grip efficiency in both tasks. In Fig. 1-right, we present the results of four healthy children (age 11.4 on average – top). Results show that they use less excessive grip force in task-S than in task-E, as healthy adults do. Results for YP are presented in the bottom-right frame of Fig. 1, for before and after rTMS over the right temporo-parietal junction (TPJ). Before rTMS, YP revealed similar response patterns than adults with schizophrenia. However, after rTMS, YP's response patterns were normalized and revealed a significant efficiency difference between self and experimenter-imposed collisions.

4.2. Source monitoring

Source monitoring is a classic procedure to evaluate whether a subject is impaired in determining the source of a word, i.e., whether it was self-generated or whether it was provided by the experimenter. In the present clinical study, we used two source-monitoring scales of increasing cognitive complexity.

The scale by Brunelin, Combris, et al. (2006) consists in two different tasks. In the first task, "Hear-Imagine", YP was required to either listen to a word that was visually presented and read out loud by the experimenter, or simply imagine that he had heard the word. The stimuli were current French words extracted from a verbal fluency task with the same emotional valence, frequency and length. The words were presented on a computer-screen during 3 s, preceded each time by the following instruction: "Listen to this word" or "Imagine that you are hearing this word". After a 15-min delay, YP was required to determine from a list of words (1) those which he had truly heard (range 0–8), (2) those he had imagined that he had heard (range 0–8) and (3) those who had not been presented and were in fact distractors (range 0–8). In the second task, "Say-

Imagine", YP had to either read aloud the word presented to him or imagine that he was reading the word. The assessment of false internal and false external attributions was made after a 15-min delay. The second scale for 'source monitoring' is the one by Larøi, Van der Linden, and Marczewski, (2004). This test is more complex from a cognitive point of view but has the advantage of letting the subject to generate the words himself in the self-condition. A list of words was presented to YP and read by the experimenter. For each word, YP was required to generate another word, i.e., the first word that came to mind except for proper names. Twenty minutes later, words were randomly presented to him on a computer-screen and YP's task was to say whether the word was the one given by the experimenter (range 0–16), generated himself (range 0–16) or whether the word was a distractor (range 0–16). For both scales, two distinct lists of words were used at each assessment periods to avoid memory and learning biases.

YP's first evaluation revealed a high rate of misattributions and more specifically, false internal attributions (4/8 and 12/16 for Brunelin and Larøi's scales, respectively) and false external attributions (6/8 and 9/16 for the same scales). YP was tested once more after rTMS over the right TPJ. The results showed then a significant improvement in YP's source-monitoring capacities with significant decreases in the false internal and external attributions (2/8, 3/8 and 2/16, 3/16 for the Brunelin and the Larøi's scales, respectively).

4.3. Speech awareness

In a recent fMRI study, we used a procedure that provides the means to identify the self-monitoring neural network that is thought to be involved in the identification of the source of speech

Fig. 2. The functional neural network that is activated for agency in a self-other discrimination task. Results are presented for YP before and after rTMS treatment in comparison to that observed in a group of healthy adults ($n = 12$). fMRI data were collected in a two-factorial block-design experiment. The green plot represents the mean time-course in the “externally generated voice” condition (EGV) while the red one represents the mean time-course in the “self-generated voice” condition (SGV). The contrast statistical maps revealed a significant positive activation of the right inferior parietal lobule (IPL) in control subjects (upper panel). This differentiation was not observed in YP before treatment, i.e., at time t_0 (middle panel). However, after the 10 sessions of low frequency rTMS over the right IPL (t_1), a significant positive activation of activity in right IPL was observed in YP and this difference was similar to that observed in the control group.

in a group of healthy adults (Jardri, Pins, et al., 2007). In brief, this neural network may be based upon the medial parieto-frontal network which could modulate the activity in the right inferior parietal lobule (IPL). Using this experimental procedure in 15 adults with schizophrenia compared to matched controls, we recently reported hyperactivation in this agency network. This could reflect the physiological signature of excessive misattribution of the patients’ own voices to external agents (Jardri, Pins, & Thomas, 2008). Here, we used the same experimental procedure to identify the degree of normal function in YP of those maps involved in self-other differentiation. This task is implicit by nature and all subjects (including YP) performed the behaviour task the day before to control for familiarity effects (training phase).

A block-design experiment was run in a 1.5 T Philips Achieva MRI scanner (Philips Medical Systems, The Netherlands). Two different conditions – “self-generated voice” (SGV) and “externally generated voice” (EGV), were randomly presented eight times, each through MR-compatible ear-phones. The stimulus was a 21-s extract from a French poem written by Paul Eluard (“La ville de Paris renversée”).

In each condition, YP heard a voice that was either his own (previously recorded) or someone else’s (one of four children’s voices). When YP’s voice was presented, he was asked to sub-vocalize the text that was heard; if the voice was that of someone else, he was required to passively listen. Functional and anatomical data were pre-processed and analysed using BrainVoyager QX v1.7 software (see Jardri, Pins, et al., 2007, for a full description of the MRI sequences, pre-processing and analysis steps). The general linear model was used to contrast SGV and EGV conditions. Before rTMS and contrary to that observed in healthy adults, results in YP revealed an absence of difference in the activity level of the right IPL, part of the TPJ (Fig. 2-top and middle, for controls and YP, respectively). The greater activity at the level of premotor and motor cortices under SGV condition confirmed that YP followed the instructions of sub-vocalizing in SGV. Finally, results were confirmed in YP when considering the similar time courses of evoked fMRI signals for the SGV and EGV conditions. After the session where rTMS was applied over the right TPJ, the contrast analysis revealed in YP a significant difference in the activity level of

the right IPL between the two experimental conditions (Fig. 2-bottom). This difference was confirmed after normalization of the BOLD hemodynamic response (i.e., the blood oxygen level dependent signal) under both conditions, which was comparable to the patterns measured in the healthy controls.

5. Results for AVH and patient outcome

Altogether these results confirmed significant improvement in agency capacities in YP following rTMS over the right TPJ. However, this treatment revealed unsuccessful to reduce the AVH in this child (AHRS scores before and after this right rTMS were 29 and 31, respectively). This unexpected dissociation between agency and AVH did not provide the means to treat at the same time the two dimensions of YP's symptomatology even when using rTMS guided by dysfunctionnal fMRI maps of the self-awareness network. Consequently, we proposed to reattempt a rTMS treatment in order to target this time those cortical areas that are known to be involved in the hallucinatory process, e.g., Wernicke area (in the left TPJ). Here, the results revealed that YP benefited significantly from the rTMS treatment. Indeed, rTMS over the left TPJ was successful in stopping the AVH (AHRS, 47% decrease). The improvement obtained with left rTMS was maintained for 6 weeks (AHRS follow-up measurements were reiterated each week: baseline-score: 30 (range 0–41); w1: –47%; w2: –40%; w3: –36%; w4: –31%; w5: –28%; w6: –25%). Recently, the clinical relevance of rTMS maintenance treatment before relapse has been evidenced (Poulet, Brunelin, Kallel, D'Amato, & Saoud, 2008). Even if YP has not yet benefited from this form of stimulation, the duration of the after-effect in this child (6 weeks) suggests that he may be a good candidate for a rTMS maintenance treatment program.

To assess whether the effects of the later rTMS treatment was due to the left rTMS or rather to a possible bilateral stimulation because the two rTMS sessions were performed rather close in

time, we waited for the reappearance of YP's symptoms (AVH and self-agency). Then, the test battery was reiterated before and after 10 new sessions of unilateral left rTMS. Results revealed that unilateral left rTMS treatment allowed a joint improvement in YP of agency capacities and AVH (Fig. 3). These findings demonstrate that results cannot be attributed to task familiarity but can be directly related—at least in YP—to the presence/absence of AVH and to a decrease/increase in the quality of daily living.

More specifically, YP's motor agency profile in the pendulum task was normalized compared to age-matched children controls (Fig. 1-right). Source monitoring tasks revealed very few misattribution errors for both internal and external sources (5/16, 2/16 and 1/8, 1/8 for the scales of Larøi and Brunelin, respectively). Finally, hallucinations were significantly reduced with AHRS score decreasing by 10 points. It is important to note at this point that YP's clinical improvement was confirmed by a significant improvement in YP's adaptive functions, with a decrease of 40% in the Children's Global Assessment scale. The results for the rTMS treatment over the left TPJ are consistent with those reported in the literature in adults with schizophrenia (Brunelin, Poulet, et al., 2006).

6. Discussion

The use of cognitive tests before and after rTMS treatment provided the means to objectively demonstrate the functional improvement that was subjectively perceived by YP. Furthermore, from a theoretical perspective, our behavioural results revealed a functional dissociation between impaired agency and auditory-verbal hallucinations. Indeed, we demonstrated that rTMS over the right TPJ was successful in improving agency in YP, but that the hallucination episodes persisted. It is only when rTMS was applied over the left TPJ that a significant reduction was obtained in both the frequency and the strength of the hallucination episodes (based on the AHRS). Such dissociation between agency impairments and AVH in schizophrenia was unexpected because it had never been evidenced before clinically; we here evidenced it artificially through the use of rTMS. From a theoretical standpoint, our results question the physiopathology of the hallucinatory process by suggesting that agency and hallucinations may be sub-served by different neural substrates. From a clinical standpoint, the dimensional approach presented here to treat a child with COS gave us the means to help a child with true moral-suffering and treat him as a person by considering his difficulties as a whole. Antipsychotic drugs were largely unsuccessful in reducing YP's first-rank symptomatology. However, benzodiazepines were effective in treating catatonia, while rTMS revealed to be efficient in improving both AVH and agency. Of course these improvements did not mean a definitive cure of schizophrenia in YP, but allowed him to regain a certain level of quality of life by providing him with the possibility to go back home and attend school. Finally, because of his significant improved functional state, YP was able to receive psycho-education about his illness and to follow regular psychotherapeutic sessions. This result must now be replicated and confirmed in future studies (case or group).

6.1. Theoretical implications

The complex cognitive relationship between agency and AVH could effectively be enhanced by considering their anatomical interactions. In the literature, it is suggested that the IPL constitutes effectively a convergence region for prefrontal, cingulate and temporal cortices as well as cerebellar sensory-motor afferences, which has led some authors to postulate its implication in motor-awareness via 'predictive forward models' (Blakemore,

Fig. 3. An evolution diagram of the agency and the hallucination parameters in YP. Scores for source monitoring (misattribution to an external or an internal source), motor agency (evidenced by the pendulum task) and auditory-verbal hallucinations (AVH measured using the AHRS) were normalized between 0 and 1 and plotted across sessions. Session T0 = before rTMS; session T1 = after rTMS over right TPJ; sessions T2 and T4 = rTMS over left TPJ; T3 = measure before the second session over the left TPJ. Results show that rTMS over the right TPJ was only successful in reducing agency abnormalities whereas rTMS over left TPJ improved both agency and AVH episodes. We here evidence a clear dissociation at T1 between AHRS scores and the measures evaluating agency in a drug-resistant patient with schizophrenia.

Wolpert, & Frith, 2002). Involvement in agency of the bilateral IPL with a right predominance supports such an hypothesis and has previously been evoked (Farrer et al., 2003; Jardri, Pins, et al., 2007). However, the study of IPL in humans is difficult because of a high degree of lateralization and the immediate contiguity of the planum temporale. Tractography data of the peri-sylvian region has shown that left IPL is a relay station between Wernicke and the language-related prefrontal areas via the arcuate fasciculus (Catani, Jones, & Ffytche, 2005). It is however not clear to date whether this macroscopic region (left IPL)—that may be involved in agency and language-related functions—is sub-served by several different neuronal populations at a microscopic level. A first possible interpretation of our results is that these two pathological dimensions rely on partially common neural networks (at the level of the left IPL) but maintain a somewhat hierarchical relationship. Indeed, in order to account for the single dissociation reported here, one must consider that the two neural networks can interact but only in a uni-directional manner. Even if such a hypothesis is tempting because it relies less on a lesional but more on a connectionist model of the rTMS after-effect, more research is required to refine the model. A second possible hypothesis is that the two functional networks for AVH and agency rely on distinct but adjoining areas of the brain. On the one hand, rTMS over the right TPJ would have modulated only the agency network at the level of the right IPL; this network would be bilateral but with a right predominance. On the other hand, rTMS over the left TPJ would have targeted two adjoining networks – the language network for AVH and the left part of the agency network – because, e.g., of TMS poor spatial resolution (around cm^3).

6.2. Clinical implications

A debate is enduring in the scientific community to determine the state/trait status of agency impairments in schizophrenia. Such a distinction will have indeed significant implications in early screening strategies for schizophrenia. It has been reported that patients suffering from schizophrenia with AVH are significantly more deficient in an online verbal-source attribution task than controls (Johns, Gregg, Allen, & McGuire, 2006) and than non-hallucinating patients (Brunelin, Combris, et al., 2006). The confirmation of these observations would support the state phenomenon hypothesis. However, Johns et al. evidenced an increased misattribution frequency in schizophrenia without hallucinations but not in those that were only deluded (Johns et al., 2006). These authors noted in addition that the frequent association between AVH and delusions in schizophrenia could lead to biased interpretation of those results found in the literature and thus, proposed that source-monitoring impairments may be associated more to delusions than to AVH. Other authors have also described that misattributions are associated not only to hallucinations but also to delusions (Allen et al., 2004). In the same train of thought, our results confirm the ambiguous status of agency impairments in schizophrenia as a state-marker (associated with the presence of AVH) or as a trait-marker (vulnerability to AVH). Indeed, the dissociation between agency and AVH that we evidenced in YP contradicts the strict state-marker hypothesis. As such, our results rather favor the idea that agency impairments are in fact an ‘intermediate trait vulnerability marker’ as suggested by Brunelin et al. (2007).

In conclusion, the dimensional approach proposed in the present case-study provided the means to clearly differentiate the cognitive impact of delusional-like catatonia, AVH and agency. On the one hand, we showed that catatonia can be reduced without impacting on either AVH or agency. On the other hand, we demonstrated the importance of rTMS as a tool to reveal a functional dissociation between AVH and agency, a dissociation that is not clinically observable. As such, agency should not be used as a

vulnerability-factor for AVH, at least not before a better description of the nature of the hallucinatory episodes is provided. This work would be essential in order to be able to identify the heterogeneity of the clinical aspects of AVH and thus, gain a better insight of those clinical symptoms that are more directly linked to deficits in the sense of agency. Only such a systematic and detailed approach will be helpful in the end in improving our general understanding of the cognitive deficits associated with schizophrenia, and in developing psychiatric dimensional classification tools for cognitive rehabilitation.

6.3. Conclusions

This extensive case-study is to our knowledge the first published case demonstrating the efficacy of fMRI-guided rTMS in the treatment of AVH and agency impairments in a child with COS. Furthermore, rTMS over the right TPJ provided the means to reveal functional dissociation between these two clinical dimensions.

Conflict of interest

None declared.

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