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Neurobiological substrates of reality-monitoring in schizophrenia

Layla Lavallé

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Étude des substrats neurobiologiques de la mémoire de réalité dans la schizophrénie

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Résumé

Le reality-monitoring désigne notre capacité à nous souvenir de la source perçue ou imaginée d'une information. Le reality-monitoring est un type de mémoire de source, un processus cognitif plus large nous permettant de nous souvenir de la source des informations. La mémoire de source comprend aussi l'internal source-monitoring, qui désigne notre capacité à discriminer deux sources internes, et l'external source-monitoring, qui désigne notre capacité à discriminer deux sources externes. Au niveau cérébral, le reality-monitoring a particulièrement été associé au fonctionnement et à la structure du cortex préfrontal antéro-médian. Le reality-monitoring est déficitaire chez les patients atteints de schizophrénie, et particulièrement chez ceux qui présentent des hallucinations. Ces derniers montrent une altération spécifique appelée « biais d'externalisation », c'est-à-dire qu'ils tendent à attribuer une source externe aux informations de source interne. Cette thèse vise à mieux comprendre l'altération du reality-monitoring dans la schizophrénie.

Dans le premier chapitre de ce manuscrit, nous nous sommes intéressés à la spécificité de l'altération du reality-monitoring en adoptant une approche transdiagnostique. Au sein d'une première étude, nous avons établi une revue qualitative des potentielles altérations de la mémoire de source au sein d'une pathologie possédant des caractéristiques communes avec la schizophrénie, le trouble obsessionnel-compulsif. Cette revue a mis en évidence des résultats mixtes et des limites méthodologiques dans l'évaluation de la mémoire de source. Au sein d'une deuxième étude, nous avons directement comparé les performances de mémoire de source entre des patients atteints de trouble obsessionnel-compulsif, des patients atteints de schizophrénie et des contrôles sains. Cette étude a révélé une altération spécifique du reality-monitoring chez les patients avec schizophrénie et une altération partagée de l'internal source-monitoring au sein de ces deux pathologies. Dans le deuxième chapitre de ce manuscrit, nous avons examiné la

spécificité de l'altération du reality-monitoring au sein du continuum de la psychose. Au sein d'une troisième étude, nous avons réalisé une méta-analyse des études comparant les performances de reality-monitoring et de self-monitoring entre des individus appartenant à ce continuum, i.e., des individus considérés à risque clinique et/ou génétique de schizophrénie et des individus présentant des hallucinations non-cliniques, et des contrôles. Cette étude a montré que les individus sains inclus dans le continuum de la psychose présentent aussi des altérations du reality-monitoring et du self-monitoring. Le troisième chapitre de ce manuscrit est consacré aux bases cérébrales du reality-monitoring. Au sein d'une quatrième étude, nous avons réalisé une méta-analyse basée sur les coordonnées visant à identifier les régions cérébrales associées fonctionnellement au reality-monitoring, au self-monitoring et de potentielles régions partagées entre ces deux processus. Cette étude a notamment confirmé l'implication du cortex préfrontal antéro-médian dans le reality-monitoring, a associé le self-monitoring à un vaste réseau de régions fronto-temporo-pariétales et a montré une activation partagée du lobule VI du cervelet gauche au sein de ces deux processus.

Abstract

Reality monitoring is the cognitive process by which an individual is able to distinguish between memories of events that actually occurred and those that were imagined. Reality-monitoring is a type of source-monitoring, a broader cognitive process that allows us to remember the source of information. Source-monitoring also includes internal source-monitoring, which refers to our ability to discriminate between two internal sources, and external source-monitoring, which refers to our ability to discriminate between two external sources. At the cerebral level, reality-monitoring has been particularly associated with the functioning and structure of the anteromedial prefrontal cortex. Reality-monitoring is deficient in patients with schizophrenia, and particularly in those who present hallucinations. The latter show a specific alteration called "externalization bias", i.e., they tend to attribute an external source to internally generated information. This thesis aims to better understand the alteration of reality-monitoring in schizophrenia.

In the first chapter of this manuscript, we adopted a transdiagnostic approach focused to better understand the specificity of impaired reality-monitoring. In a first study, we established a qualitative review of potential source-monitoring alterations in obsessive-compulsive disorder, which shares common features with schizophrenia. This review highlighted mixed results and methodological limitations in the assessment of source-monitoring. In a second study, we directly compared source-monitoring performance between patients with obsessive-compulsive disorder, patients with schizophrenia and healthy controls. This study revealed a specific impairment of reality-monitoring in patients with schizophrenia and a shared impairment of internal source-monitoring within these two pathologies. In the second chapter of this manuscript, we examined the specificity of the alteration of reality-monitoring within the continuum of psychosis. In a third study, we performed a meta-analysis of studies comparing

the performance of reality-monitoring and self-monitoring between individuals belonging to this continuum, i.e., individuals considered to be at clinical and/or genetic risk for schizophrenia and individuals with non-clinical hallucinations, and controls. This study showed that healthy individuals included in the continuum of psychosis also show alterations in reality-monitoring and self-monitoring. The third chapter of this manuscript is devoted to the brain basis of reality-monitoring. In a fourth study, we performed a coordinate-based meta-analysis that aimed to identify the brain regions functionally associated with reality-monitoring and self-monitoring, as well as regions potentially shared between these two processes. This study confirmed the involvement of the anteromedial prefrontal cortex in reality-monitoring, associated self-monitoring with a large network of fronto-temporo-parietal regions, and showed a shared activation of lobule VI of the left cerebellum within these two processes.

This thesis has deepened the understanding of reality-monitoring in schizophrenia. We have detailed the specificity of impaired reality-monitoring in schizophrenia by looking at clinical groups with similarities to schizophrenia, but also by examining non-clinical groups belonging to the continuum of psychosis. We have also described the brain substrates of reality-monitoring in healthy subjects and one of the perspectives of this work is to shed light on the link between the clinical symptoms of schizophrenia, the impairment of reality-monitoring and its structural and functional bases.

List of publications

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List of abbreviations (1)

5-HT_{2A}: serotonin
ACC: anterior cingulate cortex
AD: Alzheimer disease
AH: auditory hallucinations
AHRs: auditory hallucinations rating scale
amPFC: anterior medial prefrontal cortex
APS: attenuated psychotic symptoms
ARMS: at-risk mental state for psychosis
BA 10: Brodmann area 10
BD: bipolar disease
BIDS: brain imaging data structure
BLIPS: brief and limited intermittent psychotic symptoms
BOLD: blood-oxygen-level dependent imaging
CAB-NP: Cole-Anticevic brain network parcellation
CAPS: Cardiff anomalous perception scale
CHR: clinical high-risk
CIFTI: connectivity informatics technology initiative
CNV: copy number variant
D1: dopamine receptors 1
D2: dopamine receptors 2
DA: dopamine
DAT: dopamine transporter
DICOM: digital imaging and communications in medicine
dlPFC: dorsolateral prefrontal cortex
DMN: default-mode network
dMRI: diffusion magnetic resonance imagery
DSM: diagnostic and statistical manual of mental disorders
DWI: diffusion weighted imagery
EASE: examination of anomalous self-experience scale
ECT: electroconvulsive therapy
EEG: electroencephalography
EMG: electromyography
FC: functional connectivity
FEP: first episode of psychosis
FLIRT: FMRIB's linear image registration tool
fMRI: functional magnetic resonance imagery
FNIRT: FMRIB's non-linear image registration tool
FSL: FMRIB software library
FTD: frontotemporal dementia
FWEP: familywise error protection
GABA: γ -aminobutyric acid
GBC: global brain connectivity
GMV: gray-matter volume
GRD: genetic risk and deterioration syndrome
HCP: human connectome project
ICD: international classification of diseases
LGI: local gyrification index
LSHS: Launay-Slade hallucination scale

MNI-152: Montreal neurological institute-152
MP-RAGE: magnetization-prepared rapid gradient echo
mPFC: medial prefrontal cortex
MRI: magnetic resonance imagery
N-BRIDGE: neuro-behavioral relationships in dimensional geometric embedding
NIBS: noninvasive brain stimulation
NifTI: neuroimaging informatics technology initiative
NMDA: N-methyl-D-aspartate receptor or glutamate
OCD: obsessive-compulsive disorder
PALM: permutation analysis of linear models
PANSS: positive and negative syndrome scale
PC: principal component
PCA: principal component analysis
PCS: paracingulate sulcus
PD: Parkinson's disease
PET: Positron Emission Tomography
PFC: prefrontal cortex
PSAS: psycho-sensory hallucination scale
QuNex: quantitative neuroimaging environment & toolbox
RMS: root mean square
ROI: region-of-interest
SD: standard deviation
SDT: signal detection theory
SGI: sensory gating inventory
SMA: supplementary motor area
SMF: source-monitoring framework
SNP: single nucleotide polymorphisms
STS: superior temporal sulcus
T1/T1w: T1-weighted MRI
T2/T2w : T2-weighted MRI
tDCS: transcranial direct current stimulation
Tmax: time to reach maximum serum concentration
TMS: transcranial magnetic stimulation
TPJ: temporoparietal junction
TSNR: temporal signal-to-noise ratio
UHR: ultra-high risk for psychosis
VH: visual hallucinations
VTA: ventral tegmental area

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1. Context / State of the art

1.1. Schizophrenia

1.1.1. Epidemiology

Schizophrenia is a chronic and severe mental disorder that affects the way a person thinks, perceives reality and behaves. Schizophrenia affects approximately 0.3% to 0.7% of people at some point in their life (van Os and Kapur, 2009), or more than 21 million people worldwide (Charlson et al., 2018). The median lifetime prevalence of schizophrenia is relatively low, ranging from 3.3 to 4.0 per 1000 (McGrath et al., 2008; Saha et al., 2005). As with many major psychiatric disorders, schizophrenia typically appears in late adolescence and early adulthood (Solmi et al., 2022).

Schizophrenia is a devastating medical condition listed among the top 15 leading causes of disability worldwide (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017). Schizophrenia is associated with significant impairments in psychosocial function, including unemployment, an increased risk of homelessness, and living in poverty (Charlson et al., 2018). Early onset of the disease, low remission rates and high disability all contribute to excessive burden associated with schizophrenia (Charlson et al., 2018).

Patients with schizophrenia are 2-3 times more likely to die early than the general population and have a reduced life expectancy of approximately 20 years (Laursen et al., 2014). This differential mortality gap is primarily due to suicide and somatic conditions (Laursen et al., 2014; McGrath et al., 2008). Long-term follow-up studies have shown that approximately 16.5% of individuals with first-episode of psychosis (FEP) attempted suicide prior to their first

hospital admission and that suicidal behavior occurs in approximately 50-60% of patients with chronic schizophrenia (Bertelsen et al., 2007; Mauri et al., 2013; Togay et al., 2015). On the other hand, the main somatic causes of death are difficulties in accessing and adhering to medical care, increased frequency of routine risk factors (e.g., poor diet, little exercise), substance abuse and side-effects of treatment (Laursen et al., 2014; Olfson et al., 2015).

Despite its low prevalence, the economic burden of schizophrenia is tremendous for society as a whole. In Western countries, the direct costs of schizophrenia represent between 1.6% and 2.6% of total health care expenditures. They include medications, therapies, and hospitalizations. Indirect costs are primarily responsible for the economic burden of schizophrenia on society, including lost patient productivity and social service needs (Chong et al., 2016).

1.1.2. Definition and diagnosis

1.1.2.1. Definition

Schizophrenia is a complex mental disorder. According to van Os et al., symptoms of schizophrenia can be clustered into five main dimensions (*see Figure 1*) (van Os and Kapur, 2009):

- (i) The **psychosis or positive symptom dimension** describes the presence of symptoms that are absent in healthy individuals. The main positive symptoms are hallucinations and delusions.

- Hallucinations are usually defined as perception-like experiences with the clarity and impact of true perception, but without the external stimulation of the relevant sensory organ (American Psychiatric Association, 2013). Expanding research recognizes that hallucination can occur in more than one sensory modality (auditory, visual, olfactory, gustatory, kinesthetic) either simultaneously or serially (Montagnese et al., 2021). Patients have a lifetime prevalence of 80% for hallucinations in any sensory modality (Lim et al., 2016). Of all patients diagnosed with schizophrenia, 60-80% experience auditory hallucinations while about 30% of them experience visual hallucinations (Waters et al., 2014). However, the lifetime prevalence of multimodal hallucinations is nearly twice as common as unimodal auditory hallucinations (Lim et al., 2016).

- Delusions are commonly conceived as erroneous beliefs that are held with certainty and cannot be corrected. Delusions affect more than 70% of patients with schizophrenia (Sartorius et al., 1986). The conventional classification of delusions is content-based and includes persecutory, guilt or sin, grandiose, religious, somatic, reference, being controlled, mind reading, broadcasting, thought insertion and thought withdrawal (Gutiérrez-Lobos et al., 2001; Paolini et al., 2016; Peralta and Cuesta, 2016).

- (ii) The **negative symptom dimension** describes the absence of functions that are present in healthy individuals. The National Institute of Mental Health Measurement and Treatment Research to Improve Cognition in Schizophrenia consensus panel defined five negative symptoms (Kirkpatrick et al., 2006): blunted affect (i.e., diminished facial and emotional expression), alogia (i.e., decrease in verbal output or verbal expressiveness), asociality (i.e., lack of involvement in social relationships of various kinds), avolition (i.e., a subjective reduction in interests, desires, and

goals and a behavioral reduction of self-initiated and purposeful acts), and anhedonia (i.e., inability to experience pleasure from positive stimuli).

(iii) The **disorganized dimension** describes disturbed behavior (eccentricity, mannerisms, paradoxical acts, aggression, agitation, rituals and stereotype actions) and “positive formal thought disorders” (distortion of thinking with inconsistency, disrupted speech and agrammatical construction of phrases) (Nestsiarovich et al., 2017).

(iv and v) Affective dysregulation gives rise to **depressive** (e.g., anxiety, guilt feelings, tension) and **manic** (e.g., hostility, poor impulse control) symptoms.

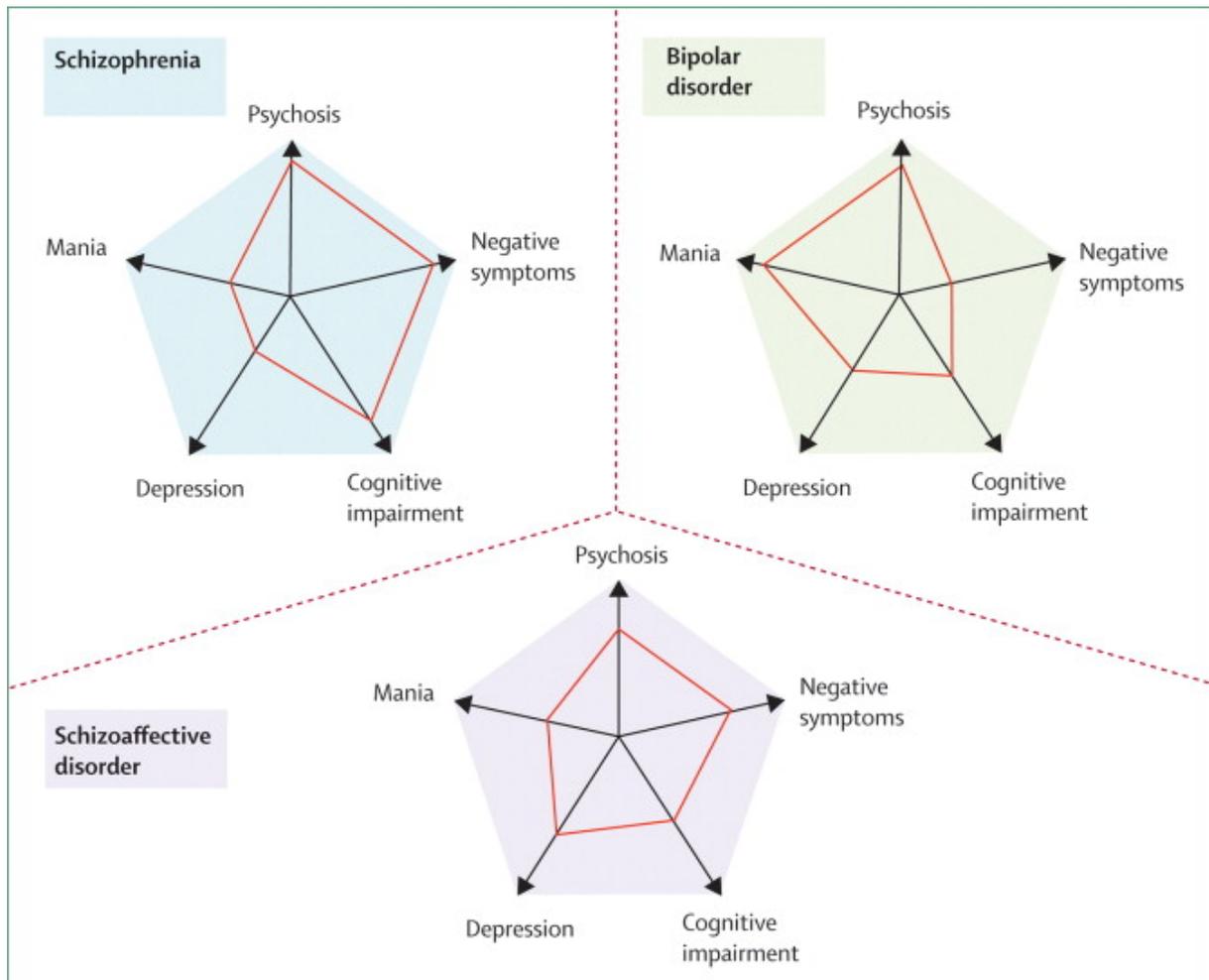


Figure 1, from Van Os et Kapur (van Os and Kapur, 2009). Three hypothetical typical patients diagnosed with a combination of categorical and dimensional representations of psychopathology. The categorical diagnoses of schizophrenia (blue), bipolar disorder (green) and schizoaffective disorder (violet) are accompanied by a patient's quantitative scores (connected by red lines) on the five main dimensions of psychopathology.

1.1.2.2. Diagnostic criteria

The diagnosis of schizophrenia is mostly based in criteria of the American Psychiatric Association's Diagnostic and Statistical manual of Mental disorders (DSM) and the International Classification of Diseases (ICD, World Health Organization).

According to the **fifth edition of the DSM (DSM-5)** (American Psychiatric Association, 2013), a schizophrenia diagnosis requires the following criteria:

- A. At least two of five main symptoms, each present for a significant portion of time during a 1-month period: (1) delusions, (2) hallucinations, (3) disorganized speech, (4) grossly disorganized or catatonic behavior, (5) negative symptoms (i.e., affective flattening, alogia, avolition). At least one of the symptoms should include 1-3.
- B. Social/occupational dysfunction in major areas of functioning such as work, interpersonal relations, or self-care
- C. Duration: Continuous signs of the disturbance persist for at least 6 months
- D. Schizoaffective and major mood disorder exclusion
- E. Substance/general mood condition exclusion: the disturbance is not attributed to the direct physiological effects of a substance
- F. If there is a history of autism spectrum disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least 1 month.

According to the **eleventh edition of the ICD (ICD-11)**, a schizophrenia diagnosis requires at least two of the following criteria (one of which must be from list (a) to (d) must be present most of the time for a period of 1 month or more):

- a. Persistent delusions
- b. Persistent hallucinations
- c. Disorganized thinking
- d. Experiences of influence, passivity, or control
- e. Negative symptoms
- f. Grossly disorganized behavior
- g. Psychomotor disturbance

In addition to these clinical criteria, patients with schizophrenia have several neurocognitive deficits. The most prominent are alterations of memory, attention/vigilance, working memory, reasoning and problem solving, processing speed and social cognition (Nuechterlein et al., 2004). Therefore, the diagnosis of schizophrenia also considers the presence of “a level of cognitive functioning suggesting a consistent severe impairment and/or a significant decline from premorbid levels considering the patient’s educational, familial, and socioeconomic background” (Keefe and Fenton, 2007).

1.1.3. Etiology and neurobiology

1.1.3.1. *Causes of schizophrenia*

No specific cause of schizophrenia has been identified. However, it has been established that schizophrenia is a multifactorial disease characterized by high heritability and various environmental risk factors.

Genetic risk

Schizophrenia is a complex genetic disorder involving many genes. Family studies have shown that having a first degree relative with schizophrenia is one of the greatest risks for the disorder. The heritability of schizophrenia is estimated to be ~80% and the concordance of monozygotic twin ~45% (Gejman et al., 2010). The disorder is associated with polygenic risk mediated by multiple single nucleotide polymorphisms (SNP), each individually contributing a very small component of risk (Bergen et al., 2019; Gejman et al., 2010; Hall et al., 2015). Another major insight regarding the genetics of schizophrenia has been the involvement of rare inheritable chromosomal deletions and duplications, known as copy number variants (CNV) which

individually have a much larger impact on risk (Bergen et al., 2019). For example, a specific CNV on chromosome 22 results in the 22q11 deletion syndrome and induces a lifetime prevalence of schizophrenia of approximately 25%, compared to less than 1% in the general population (Owen and Doherty, 2016).

Environmental risk factors

In addition to genetics, exposure to several psychological, social and biological risk factors contribute to the risk of developing schizophrenia. These factors include peri-natal risk (e.g., infection, famine, placenta pathology, low birth weight), migrant status, social defeat, childhood trauma, urbanicity, cannabis use (Mittal et al., 2008; Nuechterlein et al., 2004). It is likely that these multiple factors are cumulative and interact with each other and with key periods of neurodevelopment, from the perinatal period (e.g., malnutrition) to the late neurodevelopment (e.g., cannabis use) to contribute to schizophrenia (Davis et al., 2016).

Interplay between genetics and environment

The risk of developing psychosis increases with the accumulation of genetic risk factors and exposures to adverse environmental factors. Furthermore, it is likely that schizophrenia results from the interaction between genetic predisposition and environmental vulnerability factors rather than their independent effects (Davis et al., 2016). Thus, genetic factors may render some individuals more vulnerable to the impact of environmental risk factors. For instance, a common SNP in the AKT1 gene makes its carriers sensitive to the psychosis-inducing properties of cannabis (Di Forti et al., 2012).

1.1.3.2. The schizophrenia continuum

According to recent characterizations of psychotic disorders, schizophrenia is included in a continuum that encompasses a full range of psychotic states and symptoms.

The psychosis prodrome

Schizophrenia is generally considered as being a part of a continuum from at-risk state to chronic schizophrenia through first-episode of psychosis (FEP). Populations at high-risk for schizophrenia can be identified primarily on the basis of increased genetic and clinical risk.

Individuals considered to be at increased genetic risk are monozygotic twins, siblings, and first/second-degree relatives of patients with schizophrenia. Monozygotic twins have a lifetime concordance rate of approximately 45% and the risk for other first-degree relatives of patients with schizophrenia is about 10 times that of the general population (Chang et al., 2002).

Individuals considered to be at clinical high-risk for psychosis (CHR), at-risk mental state (ARMS) or ultra high-risk for psychosis (UHR) meet at least one of the three following criteria: attenuated psychotic symptoms (APS), genetic risk and deterioration syndrome (GRD), or brief and limited intermittent psychotic symptoms (BLIPS) (*see Table 1, Figure 2*) (Fusar-Poli, 2017; Yung et al., 2012). Follow-up studies have identified that approximately 20-35% of CHRs will convert to frank psychotic symptoms within the first 2 years (Fusar-Poli, 2017; Fusar-Poli et al., 2012). In addition, CHR status have been associated with cognitive impairments including memory, executive function, processing speed, attention, and social cognition that worsen over time and with the onset of frank psychotic disorder (de Paula et al., 2015). In a recent meta-analysis including 303 ARMS vs. 376 controls, we also showed that individuals with CHR exhibit abnormal cognitive insight, characterizing a lack of ability to question and

reconsider own beliefs and judgements. These results suggest that overconfidence in one’s own judgements reflects the predisposition to experience strong and inflexible emerging delusional beliefs in individuals with CHR with subclinical positive symptoms (*see section 7.1, (Dondé et al., 2020)*).

Attenuated Psychosis symptoms - APS	Brief Limited Intermittent Psychotic Episode - BLIPS	Genetic Risk and Deterioration Syndrome - GRD
Subthreshold attenuated positive symptoms: eg, ideas of reference, “magical” thinking, perceptual disturbance, paranoid ideation, odd thinking and speech; held with either subthreshold frequency or subthreshold intensity; present for >1 week in the past 12 months AND decline in functioning OR sustained low functioning	Transient psychotic symptoms: symptoms in the subscales of unusual thought content, nonbizarre ideas, perceptual abnormalities, disorganized speech; duration of the episode <1 wk; spontaneous remission; symptoms occurred within the past 12 mo; AND decline in functioning OR sustained low functioning	Family history of psychosis OR an individual with schizotypal personality disorder AND a decline in functioning OR sustained low functioning

Table 1 adapted from Fusar-Poli et al., 2013 (Fusar-Poli et al., 2013a). Clinical High-Risk (CHR) criteria for psychosis. The table described the criteria of the Comprehensive Assessment of At-Risk Mental State (CAARMS) interview.

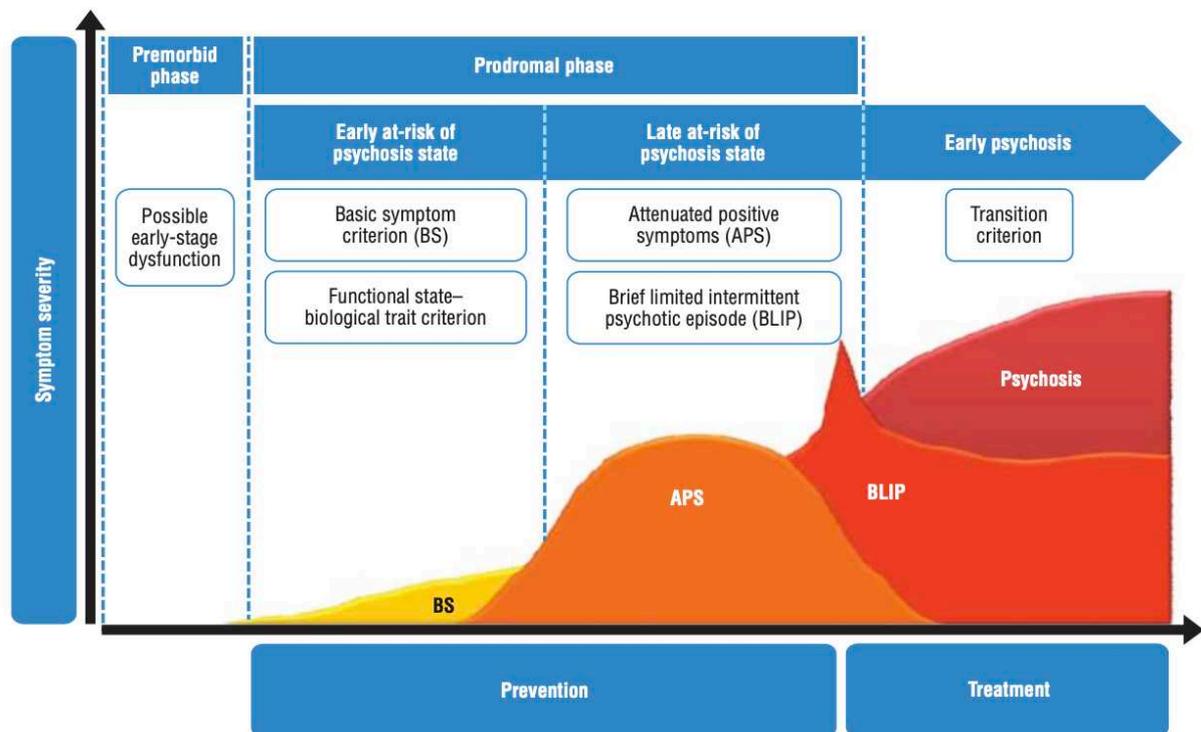


Figure 2 from Fusar-Poli et al. (Fusar-Poli et al., 2013b). Model of psychosis onset from the clinical high-risk state (CHR). According to the two-stages model of early and late risk, the earlier prodromal state is characterized by presence of basic symptoms, i.e., “subjectively experienced disturbances of different domains, including perception, thought processing, language, and attention, that are distinct from classic psychotic symptoms in that they are independent of abnormal thought content and reality testing and insight into the symptoms’ psychopathologic nature is intact.”. Later prodromal phase is characterized by UHR criteria, i.e., APS, GRD and BLIPS. The higher the line on the y-axis, the greater the severity of symptom.

From subclinical to clinically significant psychotic experiences

The continuum of psychosis is not only defined as an extended phenotype of psychosis progressively worsening into clinical syndromes. The continuum of psychosis can also be considered from a phenomenological perspective, postulating that psychotic experiences would lie on a continuum with normal experience. According to Van Os, “*psychiatric morbidity in a population may be seen as a function of the degree to which the distribution of a continuous phenotype, measurable in both healthy and ill individuals, is shifted towards higher values*”

(Van Os et al., 2009). Thus, a growing body of research suggests that psychotic experiences are common not only in individuals with schizophrenia but also in the general population with a prevalence of 7% (Linscott and van Os, 2013). For example, studies estimate the prevalence of experiencing hallucination in the general population without apparent psychiatric illness to be between 4.1% and 5.8% (Nuevo et al., 2012). These subclinical manifestations are generally distinguished from clinical hallucinations on the basis of characteristics such as emotional valence, conviction, control, and elicited distress. Similarities between hallucination with and without need for care related to loudness, number of voices, personification and underlying brain activity (Johns et al., 2014). Evidence of similarity between subclinical and clinically significant psychotic symptoms includes similar neurocognitive alterations as well as common risk factors and structural and functional correlates (DeRosse and Karlsgodt, 2015). These findings have been taken to suggest an “extended psychosis phenotype”, that is, a phenotype including demographic, environmental, familial and psychopathological features that is phenomenologically continuous with schizophrenia (van Os and Linscott, 2012; van Os and Reininghaus, 2016).

1.1.3.3. Neuro-pathophysiology

Abnormalities of brain structure and function

Structural abnormalities of the brain are repeatedly demonstrated in patients with schizophrenia. One of the most consistent morphological features of schizophrenia is the enlargement of ventricles (Kempton et al., 2010). This enlargement is thought to result from brain shrinkage in the temporal and frontal lobes (Horga et al., 2011) and/or in structures immediately adjacent to the ventricles such as the caudate and the thalamus, which have been found to be smaller in patients with schizophrenia (Gaser et al., 2004). A recent mega-analysis comparing 4474 individuals with schizophrenia and 5098 healthy controls identified that schizophrenia patients

show widespread thinner cortex and smaller cortical surface area, with the largest effect size in frontal and temporal regions (van Erp et al., 2018). In addition, large multisite studies have demonstrated an extensive pattern of gray-matter volume (GMV) decrease in patients with chronic schizophrenia and FEP, particularly involving the frontal and temporal cortices (Howes et al., 2022; Torres et al., 2016). Numerous studies also suggest altered gyrification (i.e., the pattern and degree of cortical surface folding) in patients with schizophrenia, particularly in frontal and temporal brain areas (e.g., Madeira et al., 2020; Madre et al., 2020; Nelson et al., 2020; Ohi et al., 2016; Palaniyappan and Liddle, 2014). In a recent meta-analysis including 1004 patients with schizophrenia and 925 healthy controls, we demonstrated significant reduction of gyrification in patients with schizophrenia in the left inferior frontal cortex and bilateral medial temporal cortices (Lavallé et al., *in prep*). Finally, several studies have examined much local morphometry abnormalities in two major sulci called the paracingulate sulcus (PCS) and superior temporal sulcus (STS) that run along the surface of the medial prefrontal cortex (mPFC) and the temporoparietal junction (TPJ), respectively. Bilateral PCS length shortening has been identified in patients with schizophrenia (Garrison et al., 2015) and in nonclinical individuals who experience hallucinations (Garrison et al., 2019). The depth of the STS has also been shown to be particularly reduced in patients with schizophrenia (Cachia et al., 2008; MacKinley et al., 2020), especially when they experience hallucinations (Rollins et al., 2020).

With respect to function, the disconnection hypothesis originally posited that the core symptoms of schizophrenia resulted from abnormal functional integration between brain regions (Friston, 1998; McGuire and Frith, 1996). Numerous studies across the course of psychosis, from at-risk states to chronic schizophrenia, have demonstrated altered activation and functional connectivity in various brain regions, both at rest and during specific tasks. One

of the most consistently reported alteration involves reduced frontotemporal functional connectivity. In an early study, Lawrie et al. demonstrated a reduced correlation coefficient between the left dorsolateral prefrontal cortex (DLPFC) and the left middle/superior temporal cortex in patients with schizophrenia compared to healthy controls during a sentence completion task. Interestingly, this reduced connectivity was negatively correlated with the severity of auditory hallucinations (Lawrie et al., 2002). In a later study comparing patients with schizophrenia to healthy controls, Jeong et al. demonstrated reduced connectivity between the pars triangularis (i.e., a triangular-shaped cortical region of the inferior frontal gyrus) and the left temporoparietal regions of the language network (Jeong et al., 2009). A similar reduction in connectivity between left frontotemporal brain areas has been reported in drug-naïve individuals with FEP (Boksman et al., 2005) and CHR (Crossley et al., 2009; Yoon et al., 2015).

In addition, recent neuroimaging evidence have revealed that schizophrenia is associated with aberrant brain connectivity at the network level. One of the most examined networks is the default mode network (DMN), which refers to a resting-state network with greater activity at rest than during task performance in a set of brain regions including the medial prefrontal cortex, posterior cingulate cortex, precuneus, bilateral inferior parietal lobule and temporal cortex (Greicius et al., 2003). The DMN is supposed to subserve internally-driven processes such as self-reference, autobiographical information, and theory of mind (Gusnard et al., 2001; Mars et al., 2012). fMRI studies have revealed increased functional connectivity at rest within the DMN in patients with schizophrenia (Mingoia et al., 2012) and have demonstrated abnormal activation or deactivation in the DMN during a wide range of tasks (for rev, (Hu et al., 2016)). Further investigations have revealed functional abnormalities between the DMN and other functional network such as the central executive network (Manoliu et al., 2014).

At the molecular level

According to the prominent molecular hypothesis of schizophrenia, a dopamine (DA) hyperactivity at D2 receptors would be involved in psychosis (*Figure 2*) (Meltzer and Stahl, 1976). This theory is originally based on the observation that antagonists targeting D2 receptors in the striatum have been shown to reduce positive symptoms in schizophrenia and that pharmacological stimulation of DA with amphetamines can induce psychotic-like experiences such as paranoid delusions. This hypothesis specifically postulates hyperactivity of the mesolimbic dopaminergic pathway, which projects from the ventral tegmental area (VTA) to the ventral striatum, including the nucleus accumbens. In rodents, amphetamine infusion induces the greatest DA release in the nucleus accumbens (Di Chiara and Imperato, 1988) and injection of Haloperidol into the nucleus accumbens is responsible for the abolition of amphetamine-induced locomotor activity (Pijnenburg et al., 1975). Excess dopamine in the ventral striatum is specifically associated with positive symptoms. In line with that, positive correlations have been reported between the severity of hallucinations, the level of D2 in the ventral striatum (Kessler et al., 2009), and ventral striatum metabolism in patients with schizophrenia (Epstein et al., 1999). Finally, more recent imaging studies have associated the presence of hallucinations in schizophrenia with abnormalities of functional connectivity between the ventral striatum and nucleus accumbens (Rolland et al., 2015) and correlated hallucination vividness with nucleus accumbens activation (Raij et al., 2009).

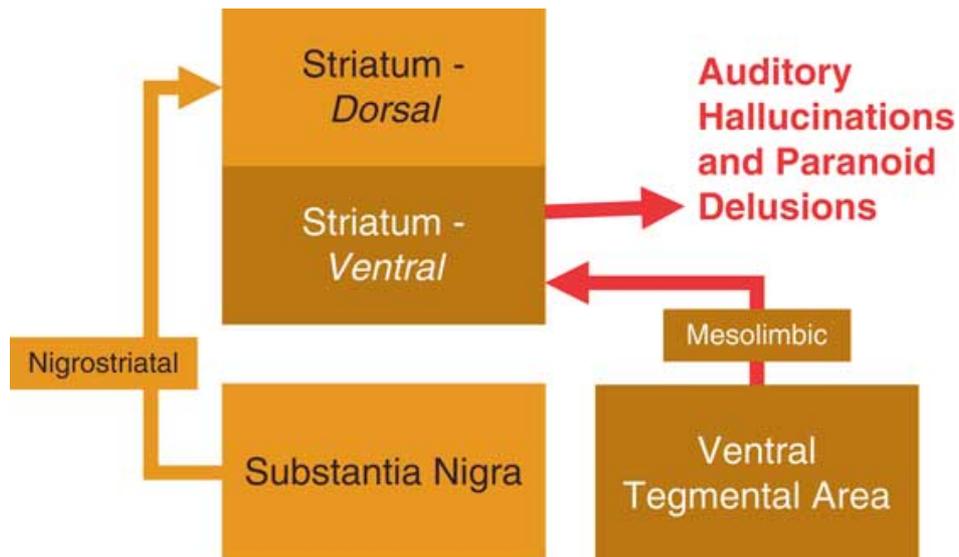


Figure 3, from Stahl et al. (Stahl, 2018). Dopamine hypothesis through the mesolimbic pathway.

Relatively more recent hypotheses posit that schizophrenia would be associated with more neurochemical abnormalities than dopamine (Stahl, 2018). The glutamate hypothesis suggests that hypofunctional NMDA receptors on GABA interneurons in the prefrontal cortex would lead to overactivation of downstream glutamate signaling to the VTA. Overactivation of this pathway may in turn lead to excess DA in the ventral striatum via the mesolimbic pathway (see Figure 3). A second theory is based on the observation that 5-HT_{2A} antagonism has proven its efficacy for reducing the psychotic symptoms due to Parkinson's disease. The 5-HT_{2A} hypothesis suggests that hyperactivation of 5-HT_{2A} receptors on glutamate neurons would lead to increased glutamate release in the VTA, resulting in excess DA in the ventral striatum (see Figure 4, Figure 5).

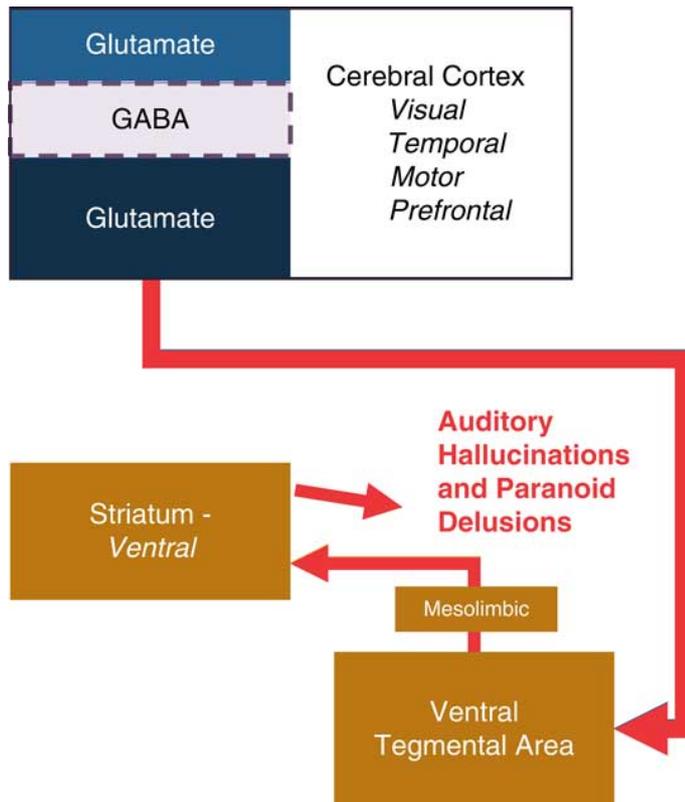


Figure 4 from Stahl et al. (Stahl, 2018). Interplay between the Glutamate and Dopamine hypotheses.

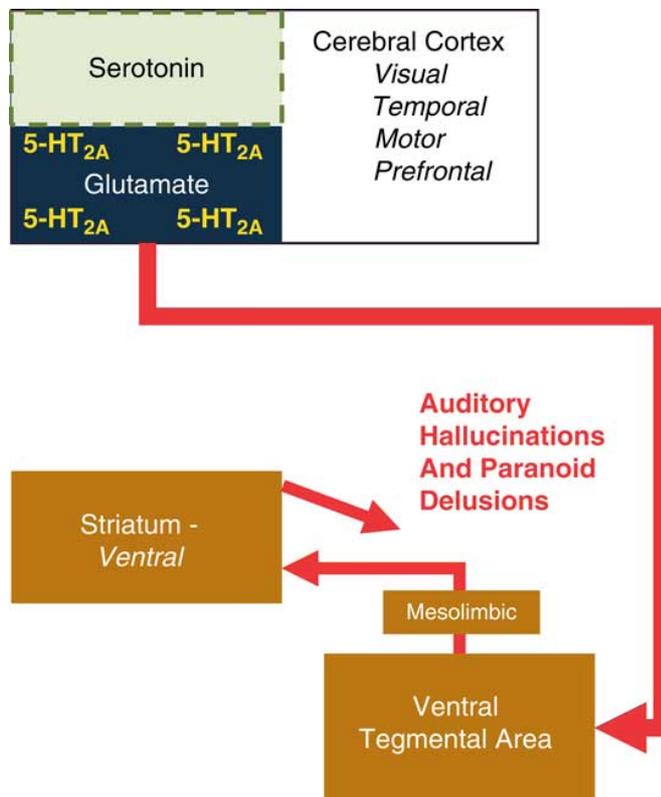


Figure 5 from Stahl et al. (Stahl, 2018). Interplay between the 5-HT_{2A} and Dopamine hypotheses.

1.1.4. Current treatments and research challenges in schizophrenia

Schizophrenia is a chronic mental disorder that requires long-term treatment. There are a variety of effective care options for people with schizophrenia, including medication and psychotherapy. Antipsychotic medications are currently the main pharmacological treatment of the disease and primarily help to reduce positive symptoms such as hallucinations and delusions. Antipsychotics are classified as first (mainly D2 antagonists), second (multi-target antagonists with greater antagonism at 5-HT_{2A} receptors than at D2 receptor) and third generation (more targeting D3 receptors than D2 receptors) antipsychotics (Stępnicki et al., 2018). A review by Sommer et al. highlighted that D2-targeted antipsychotic medications, such as olanzapine, amisulpride, ziprasidone and quetiapine may be the most effective treatment option for AH in schizophrenia (Sommer et al., 2012). Psychosocial interventions are typically provided in addition to pharmacological treatments, including cognitive behavioral therapy, cognitive remediation, psychoeducation, illness self-management training, social skills training and supported employment (Mueser et al., 2013).

Pharmacological treatments proposed for schizophrenia have several limits: (1) they induce a wide range of neurological and metabolic side effects such as weight gain and sedation (Buchanan et al., 2010; De Berardis et al., 2008), (2) they are mainly effective in treating positive symptoms, but have minimal effects on negative symptoms and cognitive impairment (Carbon and Correll, 2014), (3) adherence to treatment is often poor, resulting in high rates of relapse (Phan, 2016). Furthermore, at least 50% of patients experience persistent symptoms and disability despite taking adequate dose of treatment (Stroup et al., 2000). Treatment-resistant

schizophrenia (i.e., inadequate response to 2 different antipsychotics, each taken at an adequate dose and duration) occurs in 20 to 40% of patients (Kane et al., 2019; Samara et al., 2019), including auditory hallucinations refractory to traditional medications in 25 to 30% of cases (Shergill et al., 1998).

For patients with treatment-resistant symptoms, several alternative treatment strategies are available, including noninvasive brain stimulation (NIBS) such as electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). These techniques have shown promising results in alleviating drug-resistant AH (Loo et al., 2010; Schönfeldt-Lecuona et al., 2004; Yang et al., 2019), negative symptoms (Shi et al., 2014), and improving cognitive functioning (Kostova et al., 2020; Yu et al., 2020).

SUMMARY

Schizophrenia is a severe psychiatric illness characterized by positive symptoms (e.g., hallucinations, delusions), negative symptoms (e.g., avolition, anhedonia), disorganized behavior and cognitive impairment. Schizophrenia falls along a continuum from genetic or clinical at-risk state to chronic schizophrenia through first-episode of psychosis. The continuum of psychosis can also be view from a phenomenological perspective, including individuals who exhibit nonclinical psychotic experiences like hallucination-proneness.

Schizophrenia is associated with structural abnormalities of the brain that have been particularly identified in the frontotemporal regions. These include abnormalities in cortical surface area, gray-matter volume and gyrification. Abnormal frontotemporal activity and connectivity were also identified, both at rest and during specific tasks. Neuroimaging data revealed that schizophrenia is associated with aberrant connectivity at the network level, particularly in the DMN, which is thought to subserve internally-driven processes. At the molecular level, the main hypothesis involves abnormalities in dopamine, but subsequent hypotheses have link them to glutamate and 5-HT_{2A} imbalances.

Current treatments of schizophrenia include medications and psychotherapy. Medications primarily target dopamine receptors hyperactivity. These treatments have several limitations, including poor adherence and resistance. A better understanding of the mechanisms underlying schizophrenia may lead to more appropriate therapeutic solutions.

1.2. Interest of reality-monitoring in schizophrenia

1.2.1. The self-disorder model of schizophrenia

Although schizophrenia is associated with a wide range of symptoms and cognitive deficits, an influential attempt to define schizophrenia is the self-disorder or ipseity-disturbance model which describes how the symptoms of schizophrenia can be understood as disruptions in an individual's sense of self. (Sass and Parnas, 2003). The self-disorder model “*postulates an abnormality of basic or minimal self-awareness, of the normal, first-person quality of experience—i.e., of ipseity: the core sense of existing as the subject of one’s own experience and agent of one’s own actions*” (Sass et al., 2018). According to this model, individuals with schizophrenia experience a breakdown in the normal functioning of the self-system, which is the cognitive and neural network that underlies the experience of having a unified, coherent sense of self.

Patients with schizophrenia have been reported with significant self-disturbance and medium-to-large effect sizes regarding impaired sense of body and ownership, sense of agency and self-reported sense of self (Hur et al., 2014). The self-disorder model has also been supported by studies using the Examination of Anomalous Self-Experience (EASE) scale, demonstrating that abnormal self-experiences are a core phenotype of schizophrenia that is not shared by other psychiatric diseases (for review, see (Parnas and Henriksen, 2014)). Furthermore, a diminished sense of self is also observed in individuals with high-risk for psychosis and may predict transition to full-blown psychosis (Hauser et al., 2011; Nelson et al., 2012, 2008; Parnas et al., 2011), suggesting self-disturbances as a trait marker of vulnerability to psychosis.

The self-disorder model is consistent with one of the prominent neurocognitive theories of schizophrenia that positive symptoms emerge from a malfunctioning self-system that induces

difficulty distinguishing between the origins of endogenous and exogenous stimuli, or between imagination and reality, referred to as reality-monitoring deficit (Nelson et al., 2014).

1.2.2. Schizophrenia is associated with reality-monitoring impairment

1.2.2.1. *Reality-monitoring is a kind of source-monitoring*

Source-monitoring is a high-order cognitive process that refers to the ability to make attributions about the origin of past experiences (Johnson et al., 1993; Mitchell and Johnson, 2009). The term *source* refers to the conditions under which a memory was acquired and includes spatial and temporal context, modality (i.e., overt speech or imagination), and agent (i.e., self or external) (Lindsay, 2008).

Three main types of source-monitoring have been described based on the type of sources to be distinguished from each other. *Reality-monitoring* characterizes the ability to determine whether information was perceived from the environment or imagined, such as whether a sentence was spoken by someone or simply imagined (e.g., Did Sara tell me it was going to rain or did I just imagine it?). *Internal source-monitoring* characterizes the ability to distinguish between mental experiences originating from the subject, such as whether a sentence was spoken aloud or internally using inner speech (e.g., Did I tell Sara it was going to rain or did I just imagine it?). Finally, *external source-monitoring* characterizes the ability to distinguish between different external sources, such as knowing whether a picture appeared on the left or right side of a screen (e.g., Did Sara tell me it was going to rain or did I hear it on the radio?) (see Figure 6).

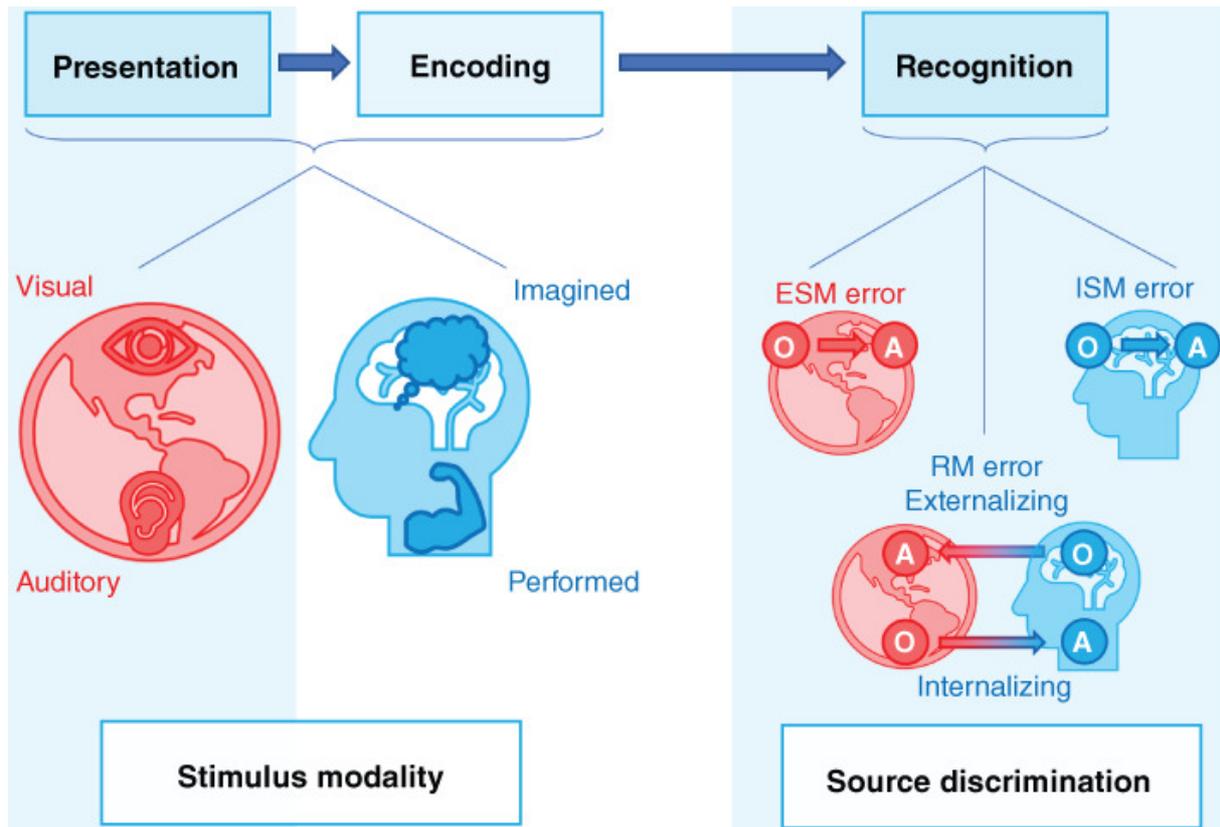


Figure 6, from Damiani et al. (Damiani et al., 2022). Source monitoring subtypes and stimulus modalities. In the encoding phase, a stimulus (e.g., a written or recorded sentence) is presented and encoded by the subject (e.g., sentence read in mind or aloud). In the recognition phase, the stimulus is presented again, and the subject discriminate whether its original source was internal/self (blue) or external/non-self (red). Arrows directions (O = original source → A = answered source) represent the four possible types of source discrimination errors. ESM: external source monitoring; ISM: internal source monitoring; RM: reality monitoring.

1.2.2.2. Experimental paradigms

Experimental tasks testing source-monitoring abilities involve presenting individuals with items coming from different sources and then asking them to recognize the source of each item. Typical source-monitoring paradigms are divided in two phases: encoding stimuli from different sources and testing (see Figure 7) (Johnson, 1988; Johnson et al., 1993; Keefe et al., 1999). The items can be presented in different ways, i.e., words, pictures, actions.

Verbal tasks

Most studies assessing source monitoring abilities use the verbal modality. In these tasks, the presentation/encoding phase consists of presenting several words in a random order. Each word is preceded by an instruction. In the reality-monitoring paradigm, the instruction is either “imagine hearing” or “listen to”. In the internal source-monitoring paradigm, the instruction is either “imagine saying” or “say”. These words are presented again during the recognition phase, along with new words. In the reality-monitoring paradigm, participants are asked to distinguish the words they imagined hearing from the words they heard. In the internal source-monitoring paradigm, participants are asked to distinguish the words they imagined saying from the words they said aloud.

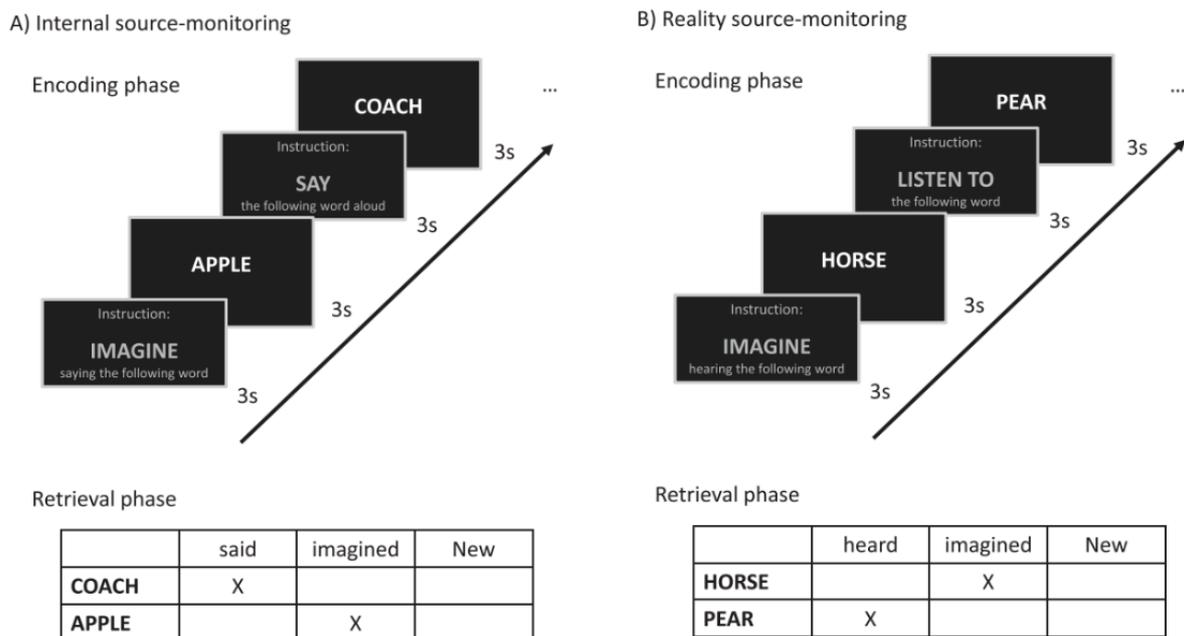


Figure 7, from Lavallé et al. (Lavallé et al., 2020a). Experimental procedures to assess reality-monitoring (right panel) and internal source-monitoring (left panel) using verbal stimuli.. During the encoding phase, 16 words are sequentially presented in randomized order. Each word is preceded by an instruction. During the retrieval phase, 24 words are presented, including the 16 words that were presented during the encoding phase. In the internal source-monitoring task, the verbal list includes 8 words with the “imagine saying” encoding condition and 8 words with

the "say aloud" encoding condition. Internal source-monitoring abilities are assessed by asking subjects to identify whether each word was said aloud, imagined or new. In the reality-monitoring task, the list includes 8 words with the "imagine hearing" encoding condition and 8 words with the "listen to" encoding condition. Reality-monitoring abilities are assessed by asking participants to identify whether each word was heard, imagined or new.

Non-verbal tasks

Similar tasks have been developed with nonverbal stimuli. For example, Brébion et al. developed a visual reality-monitoring task specifically designed to facilitate confusion between items presented as words and those presented as pictures (*a similar visual task is depicted Figure 8*). In the encoding stage, participants were presented with a mixture of pictures of common items and labels designating common items (e.g., the word "CARROT" and the picture of a potato). Then, they were asked to indicate whether the items read from a list had been presented previously as a picture, a word, or not at all. It was expected that the presentation of words for common items would trigger mental images, and that participants would have difficulty remembering afterwards whether an image had actually been presented or only imagined (Brébion et al., 2008; Gonsalves et al., 2004). An example of an action reality-monitoring task is the one developed by Brandt et al. in which participants performed or imagined performing specific actions with real objects drawn from one of two boxes (*see Figure 9*) (Brandt et al., 2014). Recently, a reality-monitoring task has been developed in the olfactory modality where participants were asked to either smell or imagine smelling odors, followed by a source memory test (Leclerc et al., 2019).

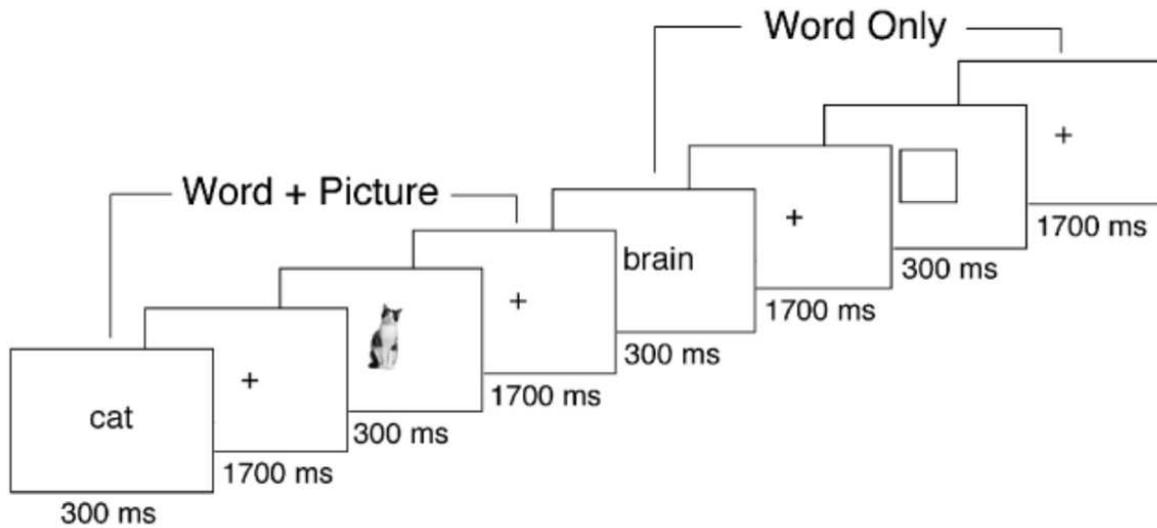


Figure 8 from Gonsalves et al. (Gonsalves et al., 2004). Experimental procedure to assess reality-monitoring using visual stimuli. In the test phase, subjects read names of objects and mentally visualized the referents. Half of the names were followed 2 s later by a photographic representation of the named object. In a test phase given outside the scanner, subjects listened to object names and decided whether they had seen a picture of the object corresponding to each name.

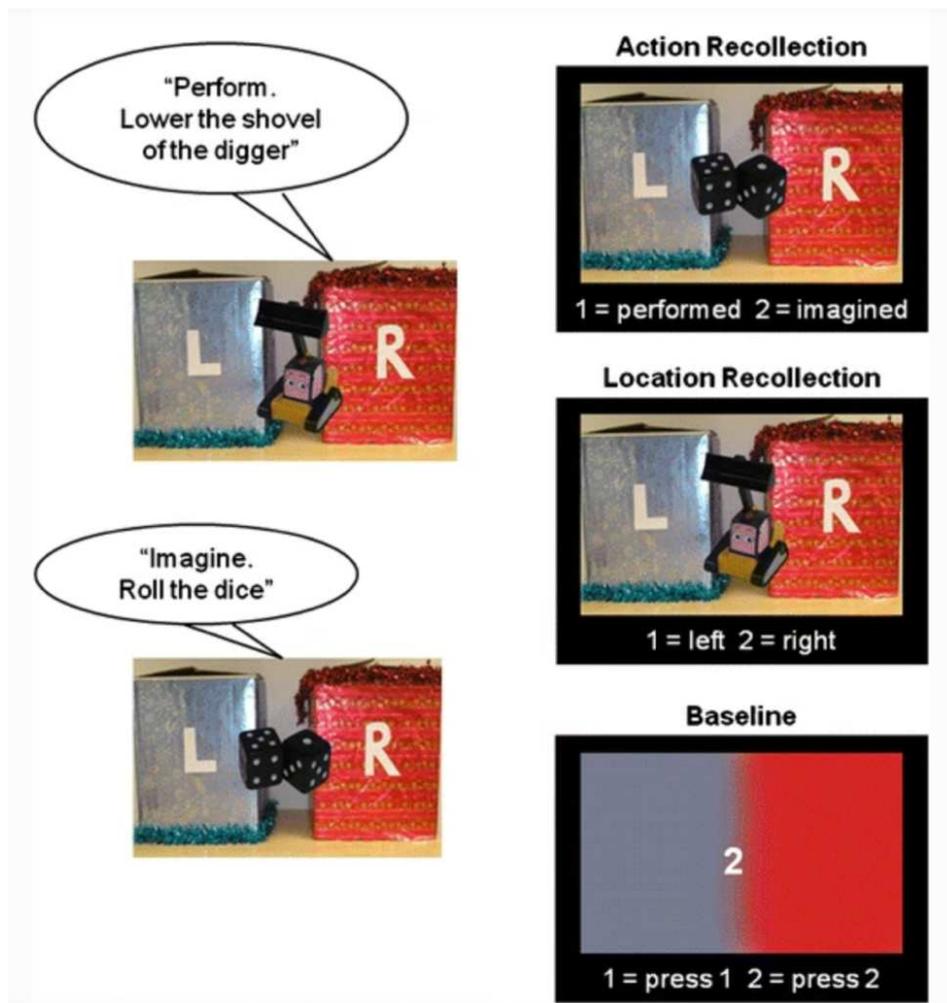


Figure 9 from Brandt et al. (Brandt et al., 2014). *Experimental procedure to assess reality-monitoring using action stimuli.* During the encoding phase, objects were taken out of either the left or the right box and presented to the participant, who was asked to perform a specified action with the object or to imagine performing that action. During the test phase, photographs of the objects were presented, and participants were asked to recollect whether each object had been associated with a performed or imagined action (i.e., reality-monitoring) or whether it had been taken out of the left or the right box (i.e., external source-monitoring). In the perceptual baseline condition, participants had to press one of two buttons, according to the number on the screen.

Task variations

Some variations of the reality-monitoring task increase the cognitive load associated with the internal condition of the reality-monitoring task. These tasks are thought to be closer to the

theoretical concept that the internal source must be self-generated. In this line, several studies use a reality-monitoring task that presents participants with a series of verbal word pairs (e.g., *Cookies and Cream*), which are shown either completed (perceived/externally-generated, e.g., *Cookies and Cream*) or where the second word must be provided by the participant (imagined/internally-generated, e.g., *Cookies and C____*, see Figure 10) (e.g., Garrison et al., 2017b; Vinogradov et al., 2006).

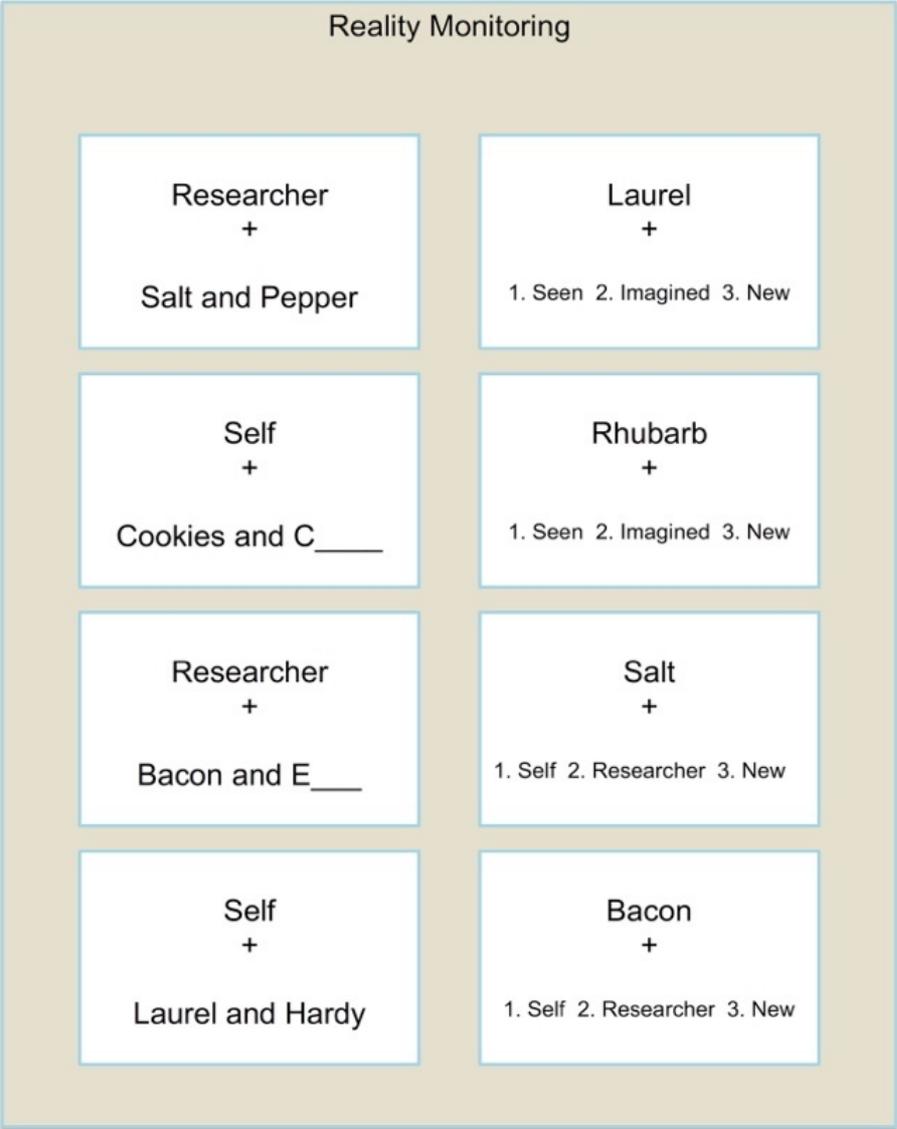


Figure 10, from Garrison et al. (Garrison et al., 2017c). Experimental procedure to assess reality-monitoring using verbal stimuli with increased cognitive load. Stimuli used in reality-monitoring tasks. During the encoding phase, stimuli are presented either complete (perceived)

or incomplete (requiring imagining the second word). Then, during the testing phase, subjects are presented with the first word of a word pair and asked to judge whether the accompanying word has been seen or imagined, or whether the presented word is novel.

Main outcomes

Source-monitoring outcomes are usually classified using the signal detection theory (SDT), including source hits, false alarms, correct rejections and misses (Kuhlmann et al., 2021). *Source hits* are the proportion of correct source recognition. Source hits refer to either correct recognition of source A or correct recognition of source B. *Correct rejections* refer to the proportion new items correctly recognized as “new”. *False alarms* refer to participants erroneously labeling a new item as old. *Misses* refers to the proportion of old items recognized as “new”. In addition, *source-monitoring errors* occur when items are correctly recognized as old but there are confusions between exogenous and endogenous sources (i.e., reality-monitoring errors), between two endogenous sources (i.e., internal source-monitoring errors), or between two exogenous sources (i.e., external source-monitoring errors) (*see Table 2*).

		Actual			
		Participant Perform	Participant Imagine	Experimenter Perform	New
Response	Conditions	Participant Perform	Participant Imagine	Experimenter Perform	New
	Participant Perform	Source Hit	Internal SM Error	Reality Monitoring Error	False Alarm
	Participant Imagine	Internal SM Error	Source Hit	Reality Monitoring Error	False Alarm
	Experimenter Perform	Reality Monitoring Error	Reality Monitoring Error	Source Hit	False Alarm
	New	Miss	Miss	Miss	Correct Rejection

Table 2, from Humpston (Humpston, 2017). Classification of source-monitoring outcomes. Here, *source hits* refer to the correct recognition of reality-monitoring sources or internal source-monitoring sources. *Correct rejections* refer to new items correctly labelled as “new”. *Reality-monitoring errors* refer to the misattribution of externally-generated items (“experimenter perform”) to an internal source (“participant perform” or “participant imagine”) and vice versa. *Internal source-monitoring errors* refer to the misattribution of imagined items as “performed” and vice versa. *False alarms* refer to the misattribution of new items as old (“participant perform”, “participant imagine”, “experimenter perform”). *Misses* refer to the misattribution of old items (“participant perform”, “participant imagine”, “experimenter perform”) as “new”.

Source-monitoring performances can also be evaluated by:

- (a) Source-monitoring accuracy using the average conditional source identification measure (ASCIM) with the following formula (Murnane and Bayen, 1996):

$$\frac{1}{2} \left(\frac{f_{ii}}{f_{ie} + f_{ii}} + \frac{f_{ee}}{f_{ei} + f_{ee}} \right)$$

The source-monitoring accuracy is declined in internal source-monitoring accuracy and reality-monitoring accuracy, according to the task.

In the internal source-monitoring accuracy formula, *fii* is the number of correctly recognized *imagined say* words, *fee* is the number of correctly recognized *said* words, *fie* is the number of *imagined say* words wrongly recognized as being *said*, and *fei* is the number of *said* words wrongly recognized as being *imagined say*.

In the reality-monitoring accuracy formula, *fii* is the number of correctly recognized *imagined hear* words, *fee* is the number of correctly recognized *heard* words, *fie* is the number of *imagined hear* words wrongly recognized as being *heard*, and *fei* is the number of *heard* words wrongly recognized as being *imagined hear*.

- (b) The externalization bias. In internal source-monitoring tasks, the externalization bias is defined as the number of *imagined say* words wrongly recognized as *said* among all *imagined* words incorrectly judged (i.e., *new* or *said*). In reality-monitoring tasks, the externalization bias is defined as the number of *imagined hear* words wrongly recognized as *heard* among all *imagined* words incorrectly judged (i.e., *new* or *heard*).
- (c) The internalization bias. In internal source-monitoring tasks, the internalization bias is defined as the number of *said* words wrongly recognized as *imagined say* among all *said* words incorrectly judged (i.e., *new* or *imagined*). In reality-monitoring tasks, the externalization bias is defined as the number of *heard* words wrongly recognized as *imagined hear* among all *heard* words incorrectly judged (i.e., *new* or *imagined*).
- (d) Item memory accuracy is calculated as the standardized hit rate (z-score of hit rate, i.e., the proportion of old items identified as old) minus the standardized false alarm rate (z-

score of false alarm rate, i.e., the proportion of new items identified as old). This measure of item memory, also known as the Signal Detection Theory metrics' d' (Macmillan and Creelman, 2004), reflects the sensitivity to discriminate between old and new items.

1.2.2.3. Source-monitoring framework

Reality monitoring has been theorized into the “source-monitoring framework” (SMF) by Johnson et al. (Johnson et al., 1993). The central thesis of the SMF is that memories are not accompanied by a label indicating their source; but rather the source is evaluated and attributed through decision processes performed during remembering. According to the source-monitoring framework, the origin of memories is determined based on the balance between “internal” and “external” cues established during memory acquisition, such as the amount of perceptual detail, contextual information and cognitive operations. According to Johnson et al., source-monitoring decisions capitalize on average quantitative differences in characteristics of memories originating from different sources (Johnson et al., 1993). Thus, veridical perceptions are associated with more and stronger sensory detail (*see Figure 11*), whereas imagination is subject to more top-down cognitive control signals due to the richness of the cognitive operations involved in generating mental experience. A high-order reality-monitoring mechanism is then expected to make source attributions based on the amount of perceptual information and the amount of traces indicating effortful, internally-generated cognitive information. For instance, an event that is remembered as particularly vivid may be more likely recalled as originating from the external environment, whereas an event associated with a higher cognitive load may be more likely recalled as “imagined” or self-generated (Garrison et al., 2017a; Johnson, 1997; Johnson et al., 1993).

PERCEPTION



Clear and rich

IMAGINATION



Vague and less detailed

Figure 11, adapted from (Dijkstra et al., 2022). Representation of the difference between veridical perception and imagination. Veridical perception is generally experienced as clearer and more detailed compared to imagination.

In this way, Johnson and her team observed that memories of past fantasies are rated as less perceptually detailed than memories of past real events and that when they asked participants why they thought a particular memory came from a real event, they often cited such perceptual features (Johnson, 1988). According to Lindsay et al., this theory also implies that unusually vivid fantasy is likely to be misidentified as the memory of a real event (Lindsay, 2008). Consistently, several studies have reported that self-reported vividness of imagined words during reality-monitoring is associated with increased externalization bias (i.e., imagined words wrongly recognized as “heard” (Moseley et al., 2018; Sugimori et al., 2014). Finally, if source attributions are based on perceptual features associated with memories, source-monitoring may be compromised when sources are highly similar to one another. Johnson and her team introduced this idea in an early study in which participants were asked to hear an experimenter say certain words and imagine other words in their own or the experimenter’s voice. They observed that reality-monitoring was more accurate when individuals were asked to imagine words in their own voice than in the experimenter’s voice, although old/new recognition was similar in both conditions (Johnson, 1988).

According to the SMF, the strength of perceptual detail is not the only factor that determines whether an information comes from veridical perception. As the Dijkstra et al. suggest in their recent review, this is primarily demonstrated by the existence of hyperphantasia, i.e., extremely strong mental imagery, that is still experienced as mental imagery rather than veridical perception (Dijkstra et al., 2022). In this way, no difference in reality-monitoring is apparent when comparing groups scoring high or low on a measure of fantasy proneness (Aleman and de Haan, 2004). The key difference between perception and imagination is cognitive control: mental imagery can be voluntarily generated and is more proactive, whereas perception is triggered by the external appearance of stimuli and is more reactive. In an early study, Johnson and her team tested reality-monitoring using either free recall or cued recall. They demonstrated that the increase in response automaticity using cued recall reduced the accuracy of reality-monitoring compared to free recall, which requires more effort or search (Johnson et al., 1981).

Finally, it should be noted that Johnson et al. distinguished this systematic source identification based on perceptual/cognitive cues from the more reflective and strategic processes of source-monitoring. These processes tend to be more deliberate and involve retrieval of supporting memories: Does it seem plausible given what I know? (Johnson et al., 1993). In his book chapter on source-monitoring, D. Stephen Lindsay adds that strategic source-monitoring can also be engaged when the qualitative content of a memory contradicts the reality status implied by its quantitative features: *“A vivid memory of unaided flight, for example, might initially be classified as a memory of a real event by rapid, heuristic processes based on quantitative characteristics, but then be reclassified as a memory of a dream or fantasy based on the rememberer’s belief that people cannot fly”* (Lindsay, 2008)

1.2.2.4. Reality-monitoring alterations in schizophrenia

One of the most popular theories on hallucinations posits that patients with schizophrenia misattribute an external source to their internal cognitive events, such as mistaking inner speech for another person's actual voice (Waters et al., 2012). Supporting this view, numerous studies have argued that the raw material for AH is misattributed inner speech. Earlier studies using electromyography (EMG) have demonstrated subvocalization (i.e., myoelectric activity of the vocal musculature) when patients with schizophrenia experience AH (Gould, 1948; McGuigan, 1966; Rapin et al., 2013). Neuroimaging studies have shown that monitoring one's inner speech elicits activations in the primary and secondary auditory cortices (McGuire et al., 1996) and that AH elicits activations in similar brain regions (Jardri et al., 2011b).

- i) Patients with schizophrenia are more prone to confuse mental imagery with real events during a reality-monitoring task (i.e., externalization bias)*

A large body of research suggests that hallucinations arise from a reality-monitoring impairment. A recent qualitative review comparing 1566 patients with schizophrenia with 1175 healthy volunteers reported that source-monitoring performance on all measures (i.e., internal source-monitoring, reality-monitoring and external source-monitoring) is reduced in schizophrenia patients compared with healthy controls, even in the absence of recognition memory deficits. This difference was increased for tasks involving an internal/imagined stimulus source (i.e., internal source-monitoring and reality-monitoring tasks). In particular, the externalization bias of reality-monitoring was greater in patients with AH than in patients without AH (Damiani et al., 2022). The link between externalization bias and AH, both characterized by the misattribution of inner speech to an external source, is consistent with previous meta-analyses. Waters et al. demonstrated that patients with schizophrenia have poorer reality-monitoring accuracy than healthy controls and more pronounced impairment if they

exhibit AH (Waters et al., 2012). Brookwell et al. demonstrated that patients with AH specifically exhibit a pronounced externalization bias compared to healthy controls but do not make the opposite error (Brookwell et al., 2013). It is worth noting that delusions, another symptom characterized by a disturbance in the sense of self, has also been associated with abnormal reality-monitoring performance in patients with schizophrenia (Anselmetti et al., 2007; Keefe et al., 1999).

These results were replicated for the visual modality, suggesting that visual hallucinations (VH) are the result of internal mental images misattributed to external perceptions. Brébion et al. first studied visual reality-monitoring abilities in patients with schizophrenia exhibiting VH compared to patients without VH, using a task we described previously involving word/picture pairs (*see section 1.2.2.2*). These patients demonstrated a word superiority effect, and recognized words better than pictures. Patients with VH were also more likely to misattribute word stimuli to picture presentation. The authors suggested that these patients may suffer from excessive visual imagery, with visual mental images more abundant or vivid than those of other patients, and thus more easily confused with the images actually perceived (Brébion et al., 2008). Subsequent studies replicated this experiment in patients with schizophrenia exhibiting VH and non-clinical individuals with a propensity for VH. Both groups were more likely to misattribute words to pictures than vice versa (Aynsworth et al., 2017), and higher ratings of VH were associated with higher rates of false memories of non-presented pictures (Stephan-Otto et al., 2017a). Non-clinical individuals with high propensity for VH used visual imagery more frequently in their daily life, suggesting a direct link between excessive visual imagery and the propensity to misattribute internal visual images to external events in individuals exhibiting VH (Aynsworth et al., 2017).

Finally, in a recent study, we demonstrated that patients with schizophrenia displaying hallucination in two sensory modalities, i.e., auditory and visual, have a more pronounced impairment reality-monitoring than patients with hallucinations only in the auditory modality (*see appendix 3*, (Mondino et al., 2019)). In the context of the SMF, one can suggest that patients with multimodal hallucinations exhibit a more severe externalization bias due to the increased perceptual detail associated with the imagined event, which may lead to greater confusion when identifying the source of this information.

Questioning the association between reality-monitoring and hallucinations

It has been suggested that the externalization bias of reality-monitoring represents a trait marker of hallucinations. In this line, Brookwell et al. demonstrated that patients with schizophrenia with hallucinations and nonclinical individuals with hallucination-proneness have a similar externalization bias compared to healthy controls (Brookwell et al., 2013). In addition, non-psychotic alcoholic patients with a history of at least one episode of hallucinations have a worse externalization bias than patients without hallucinations and healthy controls (Gawęda et al., 2014).

While a similar link between reality-monitoring and hallucinations has been suggested in the general population (e.g., Brookwell et al., 2013; Larøi et al., 2004), recent studies have provided evidence for the absence of such an association. In a multisite study including 1375 healthy volunteers, Moseley et al. (Moseley et al., 2021) reported no significant correlation between the externalization bias and Cardiff Anomalous Perception Scale (CAPS) score and Launay-Slade Hallucination Scale-Extended (LSHS-E) (*see* (Alderson-Day et al., 2019) for similar results). When compared to a group of non-hallucination-prone participants, healthy individuals with hallucination-proneness do not appear to exhibit a deficit of source-monitoring (i.e., reality-

monitoring externalization bias or atypical internal source-monitoring performance) (Garrison et al., 2017c). One possible interpretation is that reality-monitoring would be a marker of the clinical significance of hallucination and that there is a discontinuity between clinical and nonclinical hallucination experiences.

ii) The presence of hallucinations is associated with increased vividness of mental imagery

According to the SMF, the more vivid the mental imagery, the more it will resemble an externally based perception in terms of sensory characteristics. Internally generated experiences that are too vivid could then lead patients to confuse them with perceived events and cause hallucinations. In summary, this theory postulates that i) the presence of hallucinations is associated with increased vividness of mental imagery in patients with schizophrenia, ii) these patients are more prone to confuse mental imagery with real events during a reality-monitoring task (i.e., externalization bias).

There is a long tradition of studying the relationship between hallucinations and vividness of mental imagery in patients with schizophrenia. In 1972, an initial study demonstrated that the presence of AH in schizophrenia is associated with high vividness of auditory imagery (Mintz and Alpert, 1972). These findings have been replicated multiple times, both for the relationship between AH and auditory imagery and for the relationship between VH and visual imagery (e.g., (Aleman et al., 2003; Böcker et al., 2000; Sack et al., 2005). Similar results have been reported in other neuropsychiatric diseases characterized by the presence of VH such as Alzheimer's disease (El Haj et al., 2019), in non-clinical individuals with hallucination-proneness (van de Ven and Merckelbach, 2003) and in individuals at high genetic risk for schizophrenia (Oertel et al., 2009).

Accordingly, both hallucinations and vivid mental imagery are associated with activations in modality-specific cortices. A large corpus of neuroimaging studies has demonstrated that hallucinations are the result of aberrant perception generated by hyperactive sensory brain areas, such as the superior temporal gyrus for auditory hallucinations (*see Figure 12*) (Jardri et al., 2011b) and the visual cortices for visual hallucinations (Allen et al., 2008; Zmigrod et al., 2016). The same sensory regions are also activated during vivid auditory and visual imagery (Zvyagintsev et al., 2013). A functional imaging study comparing brain activity during AH and auditory imagery revealed similar activations in the left hemisphere frontotemporal language areas and their contralateral homologues, as well as in the supplementary motor area (SMA). The distinction between AH and auditory imagery was primarily observed with respect of the relative timing of activation in prefrontal and sensory areas: activity in the SMA preceded activity in the auditory areas during imagery, whereas these activities occurred simultaneously during AH. The authors suggested that this difference may represent the lack of voluntary control in AH compared with mental imagery (Linden et al., 2011).

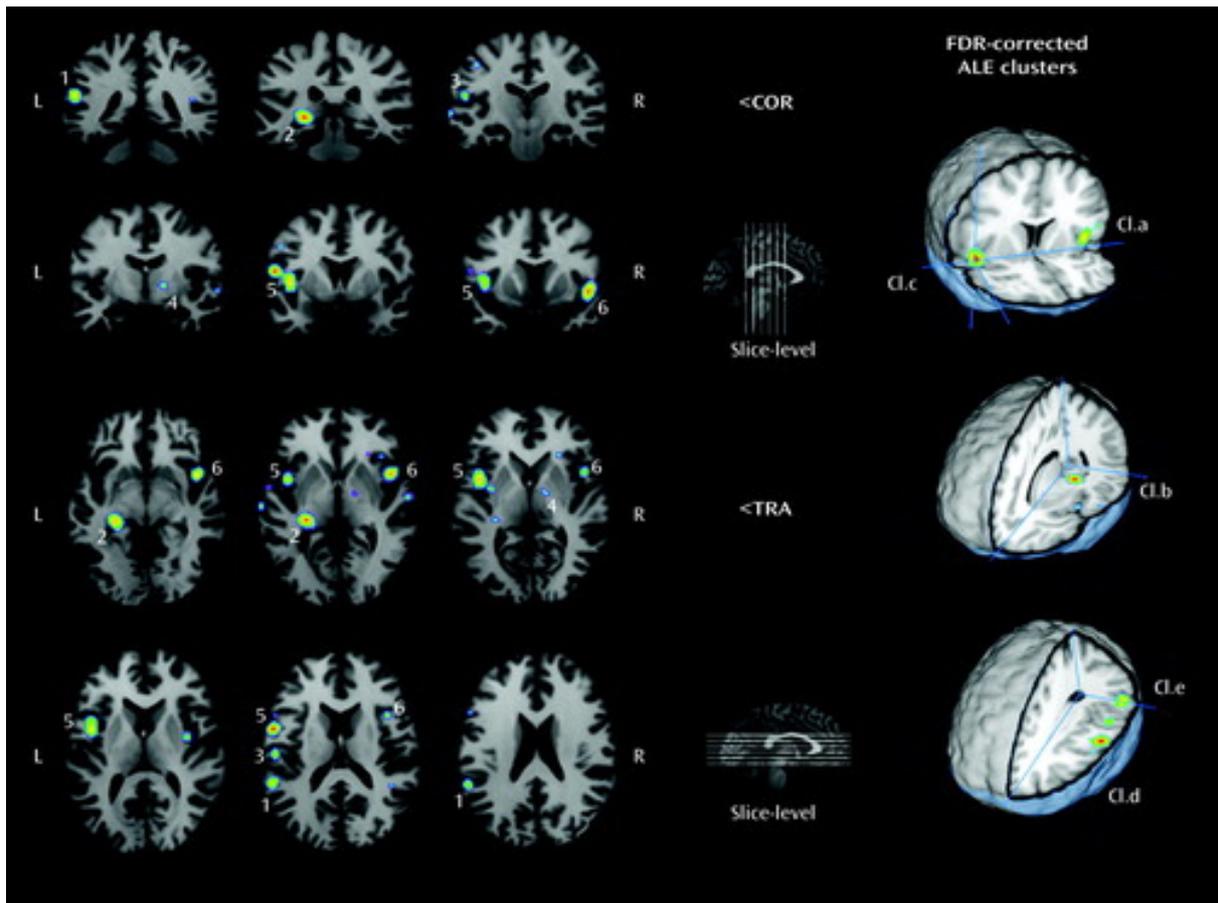


Figure 12 from Jardri et al (Jardri et al., 2011b). Results of a neuroimaging meta-analysis measuring function brain activity associated with auditory hallucinations in patients with schizophrenia. Greater likelihoods were measured within the left inferior parietal lobule, left hippocampus/parahippocampal region, left superior temporal gyrus, Globus pallidum, Broca's convolution, right anterior insula, and frontal operculum.

1.2.2.5. Reality-monitoring seems intrinsically tied with another cognitive process called self-agency

How might reality-monitoring impairment be involved in the generation of hallucinations? Reality-monitoring is defined as the ability to remember the source of encoded information, but the cognitive operations involved in monitoring the origin information might overlap with those that monitor the origin of information in real-time (Woodward and Menon, 2013). Reality monitoring seems intrinsically tied to self-monitoring, i.e., the ability to distinguish self-generated actions or thoughts from those generated by others, and more broadly to the concept

of self-agency, i.e., the experience of being the agent of one's action or thought and the feeling that self-productions are intentional and associated with a cognitive experience of voluntary control (Haggard, 2017). In a recent study, Subramaniam et al. (Subramaniam et al., 2018) showed correlated performances between reality-monitoring and verbal self-monitoring in healthy individuals, suggesting a unitary process to govern these two paradigms.

Paradigms

Experimental self-agency or self-monitoring tasks involve subjects performing a verbal or motor task while receiving congruent or incongruent (i.e., distorted or externally generated) online feedback. In the typical self-monitoring paradigm, participants are asked to perform a movement with a device while watching visual feedback on a screen. The visual feedback is either their own movement, their distorted own movement, or the movement of another person. Participants are then asked to indicate the origin of the feedback (i.e., "self", "distorted", "experimenter", see *Figure 13*) (Uhlmann et al., 2020). An example of a verbal self-monitoring task is one used by Sapara et al. in which participants were presented with single words on a computer screen and had to read the word aloud while hearing online feedback of their speech. The verbal feedback was their own voice, their distorted own voice, the voice of another person, or another person's distorted voice. Participants were asked to indicate the origin of the feedback (i.e., self, self-distorted, other, other-distorted) by pressing a button box (Sapara et al., 2015). Verbal self-monitoring tasks can also be implicit when participants are not required to explicitly indicate the origin of the feedback. During implicit verbal self-monitoring, participants are asked to phonate a vowel to a microphone while listening to real-time audio feedback via headphones (*see Figure 14*). On each trial, the onset of speech triggers a brief perturbation of the pitch of the auditory feedback. The perturbations shift the pitch of the auditory feedback by either $1/3^{\text{rd}}$ octave (i.e., maximal distortion) or $1/12^{\text{th}}$ octave (i.e., minimal

distortion). In this context, minimal perturbations are expected to yield small mismatch between internal predictions and auditory feedback. These small mismatches are within the range of variation expected during normal speech production and are interpreted as self-generated. In response, participants are expected to raise their voices to partially compensate for the effects of the perturbation. By contrast, larger pitch perturbations are thought to be interpreted as non-self-generated, warranting corrective responses (Sapara et al., 2015; Subramaniam et al., 2018).

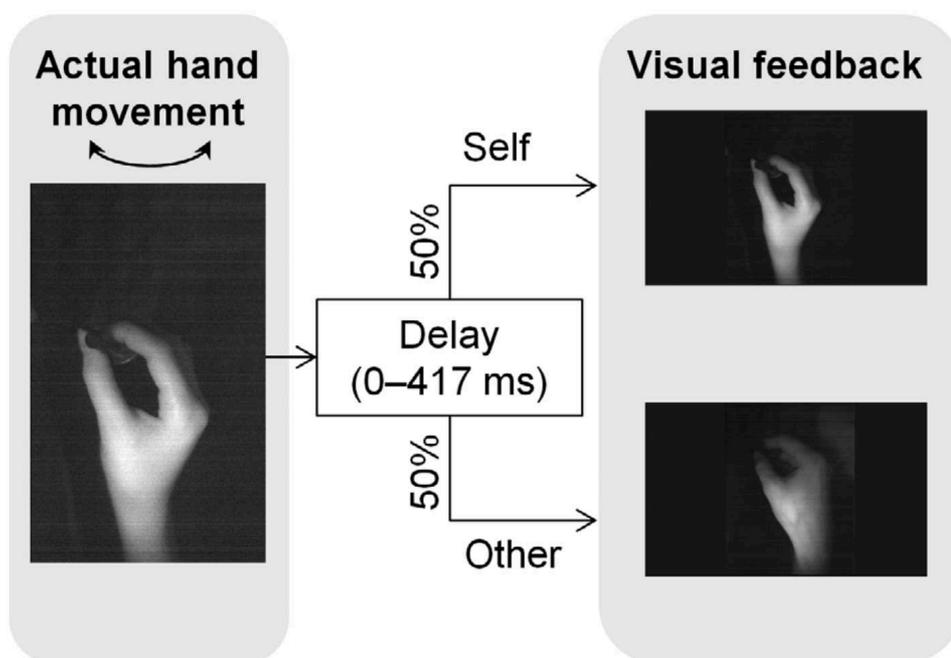


Figure 13 from Uhlmann et al. (Uhlmann et al., 2020). *Explicit motor self-agency task*. The participant's own hand or someone else's hand was displayed. Movements could either be generated by the participant ("active" condition) or by the device using air pressure ("passive" condition). Videos were either presented in real time or delayed. Subsequently, a question ("Delay?") appeared on the screen, indicating that participants could now report whether they detected a delay or not.

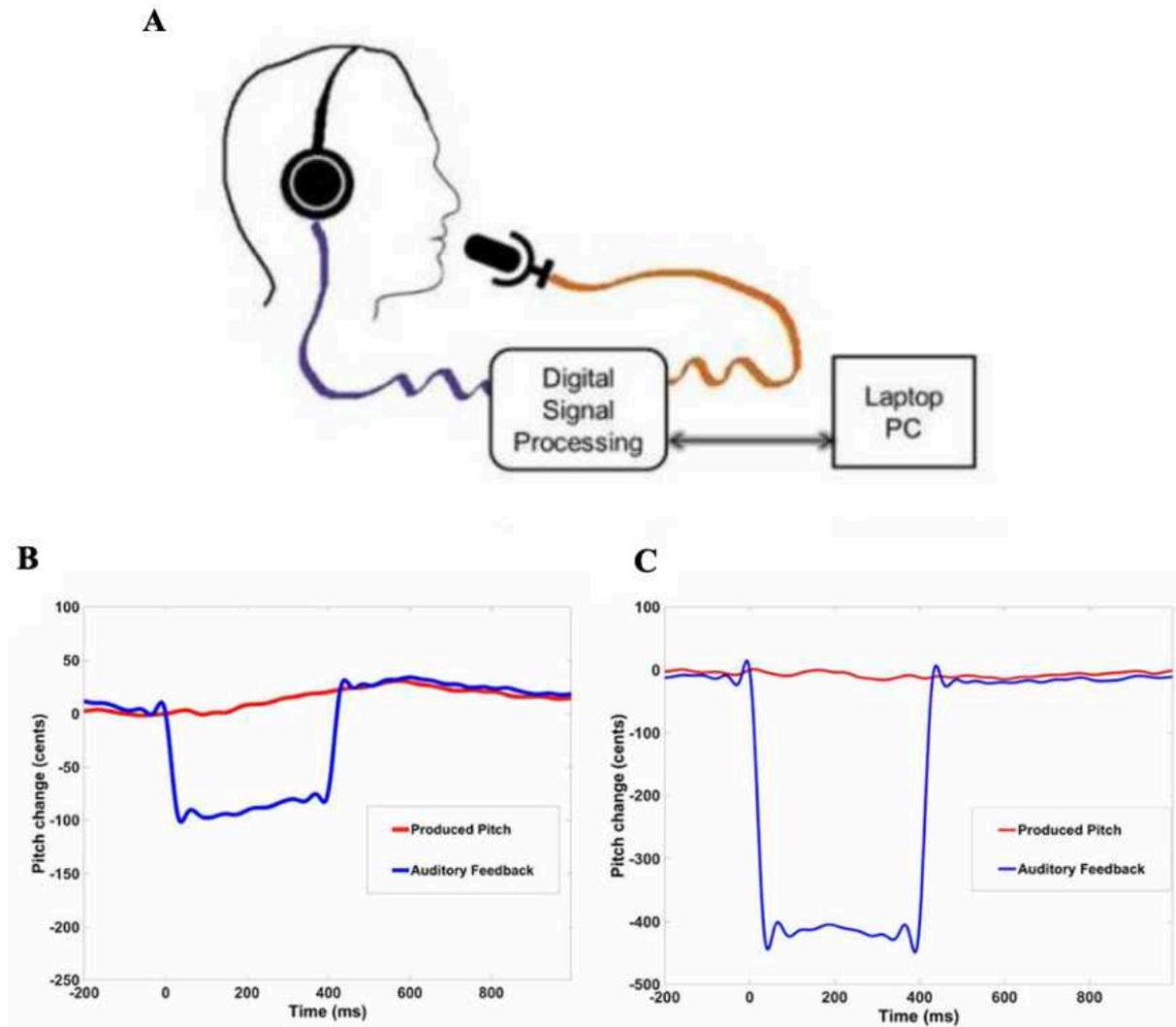


Figure 14 from Ranasingh et al. (Ranasinghe et al., 2017) and Subramaniam et al. (Subramaniam et al., 2018). *Implicit verbal self-agency task*. (A) Diagram of the pitch-perturbation apparatus. A digital signal processing method was used to shift the pitch of participants' vocalizations (orange line) and delivered this auditory feedback (purple line) to participants' earphones. In each trial, participants phonated the vowel /a/ to a microphone while listening to the real-time audio feedback via headphones. In each trial, onset of speech triggered a brief perturbation of the pitch of the auditory feedback. This perturbed auditory feedback is conveyed to auditory areas in the central nervous system, where it is mismatched with the motor-derived predictions. This mismatch gives rise to a feedback prediction error which then modulates the ongoing speech output to compensate for the perturbation. The pitch-perturbation experiment consisted of two successive 74-trial sessions. (B) and (C) Perturbations shifted the pitch of auditory feedback upwards or downwards by 100 cents (1/12th of an octave) for 400ms and occurred with a randomly jittered delay (200–500ms) from the vocalization onset. (B) In

response of the 100 cents' perturbation, the participant raised his/her pitch to partly compensate for the effects of the perturbation.

Forward model

A key difference between self-generated and other-generated stimuli is that the former are predictable and controllable while the latter are not. According to the forward model (*see Figure 15*), when a self-production is intended/prepared (including actions, vocalizations and subvocalizations during speech or inner speech), a copy of the motor command, the efference copy is generated to build a prediction about the sensory consequences of the forthcoming action. This sensory prediction is compared to the actual sensory feedback. A match results in the dampening of the sensory feedback and the experience of self-agency. An example of such a sensory attenuation is the phenomenon that people cannot tickle themselves. A mismatch between sensory feedback and model prediction when the stimulus is externally generated would lead to an increase of the level of sensory discrepancy between predicted and actual sensory feedback. The amount of possible attenuation would consequently decrease and an error signal is assumed to update the forward model (Blakemore and Frith, 2003; Frith, 2002; Jones and Fernyhough, 2007). The experience of self-agency is described as an approximation, resulting from continuous update of the forward model and leading to compensatory corrective responses when inaccuracies are detected between predicted and actual sensory feedback (Franken et al., 2018; Subramaniam et al., 2018). Early evidence for the forward model comes from studies of monkeys in which auditory cortex activity is inhibited during vocalizations (Eliades and Wang, 2003; Müller-Preuss and Ploog, 1981). Using a speech-feedback self-monitoring paradigm, Heinks-Maldonado et al. demonstrated that subjects' unaltered voice feedback elicited a dampened auditory N100 relative to the N100 elicited by altered or alien auditory feedback. This is consistent with the forward model modulation of the auditory cortical response to self-generated speech (Heinks-Maldonado et al., 2005).

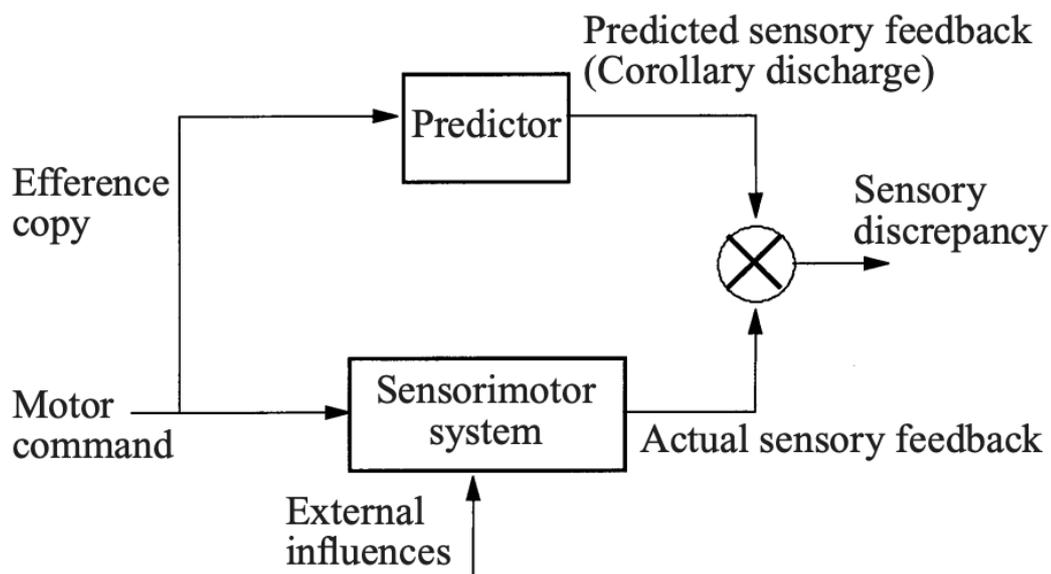


Figure 15, from Blakemore et al. (Blakemore et al., 2000). Model for predicting the sensory consequences of a movement. An internal forward model makes predictions of the sensory feedback based on the motor commands. These sensory predictions are then compared to the actual sensory feedback. The lower the sensory discrepancy resulting from this comparison the greater is the attenuation of the sensory feedback. When the tactile stimulation is self-produced, the model correctly predicts the sensory consequences of the movement so no sensory discrepancy ensues between the predicted and actual sensory information. In this case the motor command can be used to attenuate the sensation on the left palm.

Alterations of self-agency in schizophrenia

Interestingly, in patients with schizophrenia with auditory hallucinations and passivity phenomena, self-generated stimuli can be experienced in the same way than externally-generated stimuli. Whereas healthy controls experience self-generated tactile stimuli as less intense and tickly than externally-derived stimuli, these patients show no difference of perceptual rating between tactile stimuli produced by themselves and those produced by the experimenter. In accordance with the forward model, these findings suggest that auditory hallucinations and passivity experiences in schizophrenia are associated with a lack of attenuation of the sensory feedback of their own movements (Blakemore et al., 2000). Using a

speech-feedback paradigm where voices are pitch-shifted during speaking or substituted by an alien voice, Johns et al. demonstrated impaired self-monitoring in patients with schizophrenia with and without AH and a specific tendency to misattribute their distorted voice to someone else in patients exhibiting AH (Ford and Mathalon, 2004; Johns et al., 2001).

Transmission of the corollary discharge to the auditory cortex was assumed to downregulate its response to self-generated speech, inducing a dampening of the N100 event-related potential (ERP). In this way, the N100 triggered by spoken vowels is smaller than the N100 elicited by played-back vowels in healthy subjects. This reduction in the N100 triggered by spoken vowels is not observed in patients with schizophrenia (Ford et al., 2001). Magnetoencephalography indicates that the N100 ERP component originates from the auditory cortex (Krumbholz et al., 2003). Using a speech-feedback paradigm, Heinks-Maldonado et al. observed that the N100 triggered by unaltered self-voice feedback is dampen relative to the N100 triggered by altered auditory feedback in healthy individuals. The authors did not observe this pattern in patients with AH and this inaccuracy correlated with hallucinations and the percentage of misattribution errors. This failure of the N100 to distinguish between self and distorted or “alien” feedback may reflect dysfunction of the efference copy system in these patients (Heinks-Maldonado et al., 2007). According to this theory, an abnormal efference copy / corollary discharge mechanism would lead patients to fail to distinguish between their own thoughts and externally-generated voices, resulting in AH (*see Figure 16*) (Ford and Mathalon, 2005). A defect in self-monitoring has also been reported in ARMS individuals who have more difficulty than controls in identifying the source of the verbal auditory feedback when their speech is distorted (Johns et al., 2010).

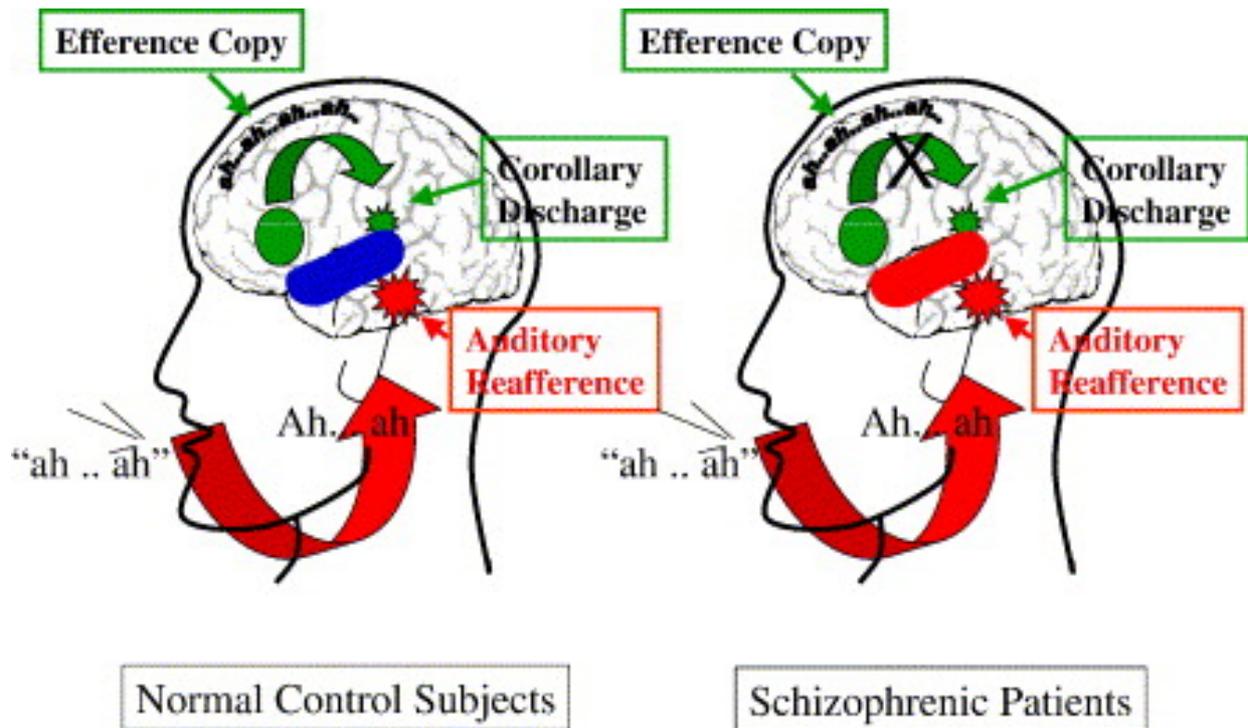


Figure 16, from Ford et Mathalon (Ford and Mathalon, 2005). Normal efference copy/corollary discharge mechanism during talking (in the left) and its possible dysfunction in schizophrenia (in the right). The plan to speak originates in the frontal lobes and is shown as a green circle near Broca's area. It sends an efference copy (green ribbon) of the thought or planned sounds to the auditory cortex where it becomes a corollary discharge (green splash). At the same time, talking is initiated and the speech sounds arrive (red ribbon) at auditory cortex as the auditory reafferent (red splash). If the corollary discharge matches the auditory reafferent the sensory experience is cancelled or reduced in its impact. The auditory cortex is colored blue (left) to represent normal suppressed responsiveness to the self-produced sound when it matches the corollary discharge. Patients with schizophrenia (right) have impaired efference copy mechanism thus the activity of auditory cortex is not suppressed during talking.

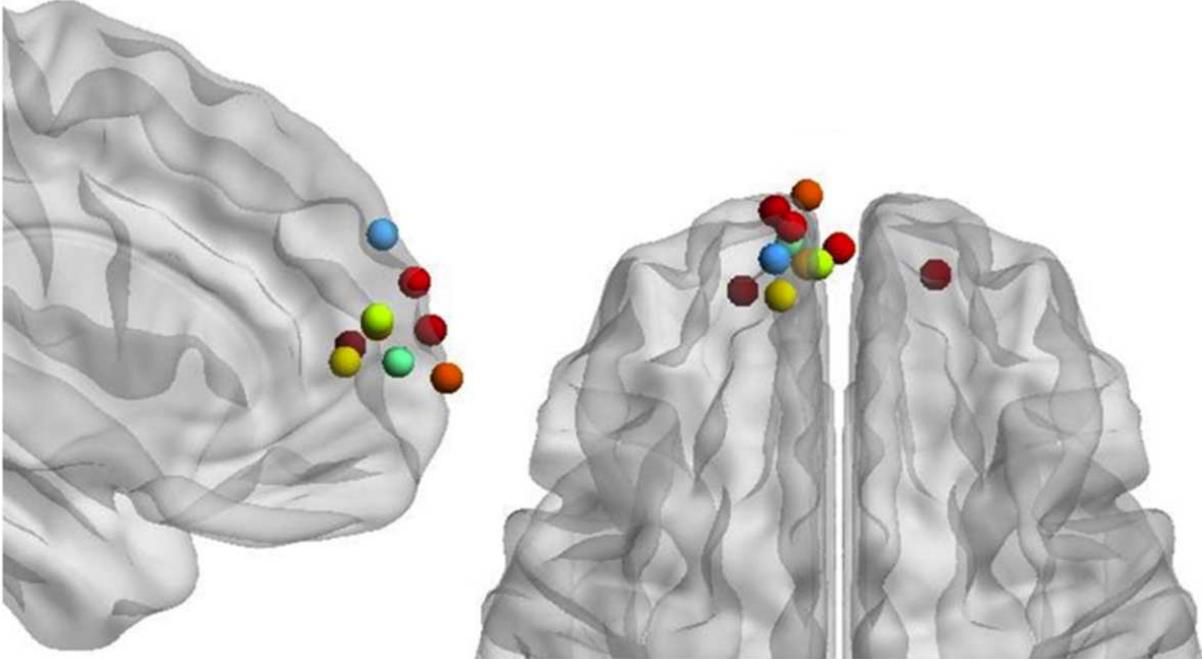
1.2.3. Neurobiological substrates of reality-monitoring

1.2.3.1. *In healthy individuals*

Prefrontal cortex

A qualitative review of imaging studies has highlighted the crucial role of the medial prefrontal cortex (mPFC) and especially its anterior part (amPFC) in distinguishing between the imagined and perceived origin of information (*see Figure 17, Figure 18*) (Simons et al., 2017). Activity in this area (also known as *Brodman Area 10 – BA 10, fronto-polar cortex, rostral prefrontal cortex or ventromedial prefrontal cortex*), located in the anterior part of the medial prefrontal cortex, was observed regardless of the type of stimulus, including verbal items but also pictures and actions (Brandt et al., 2014; Dobbins and Wagner, 2005; Kensinger and Schacter, 2006; Simons et al., 2005b, 2005a). For example, Simons et al. demonstrated that amPFC activation is significantly greater when recalling whether stimuli were perceived or imagined than when recalling the stimulus position (Simons et al., 2006). Furthermore, a causal role has also been established by noninvasive brain stimulation studies that targeted the amPFC to improve reality-performance (Mammarella et al., 2017; Subramaniam et al., 2020). In the same line, using real-time neurofeedback to self-regulate activity in the mPFC, Garrison et al. reported a trend of improved recall of imagined items during reality-monitoring (Garrison et al., 2021). Such a relationship between activity in the mPFC and reality-monitoring is highly consistent with previous studies demonstrating the involvement of the mPFC in discriminating between internal and external aspects of context. For instance, this region is more sensitive to memory of the cognitive operations performed to process the initial stimuli rather than memory of the spatial position of the item (Simons et al., 2005b) or the time at which the item was previously presented (Simons et al., 2005a). It is worth noting that the mPFC is one of the core regions of the DMN, which is more active when the brain is at rest and during internally-directed and self-referential processing (Davey et al., 2016; Qin and Northoff, 2011). An amPFC-based functional network including DMN brain regions such as the middle and superior temporal gyri, the lateral parietal regions and the precuneus, was characterized by deactivations during external source-monitoring (i.e., a non-self-referential source-monitoring task involving

distinguishing between different external sources). These deactivations were found to decrease during reality-monitoring, resulting in higher activity in this network (Metzak et al., 2015).



Trends in Cognitive Sciences

Figure 17 from Simons et al. (Simons et al., 2017). Locations of medial anterior prefrontal cortex activity reported by 12 fMRI studies of reality-monitoring in healthy volunteers.

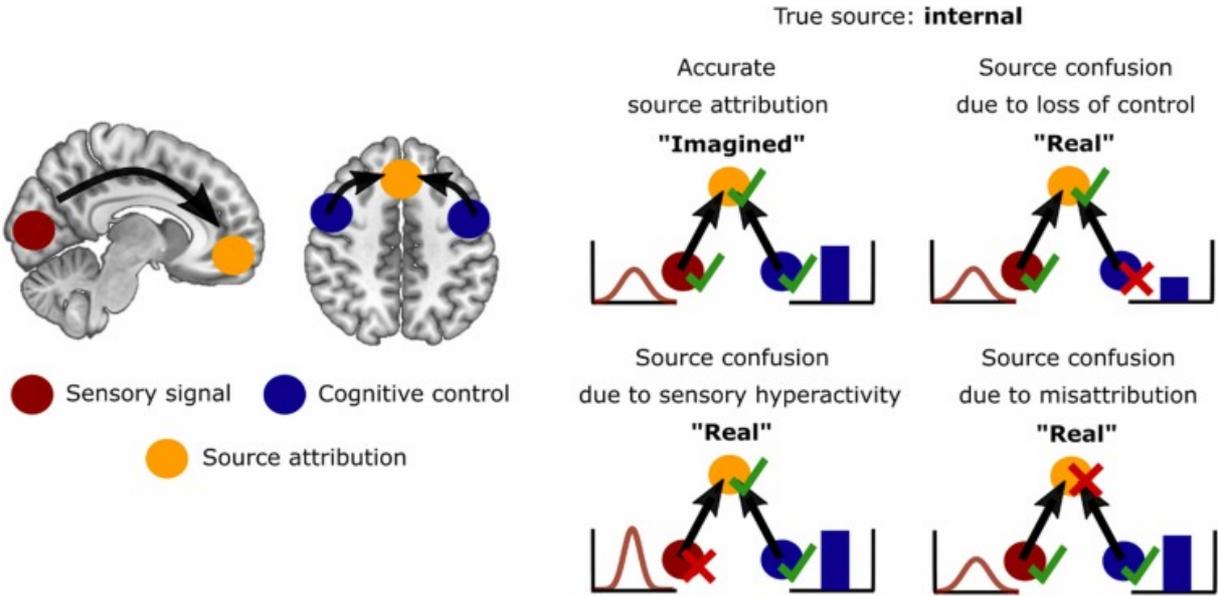


Figure 18 from (Dijkstra et al., 2022). Potential neural mechanisms for perceptual reality-monitoring. The anterior medial prefrontal cortex (amPFC; yellow circle) evaluates sensory (red circle) and cognitive control (blue circles) aspects of perception and imagination in order to make a source attribution. For accurate source attribution, the neural basis of first-order perceptual and cognitive processes that distinguish perception and imagination, and the workings of a second-order source attribution process, should both be intact. Source confusions can therefore arise from different combinations of deficits as illustrated by the examples on the right.

Any interpretation of the amPFC as the only key structure for reality-monitoring must be cautious because most of the studies included in the qualitative review by Simons et al. reported results that were bound to the scope of an a priori region of interest (ROI) in the amPFC. In a recent study, Mondino et al. (Mondino et al., 2016) used transcranial Direct Current Stimulation to investigate the role of left temporo-parietal (TPJ) and prefrontal regions in source-monitoring. Participants received either anodal (excitatory) stimulation over the left TPJ or cathodal (inhibitory) stimulation over the left PFC during the encoding and testing phases of source-monitoring tasks. The authors demonstrated that active tDCS over the left TPJ increased the externalization bias in reality-monitoring but did not modulate internal source-monitoring. Active tDCS over the left PFC did not modulate performances in either task. These findings do not support the contribution of the left PFC in reality-monitoring but highlighted the role of the left TPJ. A likely explanation for the lack of effect in the left PFC is the placement of the electrode between F3 and FP1, which does not modulate the anterior medial part of the PFC but the DLPFC. With respect to the involvement of the left TPJ, these results are highly consistent with the SMF, and suggest that hyperactivation of sensory brain areas, such as the auditory cortex, during reality-monitoring might unbalance the internal vs. external reality-monitoring discrimination in favor of a “perceived” source. Studies using self-monitoring paradigms have also demonstrated the consistent involvement of the left TPJ in self-agency

(Seghezzi et al., 2019; Sperduti et al., 2011). Finally, these results are also consistent with the forward model and may indicate that hyperactivation of auditory cortex during the encoding stage of reality-monitoring would counteract the sensory dampening associated with inner speech, leading to subsequent misattribution to an external source. To better understand the effect of the left TPJ stimulation, another study used a frontotemporal montage with cathodal stimulation over the amPFC (under electrode FP2) and anodal stimulation over the left superior temporal gyrus (electrode CP5) either during the encoding stage or the retrieval stage of reality-monitoring. They reported no significant effect of active tDCS compared to sham in either experiment and Bayesian analyses provided evidence for the null hypothesis (Moseley et al., 2018).

Studies on the functional substrates of non-verbal reality-monitoring have supported the involvement of mental imagery in this process. For example, an early study combined fMRI with a visual reality-monitoring task in which participants were presented with either words and corresponding pictures or had to visually imagine the corresponding objects (Gonsalves et al., 2004). The authors reported that the brain areas engaged in visual imagery such as the precuneus, the right inferior parietal cortex and the anterior cingulate are hyperactivated for words leading to subsequent false memories compared with words leading to later correct rejections. Supporting to the visual imagery hypothesis, words leading to false memories had significantly higher “concreteness” ratings than those leading to subsequent correct rejections.

1.2.3.2. In schizophrenia patients

Functional substrates

Early studies established the relationship between reduced activation in the amPFC and scores on scales measuring proneness to psychosis and schizotypal traits in healthy volunteers (Lagioia

et al., 2011; Simons et al., 2008). These findings demonstrated for the first time that individual variability in reality-monitoring ability and associated amPFC responses can be predicted by proneness to experience psychosis symptoms. Several studies have examined the neural correlates of impaired reality-monitoring in schizophrenia, reporting that these patients exhibit decreased amPFC activity during source retrieval of imagined items compared to externally-derived ones (Garrison et al., 2017b; Subramaniam et al., 2012; Vinogradov et al., 2008). Supporting the relationship, Subramaniam's study also suggested that cognitive training could increase amPFC activity with a significant relationship between the level of amPFC activation and task performance (Subramaniam et al., 2012).

Numerous studies have specifically explored the functional bases of impaired reality-monitoring in patients with hallucinations with the hypothesis of altered activity and connectivity between amPFC and sensory processing areas. Thus, Mondino et al. applied tDCS with a cathode over the left TPJ and an anode over the left PFC in patients with schizophrenia with resistant AH. They demonstrated that stimulation of frontotemporal regions alleviated both hallucinations and reality-monitoring performance (Mondino et al., 2015). Accordingly, an fMRI study in healthy individuals reported that increased activation of the auditory cortex during the encoding stage of reality-monitoring, with a significant correlation with hallucination-proneness (Sugimori et al., 2014). Recent studies have reported similar results in other sensory modalities. Patients with schizophrenia with VH were administered a visual reality-monitoring task whilst undergoing an fMRI protocol. When encoding words that they later misattributed to pictures, patients with VH differentially activated the right fusiform gyrus, the same area of the visual cortex that is activated when patients and healthy controls were presented with picture stimuli. These results suggest that label presentation results in the same brain activation as the presentation of pictures in these patients, such that they would

spontaneously use excessive visual imagery during word presentation and misattribute the source during the test stage (Stephan-Otto et al., 2017a).

Structural substrates

While the relationship between brain morphometry and function remains unclear, the functional involvement of the amPFC is supported by structural studies focusing on the paracingulate sulcus (PCS). The PCS is a tertiary sulcus that lies in the medial wall of the PFC and runs dorsal and parallel to the cingulate sulcus in a rostro-caudal direction (*see Figure 19*). The PCS is characterized by high interindividual and interhemispheric variability in the general population, including its fragmentation and absence. As mentioned above, morphometric features of the PCS have been associated with the presence of hallucinations in schizophrenia. In healthy individuals, reduced length of the paracingulate sulcus (PCS), a tertiary sulcus surrounding the ACC, is associated with reduced reality-monitoring performance (Buda et al., 2011; Fornito et al., 2008). In a recent study including 35 patients with schizophrenia with AH, we demonstrated a significant positive correlation between the right PCS length and reality-monitoring accuracy and a negative correlation with the externalization bias (*see appendix 4*, (Perret et al., 2021)). Lower cortical folding in the PCS has been associated with the experience of hallucinations in patients with schizophrenia (Garrison et al., 2015; Rollins et al., 2020).

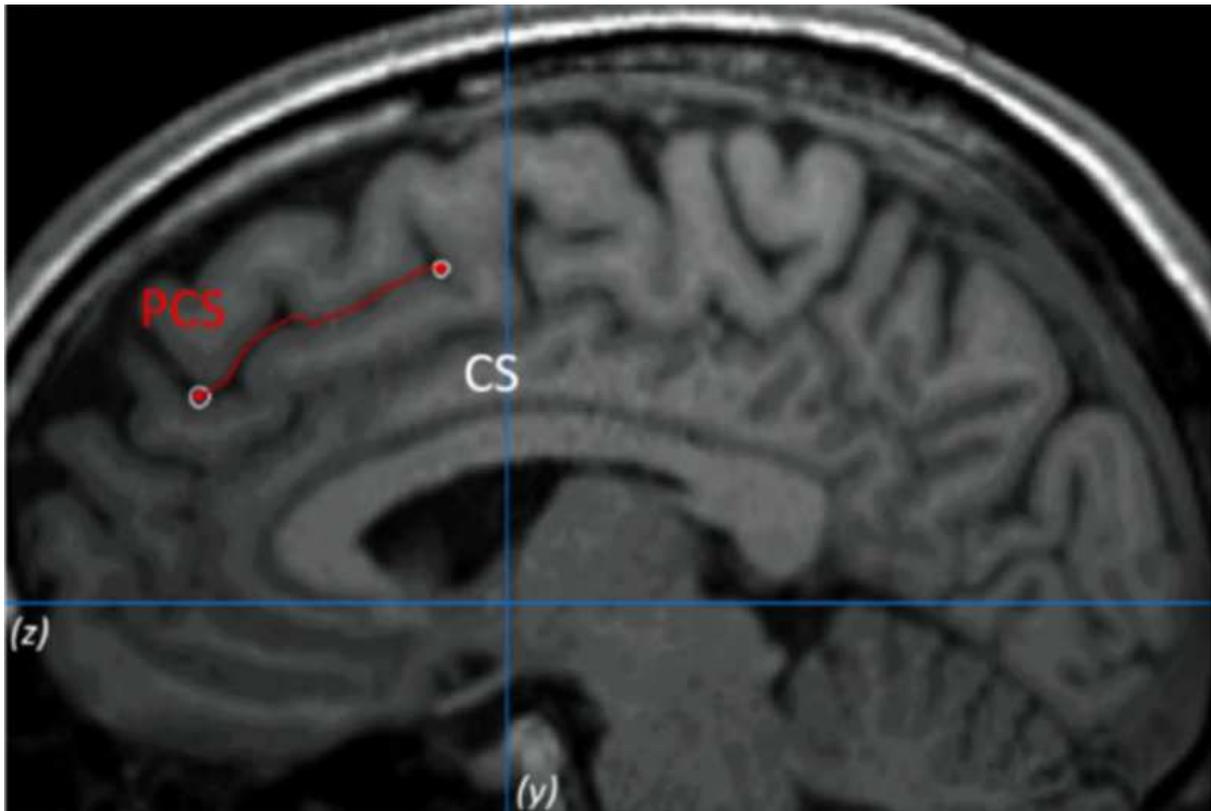


Figure 19, from Perret et al. (Perret et al., 2021). Example of the paracingulate sulcus (PCS) measurement on anatomical magnetic resonance imaging. The PCS is marked in red line and lies dorsal and parallel to the cingulate sulcus. Measurement was performed within the first quadrant (defined by $z < 0$ and $y > 0$) and on the fourth sagittal slice for both hemispheres.

SUMMARY

Reality-monitoring is the cognitive process by which an individual is able to distinguish between memories of events that actually occurred and those that were imagined. According to the SMF, the origin of memories is inferred based on the balance between “internal” and “external” cues established during memory acquisition. Thus, veridical perceptions are associated with more perceptual detail while imagined information are associated with traces indicating internally-generated cognitive information. Impaired reality-monitoring is observed in schizophrenia, especially in patients with hallucinations. These patients exhibit an externalization bias, i.e., a misattribution of an external source to their internal cognitive events.

Reality-monitoring is intrinsically tied to self-monitoring, i.e., the ability to distinguish in real-time self-generated actions and thoughts from those generated by the others. In healthy individuals, reality-monitoring and self-monitoring performances are correlated. In the context of self-monitoring, a forward model compare an individual’s predicted performance with actual performance. A match results in the dampening of the sensory feedback and the experience of self-agency. A mismatch results in an error signal leading to update and corrective response. Schizophrenia has also been associated with altered self-monitoring.

Neuroimaging and NIBS studies revealed the key role of the amPFC in reality-monitoring. In patients with schizophrenia, impaired reality-monitoring is associated with altered activity and connectivity of the amPFC and variability of the PCS, a sulcus that lies in the medial wall of the mPFC.

1.3. Thesis statement and specific aims

Reality-monitoring is a type of source-monitoring and characterizes the cognitive process by which an individual is able to distinguish memories of events that actually occurred from those that were imagined. Reality-monitoring has been linked to the source-monitoring framework, which posits that the origin of memories is inferred on the basis of the balance between cognitive cues produced during self-generation of information and sensory details associated with actual perception in the environment. Reality-monitoring is impaired in schizophrenia, especially in patients with hallucinations, who are more likely to misattribute internally-generated information to an external source, i.e., externalization bias. Reality-monitoring is also intrinsically tied to another process called self-agency, which characterizes the ability to monitor the self/other origin of information in real-time. Self-agency has previously been associated with the feed-forward model, whereby comparing predictions with the actual consequences of one's actions or speech leads to sensory dampening and a sense that information is self-generated.

The main goal of this thesis is to better understand impaired reality-monitoring in schizophrenia. To do so, we explored the specificity of impaired reality-monitoring in different clinical and nonclinical populations. We also investigated the functional bases of reality-monitoring in healthy individuals and patients with schizophrenia. In this work, we placed great emphasis on the cognitive models that have been proposed to underlie reality-monitoring. To this end, we considered reality-monitoring as a component of source-monitoring, and compared this performance with that of internal source-monitoring. We also proposed several studies that include assessments of both reality-monitoring and self-agency performances. In this way, we have argued for a reconciliation between the source-monitoring framework and the forward model and for establishing continuity between these two models.

1.3.1. Reality-monitoring deficits: a transdiagnostic approach

The extent to which impaired reality monitoring is specific to patients with schizophrenia compared to those with other neuropsychiatric illnesses remains unclear. To better understand the specificity of reality-monitoring abnormalities, we first compared source-monitoring, i.e., reality-monitoring and internal source-monitoring, between schizophrenia and obsessive-compulsive disorder (OCD), a neuropsychiatric disease sharing a phenomenological overlap with schizophrenia. The immediate perspectives of this first chapter are a larger transnosographic study that additionally recruits patients with various neuropsychiatric diseases that have clinical overlap with schizophrenia. The source-monitoring performance of these patients is evaluated for comparison with a group of patients with schizophrenia.

1.3.2. Reality-monitoring deficits across the psychosis continuum

We also sought to describe the specificity of impaired reality-monitoring across the continuum of psychosis, i.e., in individuals with an at-risk state for psychosis and in healthy individuals with hallucination-proneness. Based on previous meta-analyses demonstrating that patients with schizophrenia exhibit both impaired reality-monitoring and self-agency (Waters et al., 2012), we also sought to determine whether populations across the continuum share impairments in both of these self-recognition paradigms. To this end, we conducted a meta-analysis comparing self-recognition between individuals on the continuum of psychosis without a full-blown diagnosis of schizophrenia and healthy controls.

1.3.3. Examining the neural substrates of reality-monitoring

The neurobiological substrates of reality-monitoring in healthy individuals and patients with schizophrenia are also unclear. We adopted a meta-analytic approach to identify the functional areas that are involved during the internal vs. external recognition of the source of memories. Based on the similar impairment of reality-monitoring and self-agency in patients with schizophrenia (Waters et al., 2012) and the correlation between reality-monitoring and self-agency performances in healthy individuals (Subramaniam et al., 2018), we also investigated the functional bases of self-agency and expected an overlap between the brain areas involved in these two processes. We discussed the results in an attempt to reconcile the source-monitoring framework and the feed forward model. The immediate perspectives of this third chapter include a large-scale study assessing source-monitoring (i.e., reality-monitoring and internal source-monitoring) in patients with schizophrenia. In this manuscript, we present the method that was used to map source-monitoring performance to the clinical characteristics of these patients and their functional and structural brain connectivity from various neuroimaging acquisitions.

2. First Chapter: A transdiagnostic approach of reality-monitoring

2.1. Introduction

Source-monitoring impairments have been repeatedly identified in patients with schizophrenia. A recent review highlighted that patients with schizophrenia are particularly impaired in source-monitoring tasks involving an internal/imagined source, i.e., reality-monitoring and internal source-monitoring (Damiani et al., 2022). Whereas reality-monitoring characterizes the ability to distinguish between internal and external sources, internal source-monitoring characterizes the ability to distinguish between two internal sources, e.g., between imagined and performed stimuli. While externalization bias during reality-monitoring has been specifically associated with hallucinations, internal source-monitoring could be a general marker of abnormal self-experiences. Thus, internal source-monitoring would be impaired in other neuropsychiatric diseases sharing phenomenological overlap with schizophrenia.

To better understand the specificity of source-monitoring impairments, we investigated source-monitoring in another psychiatric disease associated with abnormal experiences of the self, called OCD. The first study is a qualitative review of source-monitoring processes in OCD. The second study is an experimental study comparing source-monitoring performance between patients with schizophrenia, patients with OCD and healthy controls.

2.2. Review of source-monitoring processes in obsessive-compulsive disorder [Article 1]

Article 1: Review of source-monitoring processes in obsessive-compulsive disorder. 2020.

World Journal of Psychiatry. Lavallé L., Brunelin J., Bation R., Mondino M.

TAKE HOME MESSAGE

- **Symptoms of obsessive-compulsive disorder (OCD) have been proposed as resulting from a source-monitoring failure.**
- **This study provides a review of the literature examining the relationship between source-monitoring performances and OCD.**
- **Most of the 13 retrieved studies did not report any source-monitoring deficits.**
- **However, the review suggests reduced confidence in source-monitoring judgments in patients with OCD and subclinical subjects.**
- **This review also highlights methodological limitations and provides recommendations regarding how source-monitoring has been evaluated in this population.**

Review of source-monitoring processes in obsessive-compulsive disorder

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Author contributions: Lavallé L wrote the first draft of the manuscript; Lavallé L and Mondino M managed the systematic literature searches; Mondino M supervised the study; Brunelin J and Bation R critically revised the manuscript. All authors approved the final version of the manuscript.

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Abstract

Obsessive-compulsive disorder (OCD) is a severe mental illness characterized by persistent, intrusive and distressing obsessions and/or compulsions. Such symptoms have been conceptualized as resulting from a failure in source-monitoring processes, suggesting that patients with OCD fail to distinguish actions they perform from those they just imagine doing. In this study, we aimed to provide an updated and exhaustive review of the literature examining the relationship between source-monitoring and OCD. A systematic search in the literature through January 2019 allowed us to identify 13 relevant publications investigating source-monitoring abilities in patients with OCD or participants with subclinical compulsive symptoms. Most of the retrieved studies did not report any source-monitoring deficits in clinical and subclinical subjects compared with healthy volunteers. However, most of the studies reported that patients with OCD and subclinical subjects displayed reduced confidence in source-monitoring judgments or global cognitive confidence compared to controls. The present review highlighted some methodological and statistical limitations. Consequently, further studies are needed to explore source monitoring with regard to the subcategories of OCD symptoms (*i.e.*, symmetry-ordering, contamination-washing, hoarding, aggressive obsession-checking, sexual-religious thoughts) and to clarify the relationship between source-monitoring subtypes (*i.e.*, reality or internal source-monitoring) and confidence in these populations.

Key words: Reality-monitoring; Source-monitoring; Obsessive-compulsive disorder;

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Subclinical compulsive symptoms

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Core tip: Symptoms of obsessive-compulsive disorder (OCD) have been proposed as resulting from a source-monitoring failure, suggesting that patients with OCD fail to distinguish actions they perform from those they just imagine doing. This study provides an updated and exhaustive review of the literature examining the relationship between source-monitoring performances and OCD. Most of the 13 retrieved studies did not report any source-monitoring deficits but reported reduced confidence in source-monitoring judgments in patients with OCD and subclinical subjects compared to controls. Furthermore, this review highlighted some methodological limitations and provided recommendations with respect to future studies focusing on source-monitoring in OCD.

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INTRODUCTION

Obsessive-compulsive disorder (OCD) is a frequent psychiatric condition that occurs in 2%-3% of the population^[1]. Symptoms consist of persistent, intrusive and distressing obsessions and/or compulsions, strongly impacting the quality of life of the affected individual^[2]. Five dimensions of symptoms have been classically defined in patients with OCD: Symmetry-ordering, contamination-washing, hoarding, aggressive obsession-checking, and sexual-religious thoughts^[3-7].

The pathophysiological and cognitive mechanisms underlying the symptoms of OCD have not yet been fully elucidated. However, several nonmutually exclusive cognitive models have been proposed to characterize OCD thought processes. For instance, according to the thought-action fusion model^[8], excessive importance is given to patients' thoughts by believing that having a thought about an event makes that event more likely to occur. A second model, the meta-memory model^[9], proposes that an imbalance between a preserved feeling of remembering (knowing) and an impaired ability to remember physical details (remembering) leads to checking behavior to restore an adequate level of confidence. A third cognitive model proposes that patients with OCD have source-monitoring disabilities^[10]. Source-monitoring is defined as the ability to discriminate the origin of a remembered piece of information^[11]. According to this model, patients with OCD would be more likely to confound memories of performed and imagined actions. The resulting uncertainty could therefore contribute to obsessive thoughts that in turn lead to compulsive behaviors to ensure that the intended actions have been carried out.

Three types of source-monitoring processes have been described in the literature^[12]. The first type is reality-monitoring, which characterizes the ability to distinguish whether information was perceived from the environment or imagined (*e.g.*, Did I see my partner turn off the gas or did I only imagine it?). A second type of source monitoring is internal source monitoring, which characterizes the ability to determine whether an internally generated event was expressed in the external space or kept in the internal space (*e.g.*, Did I turn off the gas or did I only think about doing it?). Finally, external source monitoring refers to the discrimination between different externally derived sources (*e.g.*, Did John tell me this information, or did I hear it on the radio?). Deficits in source-monitoring processes have already been associated with some clinical features, such as delusions and hallucinations in schizophrenia. Namely, an incorrect flagging of thoughts as self-generated events may be responsible for altered self-recognition in patients with psychosis. In addition, their propensity to misattribute inner speech to external sources has been associated with the presence of auditory verbal hallucinations^[13,14].

Here, we aimed to provide an updated overview of the literature examining the relationship between source-monitoring performances and OCD symptoms. Special attention was given to internal source monitoring since its alteration (*i.e.*, a confusion

between imagined and performed events) seems more related to OCD symptoms than reality- or external source monitoring. Finally, rather than only exploring source monitoring as an OCD trait, this review included both patients with OCD and subjects with subclinical checking rituals (defined as persons with similar checking symptoms as those observed in clinical subjects but with less-disabling consequences^[45]). This will allow us to explore the relationship between source-monitoring deficits and OCD's related checking symptoms.

To achieve our goal, a systematic review was conducted according to the recommendations from the Cochrane group and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines^[46]. Details of methods are given in the [Supplementary material 1](#)^[47,48]. The primary electronic search in the PubMed, ScienceDirect and psycINFO databases identified 102 articles, and cross-referencing provided 6 additional articles. Removal of duplicate records yielded 100 articles. After reading the titles and abstracts, 24 articles were retained. Eleven records were excluded because they did not use source-monitoring tasks. This process resulted in a total of 13 full-text articles, comprising 10 studies in patients with OCD and 3 studies in a subclinical population of checkers. Main results and methods from the 13 selected studies investigating source-monitoring in patients with OCD and subjects with subclinical checking rituals are given in the [Table 1](#)^[49,15,16-20].

INTERNAL SOURCE-MONITORING IN OBSESSIVE-COMPULSIVE DISORDER

Our systematic review yielded 9 studies that investigated internal source-monitoring abilities. These studies included either patients with OCD or subclinical checking-prone individuals. Among them, 2 studies reported that participants had significantly impaired internal source-monitoring abilities. These 2 studies compared participants with checking symptoms, either clinical (OCD checkers) or subclinical (checking-prone individuals). For instance, Rubenstein *et al.*^[19] compared the internal source-monitoring abilities between checking-prone individuals and healthy controls. They used a word-recognition task requiring participants to either read the second word of a pair of words or to generate the second word from its first letters. Participants were then asked to recognize whether the words were generated in the internal space or the external space (read aloud). The authors reported that checking-prone participants were more likely than healthy controls to misattribute read words as generated. Using a task measuring the participants' ability to remember if they actually performed, imagined themselves performing or imagined someone else performing some actions, Ecker *et al.*^[16] found a significant impairment in OCD checkers compared to low-checking inpatients with other diagnoses. Namely, OCD checkers had poorer free recall of performed actions and made more confusions between performed and imagined actions. Moreover, the authors reported that high-checking inpatients made significantly more misattributions of imagined events as being performed compared to low-checking ones.

In contrast to these studies, 7 other studies did not report any significant impairments regarding internal source-monitoring abilities. Among them, 4 studies included patients specifically suffering from checking symptoms, and 3 studies included patients with general OCD symptomatology. First, McNally *et al.*^[20], Zermatten *et al.*^[21], Constans *et al.*^[22], and Cogle *et al.*^[23] used action recognition tasks requiring participants to discriminate between actual and imagined action performance. They failed to report any significant difference between OCD checkers and noncheckers or healthy controls. Interestingly, Constans *et al.*^[22] and Cogle *et al.*^[23] used anxiety-eliciting actions. Using comparable action recognition tasks, Moritz *et al.*^[24] and Merkelbach *et al.*^[25] did not report any significant difference between patients with general OCD symptoms and healthy controls. They both divided their OCD groups into two subgroups, either high and low checkers^[24] or checkers and noncheckers^[25], but failed to find any significant difference between the subgroups. Finally, by including action items relevant to compulsive OCD behaviors, Hermans *et al.*^[24] also failed to reveal any significant difference between OCD patients and healthy controls.

OTHER SUBTYPES OF SOURCE MONITORING IN OBSESSIVE-COMPULSIVE DISORDER

Seven studies investigated other source-monitoring subtypes in patients with OCD or

Table 1 Details of studies investigating source monitoring in patients with obsessive-compulsive disorder or participants with subclinical compulsive symptoms

Ref.	SM subtype	Samples (n)	SM task: Source encoding conditions	OCD relevant stimuli	Significant between-groups difference in SM performances	Significant between-groups difference in confidence
Hemmans <i>et al.</i> ^[24] , 2003	Internal	17 OCD; 17 HC	ART: Imagining performing an action a fixed number of times + performing it a various number of times	Relevant compulsive + irrelevant compulsive + neutral actions	No difference between OCD and HC; No difference between high (n = 9) and low (n = 8) checkers	OCD < HC for neutral and irrelevant compulsive actions
Merckelbach <i>et al.</i> ^[25] , 2000	Internal	19 OCD; 16 HC	ART: Imagining performing <i>vs</i> performing actions	No	No difference between OCD and HC; No difference between OCD checkers (n = 7) and OCD noncheckers (n = 12)	OCD < HC. Negative correlation between DES scores and confidence in OCD but not in HC
Cougle <i>et al.</i> ^[23] , 2008	Internal	21 OCD checkers; 24 HC	ART: Imagining performing <i>vs</i> performing actions	Bothersome + nonbothersome actions	No difference between OCD checkers and HC in both free recall and recognition tests	OCD checkers < HC
Constans <i>et al.</i> ^[22] , 1995	Internal	12 OCD checkers; 7 HC	ART: Imagining performing <i>vs</i> performing actions within action sequences	Anxiety-eliciting + neutral objects	No difference between OCD checkers and HC	No difference
Ecker <i>et al.</i> ^[19] , 1995	Internal	24 OCD checkers; 24 HCIP + 48 LCIP	ART: Imagining performing <i>vs</i> performing <i>vs</i> imagining seeing <i>vs</i> subvocal rehearsal	Not specified	OCD < LCIP for free recall of performed actions and made more confusions between performed and imagined perform actions; HCIP: More misattributions of imagined actions as performed than LCIP	OCD checkers < HC, regardless of the instruction modality
McNally <i>et al.</i> ^[10] , 1993	Internal	12 OCD checkers; 12 OCD noncheckers; 12 HC	ART: Tracing <i>vs</i> imagining tracing <i>vs</i> seeing drawings or words	No	No difference between checkers and noncheckers	OCD noncheckers < HC for words or drawings they traced. OCD checkers and noncheckers < HC for words they imagined
Moritz <i>et al.</i> ^[20] , 2009	Internal	32 OCD; 32 HC	ART: Imagining <i>vs</i> performing actions	No	No difference between OCD and HC	No difference
	External	32 OCD; 32 HC	ART: Verbal <i>vs</i> nonverbal instruction (pictogram)	No	No difference between OCD and HC	No difference
Rubenstein <i>et al.</i> ^[15] , 1993	Exp 1a: Internal + Reality	20 CP; 20 HC	ART: Seeing <i>vs</i> performing <i>vs</i> writing actions	No	CP made more SM confusions than HC	NA
	Exp 3: Internal	20 CP; 20 HC	WRT (word pair completion): Reading a word pair <i>vs</i> generating the second word of a pair	No	CP made more SM confusions than HC	NA

Zermatten <i>et al</i> ^[21] , 2006	Internal + Reality	19 CP; 35 nonCP	ART: Imagining performing <i>vs</i> performing <i>vs</i> imagining seeing <i>vs</i> seeing <i>vs</i> verbally repeating	No	CP misattributed more performed actions as seen than nonCP (significant correlation with OCI-R checking); No difference for misattribution of performed actions as imagined perform	No difference
Reese <i>et al</i> ^[26] , 2011	Reality	20 OCD; 20 HC; 20 BDD	WRT: Imagining seeing <i>vs</i> seeing words	Neutral + negative + BDD-related + OCD-related words	No difference between OCD and HC	No difference
Sher <i>et al</i> ^[10] , 1983	Reality	26 CP; 28 nonCP	WRT (word pair completion): Imagining the second word of a pair <i>vs</i> seeing it written	No	No difference between CP and nonCP	CP < nonCP
Brown <i>et al</i> ^[27] , 1994	Reality	28 OCD; 21 HC	WRT: Imagining seeing <i>vs</i> seeing words	No	OCD > HC. Among OCD, checkers (<i>n</i> = 13) < cleaners (<i>n</i> = 9)	NA
Kim <i>et al</i> ^[28] , 2009	External	14 OCD; 14 HC	WRT: Female <i>vs</i> male voices	No	OCD < HC	Cognitive confidence subscores of MCQ were significantly higher in the OCD group than the control group; No correlation between confidence scores and SM

¹Source-monitoring subtypes investigated in the selected studies were reclassified according to Source-Monitoring Framework as described in Johnson 1993. ART: Action recognition task; BDD: Body dysmorphic disorder; CP: Checking-prone subjects; DES: Dissociative Experience Scale; HC: Healthy controls; HCIP: High-checking inpatients; LCIP: Low-checking inpatients; NA: Not available; NS: Not significant; OCD: Obsessive-compulsive disorder; OCI-R: Obsessive-Compulsive Inventory- Revised; SM: Source monitoring; WRT: Word recognition task.

subclinical participants with checking symptoms.

Reality-monitoring

Among them, 4 studies measured reality-monitoring abilities in patients with OCD or subclinical participants with checking symptoms. Zermatten *et al*^[21] used an action recognition task including four conditions: A condition in which subjects performed an action, a condition in which they imagined themselves performing the action, a condition in which they saw an action and a condition in which they imagined seeing the action. They found that checking-prone participants misattributed more performed actions as seen than nonchecking prone participants. The number of confusions between performed and seen actions significantly correlated with checking symptoms. Conversely, the 3 other studies did not reveal any significant reality-monitoring deficits. Using a word recognition task with items related or not related to OCD, Reese *et al*^[26] did not find any impairments in patients with OCD compared to healthy controls. Surprisingly, Brown *et al*^[27] reported that patients with OCD were significantly better than healthy controls in discriminating between words they saw and words they imagined. However, when the group of patients with OCD was split into two subgroups (cleaners and checkers), the authors reported that checkers were significantly impaired in reality monitoring compared to cleaners. Sher *et al*^[10] did not observe any significant reality-monitoring impairments in subclinical checkers compared to noncheckers.

In addition, Rubenstein *et al*^[5] compared source monitoring between checking-prone participants and healthy controls without distinguishing between internal source- and reality-monitoring abilities. They reported that checking-prone individuals made more confusions between actions they saw, performed or wrote, reflecting a general source-monitoring impairment.

External source-monitoring

Finally, 2 other studies compared external source-monitoring abilities between patients with OCD and healthy controls. Kim *et al*^[28] found a significant external source-monitoring deficit in patients with OCD. Namely, patients with OCD showed a lower accuracy in recognizing whether words were presented with a male or female

voice compared to healthy controls. In contrast, Moritz *et al*^[29] did not report any significant external source-monitoring impairment in patients with OCD compared to healthy controls.

CONFIDENCE IN OBSESSIVE-COMPULSIVE DISORDER

Among the 13 included studies, 11 investigated confidence in source-monitoring judgments in relation to OC symptoms. These studies evaluated either specific confidence in source-monitoring judgments^[10,18-26,29] or global cognitive confidence using the Meta-Cognition Questionnaire^[24,28]. A decrease in confidence in source-monitoring judgments was observed in studies including only checkers^[10,19,20,23] and in those including patients with OCD without discriminating their clinical subtypes^[2,4,25,28].

DISCUSSION

The aim of this review was to summarize the findings from studies investigating source-monitoring abilities in relation to OCD symptoms. The analysis of the literature did not lead to clear conclusions. Indeed, 5 of the 13 studies reviewed highlighted some differences in source-monitoring processes in patients with OCD or subclinical checkers compared to controls. Among them, two found reduced internal source-monitoring abilities in OCD checkers and checking-prone individuals (*i.e.*, confusions between imagined and performed items). One study found reduced reality-monitoring abilities between patients with OCD and healthy controls (*i.e.*, confusions between imagined and seen items). One study found reduced external source-monitoring in patients with OCD compared to healthy controls (*i.e.*, confusions between two external-source items). Finally, one study found that subclinical checkers displayed reduced general source-monitoring abilities than noncheckers. While only a few studies showed differences in source-monitoring performances, most of the studies reported that patients with OCD and checking-prone participants displayed reduced confidence compared to healthy controls.

Several methodological factors could have contributed to these discrepancies between findings. Indeed, we observed high methodological heterogeneity across studies, which limited the ability to make comparisons among studies. First, the current review highlighted disparities between studies regarding the definitions of the explored subtypes of source-monitoring (*i.e.*, reality-, internal source-, or external source-monitoring). To harmonize this, we reclassified the selected studies according to the definitions given by Johnson *et al*^[1-3], where internal source monitoring refers to the distinction between two internal sources of information, reality monitoring refers to the distinction between internal and external sources, and external source monitoring refers to the distinction between two external sources. Thus, according to these definitions, some studies that announced the investigation of reality monitoring were reclassified into studies investigating internal source monitoring. In this way, action recognition tasks involving discrimination between actions that were either performed or imagined by the subject^[19,22-25] and word recognition tasks involving discrimination between imagined and traced words^[20] were reclassified as internal source-monitoring tasks (see [Table 1](#)).

Second, we observed a large heterogeneity across studies regarding the paradigm used to assess source-monitoring processes. These paradigms included either word, action, drawing voice or object recognition. However, despite this limitation, studies revealing significant differences between OCD-related symptoms and controls used either action or voice recognition tasks. This is in line with studies in patients with schizophrenia that highlighted reality-monitoring impairments using various paradigms, including action, word or speech recognition tasks^[30], indicating that the identification of source-monitoring deficits is independent of the experimental paradigm.

Beyond the specificity of the task, the diversity in methods also highlights the importance of ecological validity when assessing source-monitoring performance. Such an approach seems particularly relevant not only in action recognition tasks where patients faced real life settings but also in item choices within tasks^[31]. For instance, Constans *et al*^[22], Cogle *et al*^[23], Hermans *et al*^[24] and Reese *et al*^[26] investigated source monitoring for anxiety-evoking situations (turning on/turning off the lights). However, these studies did not report any significant impairment in patients, suggesting that this approach may not be useful for investigating source monitoring in patients with OCD. Furthermore, this large heterogeneity could partly

explain the inconsistencies observed between studies. The different categories of stimuli used in each of the retrieved studies (*e.g.*, neutral, OCD-relevant, personally relevant, bothersome, real-life action) limit any comparisons among studies, and therefore, any meta-analysis.

The present review also highlighted a large heterogeneity among studies regarding the included population. Indeed, the various studies investigated source monitoring in patients with general OCD symptomatology^[24,29], in patients with OCD specifically displaying checking symptoms^[19,20,22,23] and in subclinical checking-prone individuals^[10,13,21]. Most studies failed to reveal any significant source-monitoring deficits. However, it should be noted that among 5 important studies^[13,19,21,27,28], 4 revealed internal source-, reality-, or external source-monitoring deficits in checkers (clinical or subclinical) compared to noncheckers^[13,19,21,27]. This suggests that a possible general deficit in discriminating the source of information may specifically affect subjects with checking compulsive behaviors. Current observations emphasize that research on source-monitoring deficits in OCD should consider the type of OCD as an essential variable (*i.e.*, checking, symmetry-ordering, contamination-washing, hoarding). Nevertheless, several studies we reviewed here show a great heterogeneity or even a lack of measurement of OCD symptoms, preventing us from distinguishing source-monitoring abilities across subgroups of patients^[24-26,28,29,31]. Consequently, future research would benefit from considering the multidimensional property of OCD and incorporating a more comprehensive measure of OCD symptoms by a systematic use of standardized classifications such as the Yale-Brown Obsessive-Compulsive Scale^[32,33].

Finally, several confounding factors were not controlled: the duration of the disease, age of onset were not reported, pharmacological treatments were either heterogeneous or not reported, and patients with comorbidities were excluded, included or not controlled. Moreover, although consistent differences between gender and ethnicity have been reported regarding OCD phenomenology^[34,35], most of the studies retained in the current review did not provide results or did not assess their influence on source monitoring performances. Furthermore, the number of subjects included in the studies (from 12 to 48, mean across studies < 25) was too small to achieve sufficiently statistical power to conclude that there was no source-monitoring deficit associated with OCD's related symptoms, gender or ethnicity. Additionally, from a methodological point of view, some authors first investigated source monitoring in patients with OCD without a priori differentiating clinical subtypes but undertook an a posteriori comparison between checkers and noncheckers^[24,25,27]. This approach did not allow an adequate a priori estimation of the sample size required to conclude with sufficiently statistical power. Another methodological limitation was the interpretation of negative findings based on p values using a frequentist approach. Further studies with Bayesian statistics could help us to determine whether to reject the null hypothesis.

A confidence impairment in general memory has been associated with OCD severity^[36]. Here, the numerous studies reviewed reported a lack of confidence in source-monitoring functioning or a lack of global cognitive confidence. Interestingly, this lack of confidence has been found in both checkers^[10,19,20,29] and noncheckers^[20,24,25], suggesting that it is a cognitive marker for general OC symptoms. These findings raise the question of whether the participant's lack of confidence participates in his or her potential source-monitoring deficit. However, only three studies that revealed a significant source-monitoring deficit also investigated confidence, leading to heterogeneous results. Namely, a single study from Ecker *et al.*^[19] revealed positive results, whereas Zermatten *et al.*^[21] found no difference in confidence between groups, and Kim *et al.*^[28] found no correlation between source-monitoring results and confidence. This observation should be carefully considered since Kim *et al.*^[28] evaluated the participants' global cognitive confidence, whereas the other two studies specifically measured confidence in source-monitoring judgments. Future studies should systematically investigate the relationship between source-monitoring scores and source-monitoring confidence.

CONCLUSION

With most of studies concluding with negative results, the present review suggests a lack of global source-monitoring or specific internal source-monitoring deficits in patients with OCD. However, this review highlighted several methodological limitations regarding the tasks used and the statistical power of the included studies. A crucial factor to explain this is the age of the studies, which were published between 1983 and 2011. Future studies with sufficiently powered samples of patients

with OCD should consider the multidimensional property of OCD (*i.e.*, symmetry-ordering, contamination-washing, hoarding, aggressive obsession-checking, sexual-religious thinking), explore the subtypes of source-monitoring abilities (reality-, internal source-, external source-monitoring), and systematically investigate source-monitoring scores in relation with an evaluation of confidence in judgments.

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SUPPLEMENTARY MATERIAL

Methods

The systematic literature search and study selection were conducted independently by two authors (LL and MM), and any discrepancies were resolved by consensus after discussion with a third author (JB). The search and selection processes are depicted in Figure 1.

Search Strategy

We searched for articles published through January 2019 in the PubMed, ScienceDirect and psycINFO databases. Combinations of the following keywords were used: “source-memory”, “source-monitoring”, “reality-monitoring”, “internal-monitoring”, “external-monitoring”, “autonoetic agnosia”, “OCD”, “obsessive-compulsive disorder”. Additional articles were retrieved by cross-referencing the reference lists of selected articles investigating source monitoring in OCD.

Selection criteria

The selection criteria were as follows: 1) original articles written in the English language and published in peer-reviewed journals; 2) studies that included patients with OCD according to the Diagnostic and Statistical Manual of Mental Disorder (DSM) or the International Statistical Classification of Disease (ICD) and studies that included subclinical subjects with OCD-related symptoms based on the Maudsley Obsessive-Compulsive Inventory (MOCI^[17]) or the Obsessive-Compulsive Inventory (OCI^[18]) scales; 3) studies that included a group of healthy controls (HC); and 4) studies that provided a detailed description of the source-monitoring tasks used to measure internal source monitoring, reality monitoring or external source monitoring.

Data extraction

For each study, the following data were extracted: (1) author and year; (2) the source-monitoring subtype that had been measured; (3) sociodemographic and

clinical characteristics of the participants (sample size, population type, clinical measures, treatments and comorbidities); (4) source monitoring experimental procedure; (5) main results; (6) the measure of confidence, when available.

The source-monitoring subtype measured in each retrieved study was reclassified according to Johnson et al.'s definition^[12] to allow comparisons among studies. Thus, studies requiring discrimination between two internally generated events, one being expressed in the external space and one kept in the internal space, were classified as studying internal source monitoring, even if some authors refer to this as reality monitoring. Studies requiring discrimination between internally generated events and externally perceived events were classified as studying reality monitoring, even if the internally generated information was performed by the subject in the external space. Finally, studies requiring discrimination between events from two external sources were classified as studying external source monitoring.

Study selection

The retrieved articles were published between 1983 and 2011. A PRISMA flowchart depicting the study selection process is shown in Figure 1.

2.3. Dissociable source-monitoring impairments in obsessive-compulsive disorder and schizophrenia [article 2]

Article 2: Dissociable source-monitoring impairments in obsessive-compulsive disorder and schizophrenia. European Psychiatry. 2020. Lavallé L., Bation R., Dondé C., Mondino M., Brunelin J.

TAKE HOME MESSAGE

- **Schizophrenia and obsessive-compulsive disorder (OCD) have a phenomenological overlap.**
- **These two diseases could share a failure in their abilities to monitor their own thoughts (i.e., source-monitoring).**
- **This study compared source-monitoring performances between patients with OCD, patients with schizophrenia and healthy controls.**
- **Both patients with OCD and patients with schizophrenia had impaired internal source-monitoring.**
- **Only patients with schizophrenia had impaired reality-monitoring.**

Dissociable source-monitoring impairments in obsessive-compulsive disorder and schizophrenia

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Research Article

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Cognitive continuum; obsessive-compulsive disorder; schizophrenia; source-monitoring

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Abstract

Background: Based on the observed clinical overlap between obsessive-compulsive disorder (OCD) and schizophrenia (SCZ), both conditions may share, at least in part, common cognitive underpinnings. Among the cognitive deficits that could be involved, it has been hypothesized that patients share a failure in their abilities to monitor their own thoughts (source monitoring), leading to confusion between what they actually did or perceived and what they imagined. Although little is known regarding source-monitoring performances in patients with OCD, numerous studies in patients with SCZ have observed a relationship between delusions and/or hallucinations and deficits in both internal source- and reality-monitoring abilities.

Methods: The present work compared source-monitoring performances (internal source and reality monitoring) between patients with OCD ($n = 32$), patients with SCZ ($n = 38$), and healthy controls (HC; $n = 29$).

Results: We observed that patients with OCD and patients with SCZ displayed abnormal internal source-monitoring abilities compared to HC. Only patients with SCZ displayed abnormalities in reality monitoring compared to both patients with OCD and HC.

Conclusions: Internal source-monitoring deficits are shared by patients with OCD and SCZ and may contribute to the shared cognitive deficits that lead to obsessions and delusions. In contrast, reality-monitoring performance seems to differentiate patients with OCD from patients with SCZ.

Introduction

Obsessive-compulsive disorder (OCD) and schizophrenia (SCZ) are two frequent psychiatric diseases that strongly impact the quality of life [1,2]. Among the diversity of symptoms that can be experienced, one key similarity between obsessive thoughts in OCD and delusional ideations in SCZ is that both involve intrusive, unwanted and foreign thoughts [3,4]. Obsessions in OCD are recurrent and persistent thoughts, impulses or images that are experienced as intrusive and inappropriate and that cause marked anxiety or distress. Delusions in SCZ are false beliefs based on incorrect inferences about external reality that are firmly sustained despite what almost everyone else believes and despite what constitutes incontrovertible evidence to the contrary [5]. Although the definitions traditionally suggest the level of insight into the senseless of thoughts to differentiate obsessions in OCD from delusions in SCZ, patients with OCD have been reported to display a wide range of degree of insight about their obsessional thoughts [6]. Furthermore, the frequent comorbidity between OCD and SCZ [7,8] have led to the definition of new clinical entities, including SCZ with obsessive-compulsive symptoms (up to 30% [9]), SCZ with OCD (schizo-obsessive disorder, 12–14% [9,10]), schizotypal personality with OCD (5–50% [11]), and OCD with poor insight (13–36%, [6,12–20]) [3–5]. These observations suggest a continuum between the obsessive thoughts in OCD and the delusional ideas in SCZ and suggest that these clinical features would share, at least in part, a common cognitive substratum. Among the cognitive deficits that could underpin these two phenomena, it has been hypothesized that patients with OCD [21] and patients with SCZ [22] would share a failure in their abilities to monitor their own thoughts (source monitoring), leading to confusion between what they actually did and what they only imagined doing.

Source monitoring is a higher-order cognitive process that refers to the ability to remember the source of information. Several subtypes of source monitoring have been identified [23]. A first subtype of source monitoring is reality monitoring, which characterizes the ability to determine whether information was perceived from the environment or imagined (e.g., Did I see my partner close the door or did I only imagine it?). A second subtype of source monitoring is internal source monitoring, which characterizes the ability to distinguish whether an internally generated event was expressed in the outer space or kept in the inner space (e.g., Did I close the door or did I only

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think about it?). A third subtype is external source monitoring, which refers to the discrimination between different externally derived sources (e.g., Did John tell me that it was going to rain, or did I hear it on the radio?).

Failures in source-monitoring processes have been repeatedly reported in patients with SCZ with particular difficulties in distinguishing internal from external sources of events [24–27]. Both internal source- and reality-monitoring deficits have been found to be associated with positive symptoms, such as delusions [28,29] and hallucinations [22,24,27].

Only a few studies have investigated source-monitoring abilities in patients with OCD symptoms, compared with the number examining patients with SCZ, and they have provided mixed results [30–34] for positive results and [21,35–41] for negative results). This heterogeneous literature has suggested that patients with OCD, especially those with checking symptoms, displayed reduced confidence in internal source-monitoring judgments compared to healthy controls [42]. To the best of our knowledge, no studies have directly compared the source-monitoring performances of patients with SCZ with the performances of patients with OCD.

The aim of the present work was therefore to compare patterns of source-monitoring performances between patients with OCD, patients with SCZ, and healthy controls. We hypothesized that patients with OCD will display impaired internal source-monitoring abilities but intact reality-monitoring abilities, whereas patients with SCZ will display alterations in both source-monitoring processes.

Methods

Subjects

We tested a total of 99 participants. Thirty-two patients meeting Diagnostic and Statistical Manual of Mental Disorders, Fourth

Edition, Text Revision (DSM-IV-TR) [5] criteria for OCD, 38 patients meeting DSM-IV-TR criteria for SCZ, and 29 healthy controls (HC), free from any personal or familial neurological or psychiatric condition, were included. At baseline, symptoms were assessed at a screening level, each included patient should not present with other comorbid psychiatric syndrome according to DSM-IV-TR. All participants included presented with intellectual quotient >70. The severity of symptoms was assessed in the OCD group with the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS [43]) and in the SCZ group with the Positive and Negative Symptoms Scale (PANSS [44]). Patients with OCD and patients with SCZ were on psychotropic medications at the time of testing (Table 1). Duration of illness was 22.3 ± 13.9 for patients with OCD and 13.5 ± 7.8 for patients with SCZ. Patients with SCZ presented with delusional ideation as measured by the PANSS item #P1 (median = 4.0, mean = 4.0, standard deviation = 1.6) and hallucinations as measured by PANSS item #P3 (median = 6.0, mean = 5.5, standard deviation = 1.4). Patients with OCD presented with obsessions (median = 13.0, mean = 12.5, standard deviation = 3.4) as measured with YBOCS items #1–5 and compulsions (median = 13.0, mean = 12.2, standard deviation = 3.6) as measured by the YBOCS items #6–10. Within the five dimensions of OCD symptoms, 1 patient fitted with the symmetry-ordering dimension, 16 patients fitted with the contamination-washing dimension, 6 patients fitted with the sexual-religious dimension, 9 patients fitted with the aggressive obsession-checking dimension, and 0 patients fitted with the hoarding dimension. All participants were native French speakers and provided written informed consent after a detailed description of the study. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Table 1. Sociodemographic and clinical characteristics of the included population.

	OCD	SCZ	HC	<i>p</i>
<i>n</i>	32	38	29	
Age (years)	42.75 ± 14.41	41.05 ± 6.57	40.45 ± 9.31	0.46
Gender (F:M)	22:10	18:20	20:9	0.10
Educational level	12.86 ± 2.82	12.21 ± 3.17	14.21 ± 2.93	0.03*
YBOCS-obsessions	12.5 ± 3.42	NA	NA	
YBOCS-compulsions	12.21 ± 3.62	NA	NA	
YBOCS-total	24.72 ± 6.47	NA	NA	
PANSS-positive	NA	20.58 ± 4.79	NA	
PANSS-negative	NA	20.71 ± 5.15	NA	
PANSS-total	NA	77.71 ± 13.78	NA	
Duration of illness	22.3 ± 13.9	13.5 ± 7.8	NA	
Second generation antipsychotics	7.7%	94.7%	NA	
First generation antipsychotics	7.7%	31.6%	NA	
Mood stabilizers	0%	10.5%	NA	
Selective serotonin reuptake inhibitors	79.9%	7.9%	NA	
Tricyclics	15.4%	2.6%	NA	
Serotonin-norepinephrine reuptake inhibitors	0%	5.3%	NA	

The results are given as the mean ± standard deviation.

Abbreviations: HC, healthy controls; OCD, obsessive-compulsive disorder; SCZ, schizophrenia.

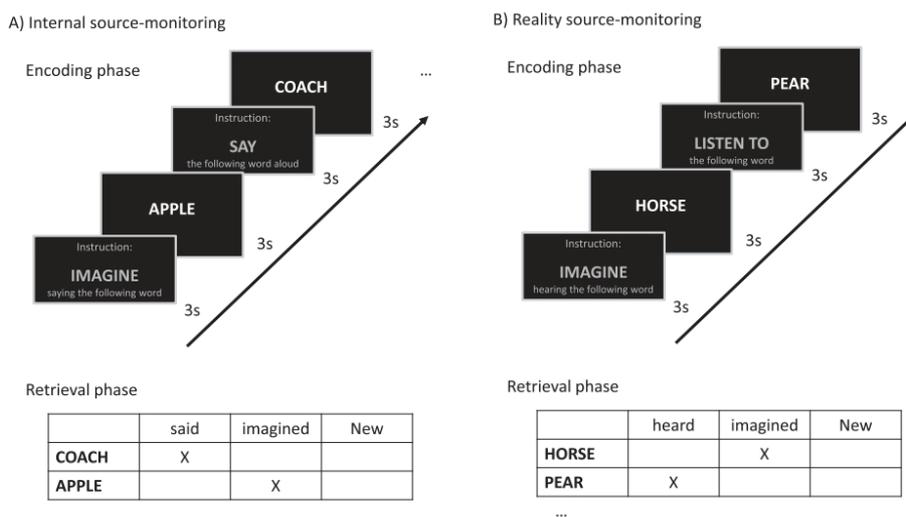


Figure 1. Experimental procedures for reality-monitoring (right panel) and internal source-monitoring (left panel) assessments.

The sociodemographic and clinical characteristics of the population are given in Table 1.

Source-monitoring tasks

The testing procedure took approximately 15 min to complete. The participants were individually tested with two source-monitoring tasks presented in a randomized order: one internal source-monitoring task and one reality-monitoring task. Each source-monitoring task was divided into two phases, an encoding phase and a memory retrieval phase, which were preceded by a short practice trial. As displayed in Figure 1, during the encoding phase, 16 words were sequentially presented in a randomized order. Each word was preceded by an instruction. During the memory retrieval phase, 24 words were presented, including the 16 words that were presented during the encoding phase and 8 new words. Our stimulus materials were similar to those described by Brunelin et al. [45].

Internal source monitoring

The verbal list included eight words with the “imagine saying” encoding condition and eight other words with the “say aloud” encoding condition. Then, internal source-monitoring abilities were assessed by asking subjects to identify whether each word was said aloud, imagined or new (Figure 1A).

Reality monitoring

The verbal list included eight words with the “imagine hearing” encoding condition and eight other words with the “listen to” encoding condition. Then, reality-monitoring abilities were assessed by asking subjects to identify whether each word was heard, imagined or new (Figure 1B).

Analyses

Statistical analyses were carried out using SPSS software (version 26.0). Statistical significance was set at $p < 0.05$, and eta-squared (η^2) was also reported.

The differences in age and educational level among groups were examined using one-way ANOVA tests. Gender differences were examined using Pearson’s chi-squared test.

Primary outcomes were correct responses in the source-monitoring tasks. Internal source-monitoring correct responses were the number of said words that were correctly identified as said (SAY), the number of imagined words that were correctly identified as imagined saying (IMA), and the number of unrepresented words that were correctly identified as new (NEW). Reality-monitoring correct responses were the number of heard words correctly identified as heard (HEAR), the number of imagined words correctly identified as imagined hearing (IMA), and the number of unrepresented words correctly identified as new (NEW).

Correct responses were analyzed using two-way repeated-measure ANOVA models with group (OCD, SCZ, and HC) as a between-subject factor and response type (HEAR, IMA, and NEW for reality-monitoring assessment; SAY, IMA, and NEW for internal source-monitoring assessment) as a within-subject factor. When significant, ANOVAs were followed by Fisher LSD post hoc tests. ANCOVAs were performed when sociodemographic parameters significantly differed between groups.

Results

Demographic characteristics

No significant difference between groups was found for age ($p = 0.46$) or gender ($p = 0.10$), but a significant difference was observed for educational level ($p = 0.03$). Post hoc tests showed a significant difference between subjects with SCZ and HC ($p = 0.02$) but no significant difference between subjects with OCD and HC ($p = 0.15$) or between subjects with SCZ and subjects with OCD ($p = 0.73$).

Internal source monitoring

For internal source-monitoring correct responses, two-way repeated measures ANOVA revealed a significant effect of group

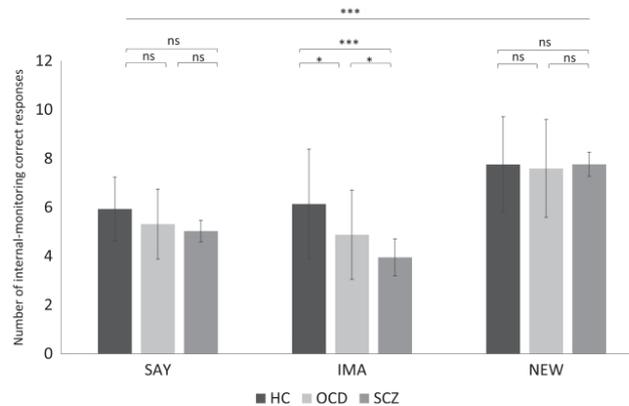


Figure 2. Comparison of internal source-monitoring types of correct responses between HC (dark gray bars), patients with OCD (light gray bars), and patients with SCZ (medium gray bars). SAY responses are measured as the number of correctly identified said words, IMA responses are measured as the number of correctly identified imagined words and NEW responses are measured as the number of correctly identified new words. The results are displayed as the mean \pm standard deviation. ns, not significant. *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$.

($F_{(2,96)} = 8.39, p < 0.001, \eta^2 = 0.149$) and response type ($F_{(2,96)} = 104.34, p < 0.001, \eta^2 = 0.52$) and a significant interaction between these two factors ($F_{(4,96)} = 5.04, p = 0.001, \eta^2 = 0.09$). Repeated measures ANCOVA revealed a significant effect of educational level on internal source-monitoring correct responses ($F_{(2,96)} = 4.123, p = 0.019, \eta^2 = 0.081$). The interaction between group and response type remained significant after including educational level in the model ($F_{(4,96)} = 4.357, p = 0.002, \eta^2 = 0.084$).

Post hoc tests revealed no significant differences among the groups for SAY and NEW correct responses (all $p > 0.05$). The patients with SCZ made significantly fewer IMA correct responses than both the patients with OCD ($p = 0.04, \eta^2 = 0.05$) and HC ($p < 0.001, \eta^2 = 0.28$), while the patients with OCD presented an intermediate level of deficit (OCD–HC comparison: $p = 0.02, \eta^2 = 0.13$) (Figure 2).

Reality monitoring

For reality-monitoring correct responses, two-way repeated measures ANOVA revealed a significant effect of group ($F_{(2,96)} = 9.71, p < 0.001, \eta^2 = 0.17$) and response type ($F_{(2,96)} = 77.47, p < 0.001, \eta^2 = 0.45$) with no significant interaction between these two factors ($F_{(4,96)} = 2.34, p = 0.056, \eta^2 = 0.05$). Repeated measures ANCOVA revealed no significant effect of educational level ($p = 0.17$) on reality-monitoring correct responses.

Post hoc comparisons among the groups revealed no significant differences in the number of NEW correct responses (all $p > 0.05$). Patients with SCZ made significantly fewer IMA correct responses than both patients with OCD ($p = 0.01, \eta^2 = 0.59$) and patients with HC ($p = 0.001, \eta^2 = 0.91$), with a significant difference between patients with OCD and HC ($p = 0.25, \eta^2 = 0.03$). Patients with SCZ made fewer HEAR correct responses than HC ($p = 0.037, \eta^2 = 0.65$) with no significant difference with patients with OCD ($p = 0.07, \eta^2 = 0.44$) and between patients with OCD and HC ($p = 0.79, \eta^2 = 0.06$) (Figure 3).

Discussion

The aim of the study was to compare source-monitoring abilities between patients with OCD, patients with SCZ, and HC. We

reported a dissociation between psychiatric condition and source-monitoring impairments. Namely, both the patients with SCZ and OCD showed impaired internal source-monitoring performances compared to the HC. Performance of patients with OCD was intermediate between that of the HC and patients with SCZ. In contrast, only the patients with SCZ showed impaired reality-monitoring performances compared to the HC.

In the internal source-monitoring task, the patients with OCD and patients with SCZ were less likely to recognize the words they had to imagine saying than the HC. However, they made a similar number of correct responses regarding said words and new words as the HC. These results suggested that OCD and SCZ share a common deficit in the recognition process of what they actually did and imagined doing. This result is in line with previous studies in patients with SCZ that observed internal source-monitoring deficits in patients [46,47] suggesting that a failure in monitoring their own thoughts may contribute to SCZ positive symptoms such as delusions and hallucinations. As a comorbid diagnosis of SCZ was ruled out in our OCD sample, one can hypothesize that the observed internal source-monitoring deficits may similarly contribute to both OCD and SCZ symptoms. Traditionally, the obsessional thoughts in OCD have been distinguished from the delusions and hallucinations in SCZ because of their lack of perceptual qualities and the high level of patients' insight. However, numerous studies have recently reconsidered this dichotomy by showing that patients with OCD have a wide range of insight levels [6,48–51] and frequently described their obsessional thoughts as perceptual irritations [52–55]. Moreover, patients with SCZ with diagnosed hearing hallucinations often describe them as less loud than real voices or without perceptual qualities but merely as strange thoughts [56]. Even if it remains speculative, these results suggest that an internal source-monitoring deficit may contribute, at least in part, to the phenomenological overlap between delusions/hallucinations and obsessional intrusive thoughts. Within this hypothesis, the deficit in internal source monitoring may lead to uncertainty regarding the source of self-generated events, and this uncertainty may contribute to the obsessive thoughts in OCD as well as to the positive symptoms in SCZ. The shared alterations in internal source

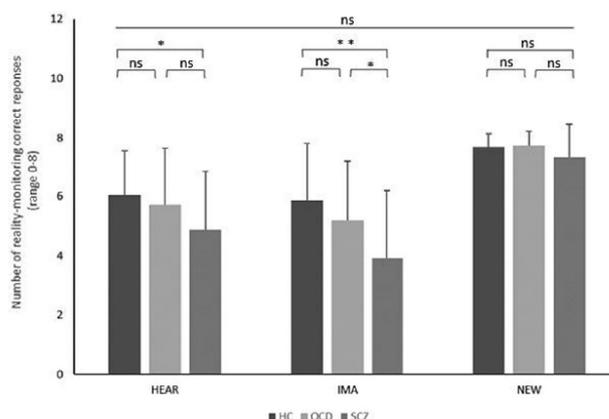


Figure 3. Comparison of reality-monitoring correct responses between HC (dark gray bars), patients with OCD (light gray bars), and patients with SCZ (medium gray bars). HEAR responses are measured as the number of correctly identified heard words, IMA responses are measured as the number of correctly identified imagined words, and NEW responses are measured as the number of correctly identified new words. The results are displayed as the mean \pm standard deviation. ns, not significant. *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$.

monitoring in OCD and SCZ is consistent with the clinical overlap between these two, including frequent comorbidities and a wide range of schizo-obsessive spectrum disorders [4]. To clarify the link between internal-monitoring scores and specific clinical features, further studies should consider evaluating source-monitoring as a transdiagnostic factor by assessing SCZ delusional symptoms in the OCD sample, OCD obsessional thoughts in the SCZ sample and analyzing correlations between source-monitoring performances and these clinical scores.

Despite shared abnormalities, the patients with OCD were significantly less impaired in internal source monitoring than the patients with SCZ. This gradation suggests that thought-recognition deficits are a cognitive dimension common to yet differentially impaired in patients with SCZ and OCD. This result is in line with earlier findings that both patients with OCD and SCZ were impaired in several neuropsychological domains (memory, attention, visual spatial, and executive functioning) with more pronounced deficits in patients with SCZ [57,58]. In the future, transdiagnostic evaluations of both OCD and SCZ symptoms should help clarifying the relationship between the gradation of internal source-monitoring scores and clinical dimensions. Furthermore, it is worth noting that the deficit in recognizing imagined items is associated with significant forgetting bias (i.e., erroneous classification of previously presented imagined items as old) in both patients with OCD and patients with SCZ (supplementary material S1). Patients with SCZ additionally displayed significant externalization bias (i.e., misattributing a self-generated item to an external source). Further studies with larger samples are warranted to validate these findings and explore their implications.

Regarding reality monitoring, the patients with OCD showed similar results to the HC and displayed significantly better results than the patients with SCZ. In other words, since both groups of patients were impaired in internal source monitoring, the only OCD group had preserved recognition of self-generated imagined words when contrasted with externally perceived words. Conversely, the patients with SCZ were additionally impaired to distinguish internally generated sources from externally perceived ones. This result is consistent with numerous studies showing that

patients with SCZ display a deficit in reality monitoring. Specifically, SCZ studies have suggested internal source-monitoring deficits as a consistent trait of the disorder and associated the presence of misattributions of agency in hallucinations with more marked reality source monitoring [45]. However, it is interesting to note that patients with SCZ did not show any externalization bias but forgetting bias, which denote strongly with previous findings [22]. In contrast, the finding of intact reality-monitoring performances in the patients with OCD seems in line with clinical observations that have reported that obsessive thoughts are generally ego-dystonic (i.e., patients recognize their intrusive and inappropriate quality [5]). The unshared reality-monitoring impairment between patients with OCD and SCZ thus provides support for the assumption that reality-monitoring impairments are specific to patients with SCZ and the misattribution of inner thoughts.

Our results should be interpreted with caution because of several limitations. First, this study suffers from a lack of control of insight levels. It is admitted that patients with SCZ hold their delusional beliefs as probably true and integrated into their belief system. In contrast, it is commonly described that patients with OCD judge their obsessive thoughts as intrusive, disturbing or senseless. However, poor insight affects between 13 and 36% of patients [6,12–20] and has been negatively correlated with the perceptual qualities that patients attribute to obsessive thoughts [52]. Furthermore, compared to patients with OCD who have normal levels of insight, patients with OCD who have poor insight present a higher rate of SCZ spectrum disorder in their third-degree relatives [49], a higher comorbidity with schizotypal personality disorder [14], and more severe OCD symptoms [17]. Accordingly, patterns of source-monitoring deficits in patients with SCZ may be more similar to patients suffering from OCD with poor insight than with normal insight. For these reasons, insight levels might be an important confound and should be integrated as a covariable in future source-monitoring studies involving patients with SCZ and OCD. The relationship between internal-source monitoring performances and insight level in patients with OCD should also be specifically investigated

in further studies. Second, the small sample of this study did not allow for performing subgroup comparisons of source-monitoring performances between the different clinical profiles of patients with OCD (i.e., symmetry-ordering, contamination-washing, sexual-religious, aggressive obsession-checking, and hoarding). Third, our study revealed different educational levels between the SCZ and HC groups. Even if educational level has been repeatedly demonstrated to interfere with memory functions [59–61], no changes were observed in source-monitoring differences when education was entered in ANCOVAs. Hence, it would be relevant to explore the relationship between level of education and memory, when memory process involves discrimination between two sources. Fourth, one can hypothesize that source-monitoring effects are a consequence of a general memory deficit or a lack of confidence in memory in the two populations of patients compared to the HC. While this is unlikely that general memory/confidence deficits are responsible for specific impairment in recognizing imagined items, these factors would be tested and analyzed in further studies. Fifth, the different types of medication regimens between the patients with OCD and patients with SCZ may be considered a confounding factor. In a small sample of patients with SCZ, antipsychotic intake has been associated with reduced reality-monitoring impairment [62]. As far as we know, no similar studies have explored the potential impact of pharmacological agents on source-monitoring in patients with OCD. However, in a study comparing source-monitoring abilities between patients with SCZ, patients with major depressive disorder (MDD) and HC, no significant source-monitoring deficit was showed in patients with MDD treated by Selective Serotonin Reuptake Inhibitors (SSRI) [63]. This finding suggests that SSRI do not have an impact on source-monitoring performance in our OCD sample (see Table 1). Since several studies have also reported that impairments of other cognitive functions associated with OCD and SCZ are independent of medication type and dosage [64–66], investigating if and how medication status could influence source-monitoring in these two population of patients seems warranted in the future. Further studies involving first-episode and drug-naïve patients may also provide more reliable evidence regarding the influence of medication on source-monitoring performances. Sixth, future research should include some evaluation of additional neurocognitive parameters, such as working memory, executive functions, and metacognitive parameters that might influence source-monitoring scores. Finally, it should be noted that there is a relatively low number of events in both source-monitoring paradigms, which prevent us from running correlations between source-monitoring and clinical scores without maximizing the risk of type II error. Future studies are warranted to validate the present findings with a larger number of stimuli.

Our results are in line with previous studies that showed that patients with SCZ displayed a dual deficit in internal source and reality monitoring. Using a categorical approach, our study points for the first-time internal source-monitoring as a transdiagnostic factor between patients with OCD and SCZ. In contrast, reality-monitoring performance distinguishes patients with OCD from patients with SCZ. A dimensional approach would be warranted in the future to explore the relationship between source-monitoring performances and specific clinical features that overlap between OCD and SCZ. Furthermore, the pattern of source-monitoring impairments reported here implies disturbances in partially overlapping brain systems in OCD and SCZ that future researches should identify.

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Conflict of Interest. The authors have declared that there are no conflicts of interest in relation to the subject of this study.

Data Availability Statement. There are no linked research data sets. Data will be made available on request.

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Supplementary Material

	Means (SD)			p-values (η^2)		
	HC	OCD	SCZ	HC-OCD	OCD-SCZ	HC-SCZ
Correct responses						
Internal source-monitoring						
Imagined	6.14 (1.43)	4.88 (1.83)	3.95 (1.99)	0.019* (0.13)	0.046* (0.05)	<0.001*** (0.28)
Said	5.93 (1.31)	5.31 (2.25)	5.03 (1.95)	0.479 (0.03)	0.696 (0.004)	0.278 (0.06)
New	7.76 (0.43)	7.59 (0.76)	7.76 (0.49)	0.151 (0.02)	0.139 (0.02)	0.148 (0)
Within-subject p-value<0.001*** Between-subject p-value=0.007** Interaction p-value=0.002**						
Reality-monitoring						
Imagined	5.86 (1.94)	5.19 (1.99)	3.92 (2.27)	0.25 (0.03)	0.015* (0.59)	0.001** (0.91)
Heard	6.03 (1.5)	5.72 (1.88)	4.87 (1.96)	0.7 (0.18)	0.07 (0.44)	0.037* (0.65)
New	7.66 (0.48)	7.69 (0.53)	7.32 (0.82)	0.79 (0.06)	0.069 (0.53)	0.147 (0.49)
Within-subject p-value<0.001*** Between-subject p-value=0.001** Interaction p-value=0.066						
Inversion bias						
Internal source-monitoring						
Internalizations	1.48 (1.09)	1.50 (1.48)	1.34 (1.3)	0.67 (<0.001)	0.47 (0.003)	0.26 (0.003)
Externalizations	0.62 (0.82)	1 (1.29)	1.47 (1.16)	0.26 (0.03)	0.09 * (0.03)	0.007 ** (0.146)
Within-subject p-value=0.005** Between-subject p-value=** Interaction p-value=0.016*						
Reality-monitoring						
Internalizations	1.31 (1.04)	1.22 (1.34)	1.74 (1.33)			
Externalizations	0.86 (1.27)	1.75 (1.59)	1.39 (1.7)			
Within-subject p-value=0.735 Between-subject p-value=0.422 Interaction p-value=0.088						
Forgetting bias						
Internal source-monitoring						
Imagined	1.24 (1.154)	2.13 (1.43)	2.58 (2.02)	0.036* (0.13)	0.246 (0.02)	0.001** (0.10)
Said	0.59 (0.78)	1.19 (1.18)	1.63 (1.81)	0.091 (0.08)	0.181 (0.02)	0.003** (0.11)
Within-subject p-value<0.001*** Between-subject p-value=0.001 ** Interaction p-value=0.007 **						
Reality-monitoring						
Imagined	1.38 (1.35)	1.81 (1.65)	2.45 (2.01)	0.329 (0.02)	0.128 (0.03)	0.014* (0.08)
Heard	0.66 (0.97)	1.09 (0.99)	1.39 (1.37)	0.139 (0.05)	0.277 (0.01)	0.01* (0.08)
Within-subject p-value<0.001 *** Between-subject p-value=0.008 ** Interaction p-value=0.669						

Supplementary Table: After significant ANOVA, groups were compared using TukeyLSD post-hoc tests. Internalization bias are measured as the number of heard words that were classified as imagined (range 0-8). Externalization bias are measured as the number of imagined words that were classified as heard (range 0-8). Forgetting bias are measured as the number of old words (imagined or said) that were classified as new (range 0-8). * p < 0.05; ** p < 0.01; *** p < 0.001

2.4. Conclusion

We adopted a transdiagnostic approach to investigate the specificity of source-monitoring impairments. The first study was a qualitative review on source-monitoring processes in OCD. The second study was a direct comparison of source-monitoring performance between patients with schizophrenia, patients with OCD and healthy controls.

OCD is a severe psychiatric disease characterized by persistent, intrusive, and distressing obsessions and/or compulsions. One cognitive mechanism proposed to explain these symptoms is an impairment in source-monitoring, whereby patients with OCD are more likely to confuse memories of performed and imagined actions (*e.g. Did I imagined turning off the gas or did I really turned off the gas?*). The resulting uncertainty could therefore contribute to obsessive thoughts and compensatory compulsive behaviors. We identified 13 experimental papers exploring source-monitoring in OCD or in people with subclinical compulsive symptoms. Most reported no source-monitoring deficit but reduced confidence in their source-monitoring judgements. Of the studies reporting alterations in source-monitoring, two assessed internal source-monitoring, one assessed reality-monitoring and a last one assessed external source-monitoring. We identified that these inconclusive results could be the result of multiple methodological caveats, including disparities in how the authors defined the different subtypes of source-monitoring, heterogeneity regarding the paradigm used to measure source-monitoring, heterogeneity regarding the clinical populations included, and the lack of control for several potential confounders.

Among the variety of symptoms that can be experienced, one of the main similarities between OCD and schizophrenia is the presence of abnormal self-experiences. For example, the obsessive thoughts of OCD and the delusions of schizophrenia both involve intrusive,

unwanted, and alien thoughts. Both conditions are associated with frequent comorbidities, including schizoaffective disorder and schizotypal personality with OCD. In addition, several neuroimaging studies have reported that patients with OCD exhibit abnormalities within the DMN, including functional connectivity in the amPFC (Beucke et al., 2014; Posner et al., 2016), a region with a key role on source-monitoring. We included 32 patients with OCD, 38 patients with schizophrenia, and 29 healthy controls. We directly compared patterns of source-monitoring performances between these three groups. We found a dissociation between the type of source-monitoring and clinical group. More specifically, we observed that both patients with OCD and patients with schizophrenia had abnormal internal source-monitoring abilities. Only the group of patients with schizophrenia had impaired reality-monitoring. These results suggest that impaired internal source-monitoring may participate in a core deficit overlapping both disorders. However, our results should be taken with caution because of several limitations, including the lack of Bayesian analyses to rule out impaired reality-monitoring in patients with OCD, the lack of subgroup comparisons according to the different clinical profiles of patients with OCD, and the lack of control of confidence in source-monitoring judgements.

Our qualitative review led to very inconclusive results on potential source-monitoring impairments in OCD, but mainly highlighted the importance of 1) systematically exploring confidence levels in source-monitoring judgements, 2) increasing the reproducibility of testing within each source-monitoring subtype. Our experimental study revealed that alterations of internal source-monitoring are a transdiagnostic factor between OCD and schizophrenia. Future studies are needed to take a dimensional approach and understand the relationship between internal source-monitoring alterations and the specific clinical features that overlap between these two diseases. Furthermore, the shared alteration in internal source-monitoring suggests disturbances in partially overlapping brain systems in OCD and schizophrenia. Future studies

are needed to explore the relationship between amPFC functional connectivity and source-monitoring in OCD.

2.5. Immediate perspectives: Investigating source-monitoring in various neuropsychiatric diseases associated with fronto-temporal alterations and hallucinations

Impaired source-monitoring has been repeatedly associated with schizophrenia, particularly in patients with hallucinations. In this first chapter, we have shown that patients with OCD, another psychiatric disease characterized by abnormalities in self experiences and prefrontal dysfunction, also exhibit impaired source-monitoring compared with healthy controls.

Interestingly, other neuropsychiatric diseases have been examined for their source-monitoring performance. For instance, several studies have reported impaired source-monitoring in Alzheimer disease (AD), a disease associated with neurodegeneration of frontal control networks and impaired DMN activity (Zhang et al., 2010). When comparing reality-monitoring performance between healthy older adults and older adults with AD, the latter showed lower performance in remembering whether each word was presented as a picture or imagined (Dalla Barba et al., 1999). A subsequent study assessed reality-monitoring, internal source-monitoring and external source-monitoring using everyday scenarios and all three categories of source-monitoring were compromised in AD patients relative to controls (El Haj et al., 2012).

To better understand the specificity of impaired source-monitoring and to clarify the involvement of the frontotemporal brain areas in source-monitoring, we designed a new study that will compare source-monitoring performance between patients with schizophrenia, healthy controls, and patients with neuropsychiatric diseases characterized by frontotemporal

alterations and certain psychotic features: Alzheimer disease (AD), Parkinson disease (PD) frontotemporal dementia (FTD) and bipolar disorder (BD). This project received ethics approval in 2018 (N° 2018-A00584-51), patient recruitment started in 2019 and is still pending.

We expect that individuals with neuropsychiatric illnesses characterized by frontotemporal alterations and psychotic features will exhibit alterations of source-monitoring similar to those of patients with schizophrenia, compared to healthy controls of the same age. Similar to schizophrenia, we also expect the presence of hallucinations to be associated with more pronounced alterations in reality-monitoring.

3. Second Chapter: Reality-monitoring alterations in the continuum of psychosis

3.1. Introduction

While alterations in source-monitoring have been repeatedly reported in schizophrenia, a recent review showed that patients with hallucinations are particularly impaired in reality-monitoring (Damiani et al., 2022). This is consistent with previous meta-analyses demonstrating that patients with schizophrenia with auditory hallucinations have impaired reality-monitoring abilities (Waters et al., 2012), and especially a greater externalization bias, i.e., they are more likely to attribute an external/perceived source to an internally-generated/imagined information (Brookwell et al., 2013) compared to patients without hallucinations and healthy controls. Interestingly, Waters et al. also reported impaired self-agency in these patients and did not report a significant difference between the reality-monitoring deficit and the self-agency deficit. Self-agency refers to the ability of to monitor the source of self-generated or perceived information in real-time. A recent study demonstrated that reality-monitoring and self-agency performance are correlated in healthy controls and suggested that both of these processes may be underpinned by a unitary experience (Subramaniam et al., 2018).

The continuum of psychosis includes individuals from the at-risk state to chronic schizophrenia, as well as individuals with subclinical symptoms of schizophrenia, like hallucination-proneness. It has been reported that individuals on the continuum without a full-blown diagnostic of schizophrenia share cognitive deficits with patients with schizophrenia. However, it remains unclear whether they also have abnormalities of self-recognition, i.e., reality-

monitoring and self-agency. In this study, we took a meta-analytical approach to better understand the specificity of self-recognition abnormalities across the continuum of psychosis.

3.2. Impaired self-recognition in individuals with no full-blown psychotic symptoms across the continuum of psychosis: a meta-analysis [Article 3]

Article 3: Impaired self-recognition in individuals with no full-blown psychotic symptoms represented across the continuum of psychosis: a meta-analysis. Psychological Medicine. 2020.

Lavallé L., Dondé C., Gaweda L., Brunelin J., Mondino M.

TAKE HOME MESSAGE

- **Impairments in self-recognition (i.e., recognition of own thoughts and actions) have been repeatedly shown in patients with schizophrenia.**
- **The current meta-analysis aims to determine whether self-recognition is affected in individuals included in the continuum of psychosis.**
- **Three populations were included: people with clinical risk, people with genetic risk and hallucination-prone healthy individuals.**
- **Two experimental paradigms evaluating self-recognition were included: source-monitoring and self-monitoring.**
- **Self-recognition was significantly reduced in all these populations compared to controls.**
- **No difference was reported between populations and experimental paradigms.**

Original Article

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Impaired self-recognition in individuals with no full-blown psychotic symptoms represented across the continuum of psychosis: a meta-analysis

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Abstract

Background. Impairments in self-recognition (i.e. recognition of own thoughts and actions) have been repeatedly shown in individuals with schizophrenia. According to classical clinical characterizations, schizophrenia is included in a continuum encompassing a large range of genetic statuses, psychotic states and symptoms. The current meta-analysis aims to determine whether self-recognition is affected by individuals within the psychosis continuum.

Method. Three populations were considered: people with an at-risk mental state for psychosis (ARMS), hallucination-prone individuals and unaffected relatives of patients with schizophrenia. Eleven studies contrasted self-recognition between these three populations ($n = 386$) and healthy controls ($n = 315$) and four studies used correlational analysis to estimate comparable effects ($n = 629$). Eligible studies used experimental paradigms including source-monitoring and self-monitoring.

Results. We observed significantly reduced self-recognition accuracy in these populations [$g = -0.44$ (-0.71 to -0.17), $p = 0.002$] compared to controls. No influence of the type of population, experimental paradigm or study design was observed.

Conclusion. The present analysis argues for self-recognition deficits in populations with no full-blown psychotic symptoms represented across the continuum of psychosis.

Introduction

Schizophrenia is a psychotic disorder associated with positive symptoms such as hallucinations and delusions (Owen, Sawa, & Mortensen, 2016). Among others, failure in self-recognition abilities (i.e. recognition of own thoughts and actions) has been proposed as a cognitive mechanism that underlies these symptoms. According to this theory, defective internal labeling of own thoughts/actions associated with their misattribution to an external source may lead patients to experience their thoughts as coming from external agents (i.e. auditory hallucinations) or their acts as arising from alien control (i.e. delusion of control) (Frith, Blakemore, & Wolpert, 2000; Frith & Done, 1988). Supporting this assumption, schizophrenia studies have repeatedly demonstrated that misidentification of internal and external sources of events is a consistent trait of the disorder (Brookwell, Bentall, & Varese, 2013; Waters, Woodward, Allen, Aleman, & Sommer, 2012). Self-recognition deficits have been investigated through self-monitoring paradigms, in which patients receive a distorted feed-back of their own spoken word/motor action and are requested to identify it online as self- or non-self-produced. In parallel, such impairments are believed to be reflected by the so-called ‘source-monitoring’ deficits (i.e. failure in remembering the source of an information) (Johnson, Hashtroudi, & Lindsay, 1993). In this framework, deficits in remembering between self-generated *v.* experimenter-generated events and between self-generated information kept in the inner space (thoughts) *v.* events produced in the outer space (Bentall, 1990; Brunelin et al., 2006a, 2006b; Woodward, Menon, & Whitman, 2007) are termed reality- and internal- monitoring processes, respectively (Johnson et al., 1993). Source-monitoring testing procedures consist of two phases: encoding and retrieval. During the encoding phase, information from different sources is presented to the subject. During the retrieval phase, the subject has to identify to which source is the information associated.

According to classical characterizations of psychotic disorders, schizophrenia is included into a continuum encompassing a large range of genetic statuses, psychotic states and symptoms. A recent model defines the ‘At-Risk Mental State’ for psychosis (ARMS) (McGorry, Hartmann, Spooner, & Nelson, 2018), a condition that includes people who have experienced attenuated

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positive psychotic symptoms during the past year (APS), or episodes of frank psychotic symptoms that have not lasted longer than a week and have spontaneously abated [Brief Limited Intermittent Psychotic Symptoms (BLIPS)], and people with schizotypal personality or genetic risk and deterioration syndrome (GRD) (Fusar-Poli et al., 2013). In addition, the psychosis continuum acknowledges observations of subclinical experiences in non-clinical populations, such as hallucination-prone people and unaffected relatives of patients with schizophrenia (often referred as genetic risk group) (Verdoux & van Os, 2002). Widespread impairments in neurocognitive functions have been demonstrated in ARMS (Bora & Murray, 2014; Fusar-Poli et al., 2012; Giuliano et al., 2012) and people with hallucination proneness (Brébion, Laroï, & Van der Linden, 2010; Gupta, DeVlyder, Auerbach, Schiffman, & Mittal, 2018; Morrison, Wells, & Nothard, 2000). Moreover, several studies observed deficits in executive functioning, attention and verbal ability in unaffected relatives (Faraone et al., 1995; Saoud et al., 2000), thereby suggesting the existence of a 'cognitive' continuum, i.e. a continuum in cognitive impairments, from healthy functioning to full-blown psychotic disorder that encompasses subclinical alterations and severe clinical manifestations (Johns & van Os, 2001). Critically, since unaffected relatives and ARMS individuals have been associated with a prospective risk of developing schizophrenia (McGorry & Killackey, 2002; Morrison et al., 2004), there has been an increasing focus on the ability of cognitive measures to predict transition to psychosis and index the physiological processes that underlie psychotic symptoms. Thus, identifying cognitive markers of the psychosis continuum has been one of the main objectives of clinical research in psychiatry over the last decades in order to identify individuals at risk to develop schizophrenia and propose early interventions.

Here, we hypothesized that individuals with no full-blown psychotic symptoms represented across the continuum of psychosis (i.e. ARMS, hallucination-prone individuals and unaffected relatives of patients with schizophrenia) would display significant deficits in self-recognition processes. In the context of growing interest for cognitive markers of the psychosis continuum and the need to extend our knowledge in the field of self-recognition processing in psychosis, we undertook a meta-analysis of the existing literature investigating self-recognition performance across the three populations.

The objectives were threefold: (i) to investigate self-recognition abilities in individuals with no full-blown psychotic symptoms represented across the continuum of psychosis, (ii) to measure the moderating effect of the population type on self-recognition abilities and (iii) to identify whether self-recognition abilities in these populations are influenced by a task-specific effect.

Methods

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009). The protocol was registered in PROSPERO (Chien, Khan, & Siassakos, 2012) (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=129873; registration number: CRD42019129873).

Literature search strategy

Eligibility

Studies were selected with the following inclusion criteria: (i) articles published in English language in peer-reviewed

journals, (ii) studies including participants with an ARMS (individuals with APS, BLIPS or GRD), hallucination-prone individuals, and/or unaffected relatives of patients with schizophrenia, (iii) studies including participants without any established clinical diagnosis of neurological and psychiatric condition according to the Diagnostic and Statistical Manual of Mental Disorders DSM-5 (or DSM-IV) criteria, (iv) studies using either self- or source-monitoring experimental paradigms and providing clear information regarding the task used, (v) studies with a within-group design (studying correlation between symptom severity and self-recognition performance) or between-group design (studying self-recognition difference between subclinical and control groups) and (vi) studies providing sufficient statistical indices for self-recognition correct responses (means \pm standard deviations or correlation coefficients \pm variance).

Search strategy

We searched for articles in the PubMed, ScienceDirect and PsycINFO databases with no limitation of date until 22 June 2019.

Combination of the following keywords was used: '((source AND (monitoring OR memory)) OR ((internal) AND (memory OR monitoring)) OR ((self) AND (memory OR monitoring)) OR ((reality) AND (memory OR monitoring))) AND ((psychosis OR psychotic OR schizophrenia) AND (risk OR prodrom* OR predict OR transition OR conversion OR relatives)) OR ((schizotyp*) AND (Ultra High Risk) AND (UHR) AND (Brief Limited Intermittent Psychotic Symptoms) AND (BLIPS) AND (Attenuated Psychotic Symptoms) AND (APS) AND (At Risk Mental States for Psychosis) AND (attenuated symptoms) AND (prepsycho*) AND (hallucination prone*) AND (genetic risk) AND (clinical high risk) AND (basic symptoms)'. Additional references were retrieved by cross-referencing the reference lists of selected articles. The 'similar articles' function in PubMed was also employed although no additional references were identified in this manner.

After excluding duplicate publications, two reviewers (authors LL, CD) independently screened the title, abstract and keywords of each study to apply the inclusion criteria. In a second time, the same procedure was applied to the full text of eligible studies. Discrepancies between reviewers were resolved by discussion with a third author (MM). Study selection is described in Fig. 1 (PRISMA diagram).

Data extraction

Authors LL and CD independently extracted the following data: (i) demographic variables (sample size, mean age, gender ratio), (ii) population studied (ARMS, hallucination-prone individuals or unaffected relatives), (iii) study design and type of self-recognition task, and (iv) statistical indices regarding correct discrimination of self *v.* other sources (i.e. self-recognition correct responses).

When data were missing, the concerned authors were contacted for additional data request. We ensured that different participants were included in the different reports from the same research groups. To measure the overall quality of the included studies, a global rating score was calculated for each study by two independent authors (LL, CD) using the Standard Quality Assessment (QualSyst tool (Kmet, Lee, & Cook, 2004)).

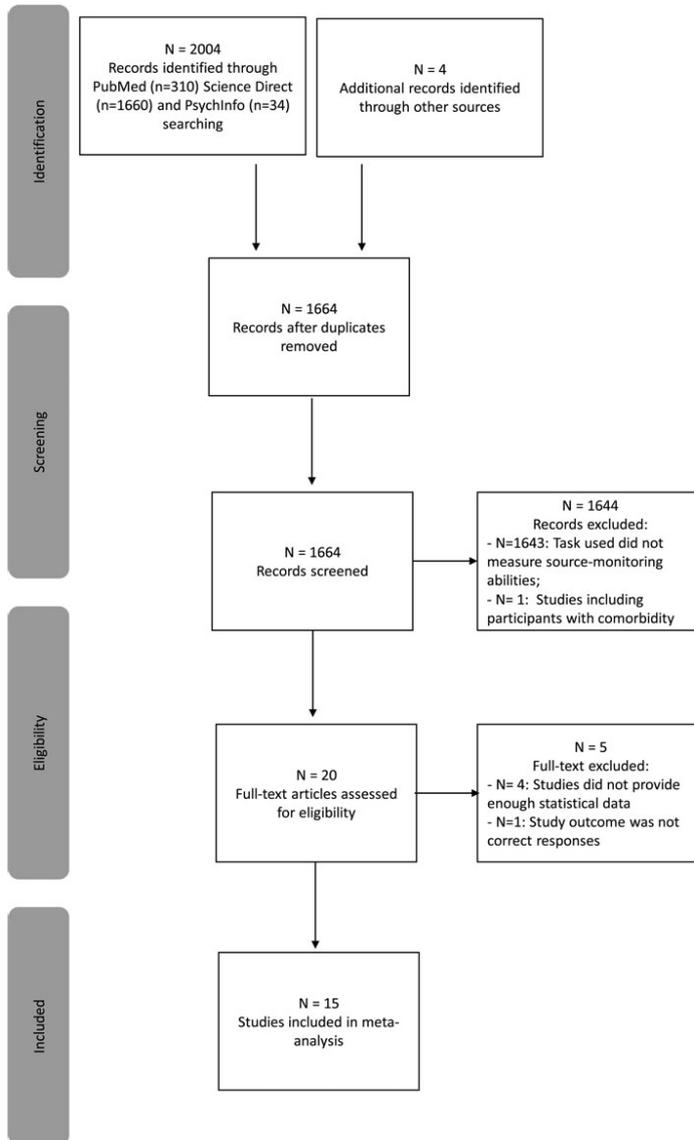


Fig. 1. PRISMA flowchart describing the literature search and screening stages.

Meta-analysis

Outcome

All Statistical analyses were carried out using R Studio software version 1.0.143 (R Core Team, 2018). Mathematical equations used to compute effect size are presented in online Supplementary Material. The alpha level for significance was set at $p < 0.05$.

When provided, we extracted means and standard deviations (s.d.) for correct recognitions (i.e. accuracy) in self- and

source-monitoring tasks in both the control group and subclinical groups. We calculated Cohen’s d effect size with 95% confidence intervals (95% CI) (Cohen, 2009). For studies investigating correlations between self-recognition scores and psychometric scale scores characteristic of the subclinical group, we extracted correlation coefficients (Pearson’s r) and variance (Vr) and transformed these values into Cohen’s d and variance (Vd) (Borenstein, Hedges, Higgins, & Rothstein, 2010). When variances

for Pearson's r were not available, we estimated them using Campbell's calculator (Polanin & Sniltveit, 2016). Regarding Spearman correlation coefficients (ρ), same transformations were applied since ρ are equivalent to Pearson's r using rank data or are slightly smaller if the data follow a binomial distribution (Gilpin, 1993). Given the small sample size, Cohen's d was finally converted into Hedges' g (Hoyt & Del Re, 2018), which use pooled weighted standard deviations instead of pooled standard deviation.

When studies reported scores on multiple outcome measures with no available overall effect but multiple dependent effect-sizes (ES) (e.g. using stimuli with multiple emotional valences or presenting different levels of distortion in self-monitoring experimental paradigm), these were aggregated prior to analysis so that each independent samples from one study contributed only to one single ES. To this end, the univariate procedure described by Gleser & Olkin (Cooper, Hedges, & Valentine, 2009) was used with imputation of $r = 0.5$, a conservative and typical starting correlation value for aggregating psychologically-based ES (Wampold et al., 1997). Then, all ES were computed to derive an overall summary effect.

As methods and sample characteristics differed across included studies, a random-effect approach was used to model the variability of the summary effect among the true ES of individual studies. We interpreted the magnitude of summary ES (g) using Cohen's interpretative guidelines (0.2 = small ES; 0.5 = medium ES; 0.8 = large ES (Cohen, 2009).

The overall summary ES was represented by a forest plot. In case of visual heterogeneity across studies, variances of the true ES were quantified by τ^2 test. The proportion of the observed variance reflecting real differences between the true ES was computed by I^2 heterogeneity statistic. The I^2 statistic values 25, 50 and 75% reflected a small, moderate or high degree of heterogeneity, respectively (Higgins, Thompson, Deeks, & Altman, 2003).

Publication bias

Publication bias was first assessed by visual inspection of the funnel plot. In the case of asymmetry of the funnel plot, a Rank Correlation Test and an Egger's Regression Test were performed to determine the significance of the publication bias. Additionally, a QQ-plot was analysed to identify potential outliers.

Moderator analysis

Subgroup analyses were performed to assess relevant categorical variables as moderators. Meta-regressions were performed when potential moderators were continuous variables or when the number of studies within each subgroup was not enough to provide necessary statistical power for subgroup analysis according to the moderator.

Meta-regressions

Several Factors that might have influenced self-recognition performance were investigated. First, as it has been reported that age may influence self-recognition performances (Henkel, Johnson, & De Leonardis, 1998), we measured its potential influence on ES. The effect of the type of subclinical group was also investigated as an exploratory analysis. Finally, we measured the influence of the methodological quality of studies on ES using the Standard Quality Assessment scores (QualSyst tool (Kmet et al., 2004), online Supplementary material S1) as a potential

moderator. We used mixed-effects meta-regression models to evaluate if these factors accounted for a multiple moderator effect.

Subgroup ANALYSIS

In similar fashion to the method described by Brookwell et al. (2013), a first subgroup analysis was carried out to compare studies using self-monitoring and studies using source-monitoring paradigms. To this end, overall effects from two independent meta-analyses were obtained by fitting two separate random-effects models within source- and self- subsets of studies. Then, we combined the true ES and standard errors within each model, to compute one summary ES per model. Finally, we analysed whether the two summaries ES differed significantly using a Wald-type test that uses a fixed-effects model.

Results

Studies selection

The primary search yielded 2008 results. Among them, 344 duplicates were removed, and 1644 abstracts were excluded according to the eligibility criteria. The remaining 20 studies were then assessed for eligibility based on full-length articles. Overall, 15 references were included in the meta-analysis with a total of 1307 subjects (Aldebot Sacks, Weisman de Mamani, & Garcia, 2012; Alderson-Day et al., 2019; Allen, Freeman, Johns, & McGuire, 2006; Brunelin et al., 2007; Garrison et al., 2017; Gawęda et al., 2018; Humpston, Linden, & Evans, 2017; Johns et al., 2010; Larøi, Collignon, & Van der Linden, 2005; Larøi, Van der Linden, & Marczewski, 2004; Marjoram et al., 2006; Peters, Smeets, Giesbrecht, Jelacic, & Merckelbach, 2007; Szöke et al., 2009; Versmissen et al., 2007a, 2007b) (Fig. 1).

Characteristics of selected studies

Among the 15 included studies, 11 used a group comparison design to investigate the mean source-monitoring differences between groups within the psychosis continuum [ARMS (nine studies, $N = 188$), hallucination prone individuals (four studies, $N = 66$), unaffected first-degree relatives (four studies, $N = 132$)] (Total $N = 386$, mean age 29.2 ± 9.7 ; range 19.2–45.7 years old) and control groups ($N = 315$, mean age 29.9 ± 10.2 ; range 20.3–46.7) (Brunelin et al., 2007; Garrison et al., 2017; Gawęda et al., 2018; Johns et al., 2010; Larøi et al., 2004, 2005; Marjoram et al., 2006; Peters et al., 2007; Szöke et al., 2009; Versmissen et al., 2007a, 2007b). The remaining four studies investigated the correlations between self-recognition and symptoms in ARMS (three studies, $N = 579$) (Aldebot Sacks et al., 2012; Alderson-Day et al., 2019; Humpston et al., 2017) and hallucination-prone (one study, $N = 57$) (Allen et al., 2006) individuals (total $N = 655$, mean age 22.2 ± 3.6 ; range 19.2–27.3. ARMS samples only included individuals with APS and BLIPS.

Types of self-recognition paradigms used across the selected articles were either source-monitoring tasks [11 studies (Aldebot Sacks et al., 2012; Brunelin et al., 2007; Garrison et al., 2017; Larøi et al., 2004, 2005; Marjoram et al., 2006; Szöke et al., 2009)] or self-monitoring tasks [four studies (Allen et al., 2006; Johns et al., 2010; Versmissen et al., 2007a, 2007b)] (Table 1).

All studies used verbal, action or drawing recognition paradigms. Details of included studies are provided in online Supplementary Material S2.

Table 1. Characteristics of the studies included in the meta-analysis

Study	ARMS, HP and/or UR				Healthy controls			Samples from correlation studies			Task used	Type of task
	n	Subgroup	Mean age	Sex ratio (F:M)	n	Mean age	Sex ratio (F:M)	n	Mean age	Sex ratio (F:M)		
Brunelin et al. (2007)	15	UR	28.5	NR	15	29.1	NR	NA	NA	NA	Source	Verbal
Marjoram et al. (2006)	25	ARMS	29.85	NR	13	29.6	NR	NA	NA	NA	Source	Drawing
Szöke et al. (2009)	37	UR	45.68	19:18	42	41.5	22:20	NA	NA	NA	Source	Verbal
Garrison et al. (2017)	25	HP	19.8	18:7	22	22.9	20:2	NA	NA	NA	Source	Verbal
Aldebot Sacks et al. (2012)	NA	ARMS	NA	NA	NA	NA	NA	420	19.18	264:156	Source	Verbal
Larøi et al. (2005)	16	HP	22.8	7:9	16	23	8:8	NA	NA	NA	Source	Action
Larøi et al. (2004)	25	HP	25.4	13:12	25	23.21	14:11	NA	NA	NA	Source	Verbal
Johns et al. (2010) *	31	ARMS	24.7	12:19	31	24.6	13:18	NA	NA	NA	Self	Verbal
Allen et al. (2006)	NA	ARMS	NA	NA	NA	NA	NA	57	27.34	8:25	Self	Verbal
Gawęda et al. (2018) **	36	ARMS	19.17	19:17	33	20.27	22:11	NA	NA	NA	Source	Action
Versmissen et al. (2007a)	78	UR + ARMS	42.2	21:18	52	47	32:20	NA	NA	NA	Self	Verbal
Versmissen et al. (2007b)	81	UR + ARMS	42.25	NR	49	46.7	NR	NA	NA	NA	Self	Action
Alderson-Day et al. (2019)	NA	HP	NA	NA	NA	NA	NA	76	20.21	65:11	Source	Verbal
Peters et al. (2007)	17	ARMS	21.41	12:5	17	21.12	11:6	NA	NA	NA	Source	Action
Humpston et al. (2017)	NA	ARMS	NA	80:22	NA	NA	NA	102	22.3	80:22	Source	Action

ARMS, At-Risk Mental State; HP, hallucination-prone; UR, unaffected first-degree relatives; NA, not applicable; NR, no data reported.

* In Johns et al. (2010), participants received medication: AP: antipsychotic (16%) + AD: antidepressant (25.8%) + CBT: Cognitive-Behavioral Therapy (51.6%).

** In Gawęda et al. (2018), participants received medication: AP (5%) + AD (63.8%).

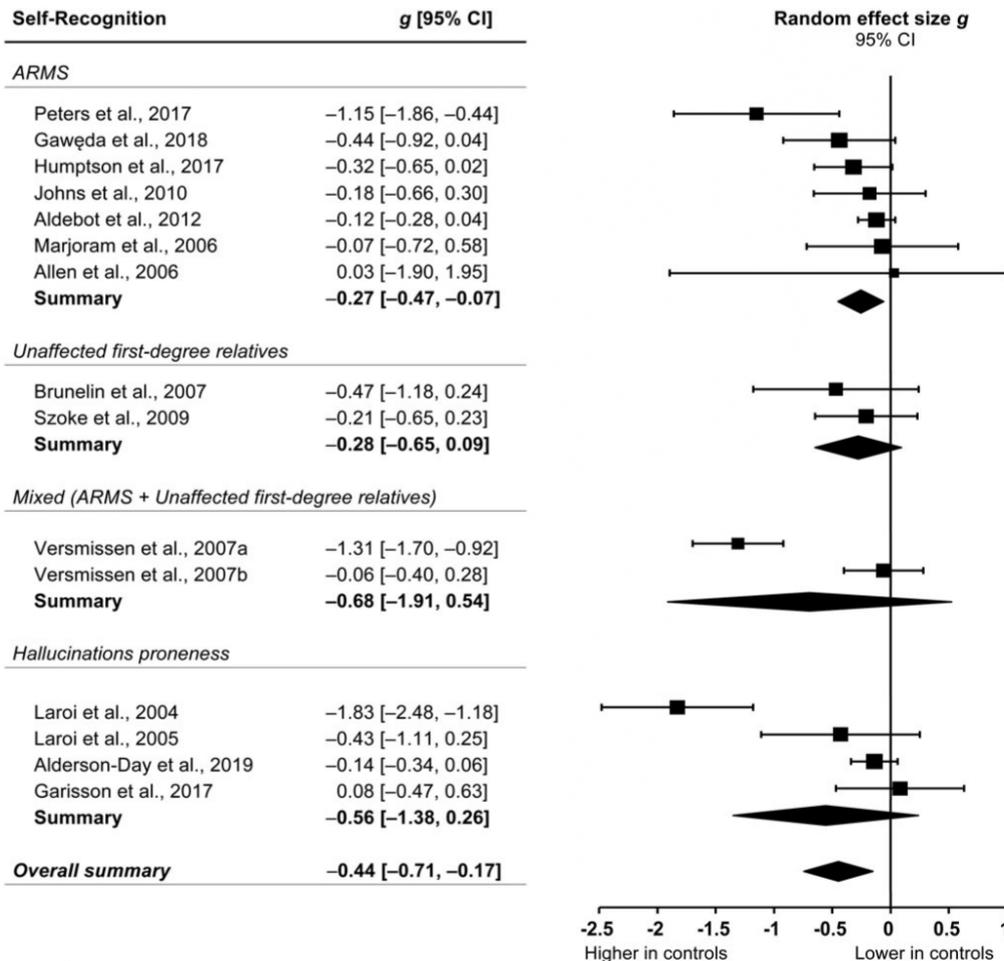


Fig. 2. Forest Plot. Effect Size estimates of self-recognition accuracy. ARMS, At-Risk Mental State.

Random effect model: self-recognition performance

The present meta-analysis investigated self-recognition performance in populations with no full-blown psychotic symptoms represented across the continuum of psychosis (ARMS, hallucination-prone individuals and unaffected relatives). Overall, 15 studies were eligible for meta-analysis (Aldebot Sacks et al., 2012; Alderson-Day et al., 2019; Allen et al., 2006; Brunelin et al., 2007; Garrison et al., 2017; Gawęda et al., 2018; Humpston et al., 2017; Johns et al., 2010; Larøi et al., 2004, 2005; Marjoram et al., 2006; Peters et al., 2007; Szöke et al., 2009; Versmissen et al., 2007a, 2007b). Our analysis associated these populations with small-to-moderate but significant impairments in self-monitoring accuracy [$g = -0.44$ (-0.71 to -0.17), $p = 0.002$]. The overall summary effect is depicted in the Forest Plot (Fig. 2).

The Q-statistic revealed a significant heterogeneity between ES (QE p value < 0.05). The amount of true ES variance was evaluated to $\tau^2 = 0.21$. With a moderate degree of uncertainty, a large proportion of this variance reflected true heterogeneity [$I^2 = 84.69\%$ (67.48–94.49)]. The Baujat plot (online Supplementary Material S2) indicated that one study (Versmissen et al., 2007a) mostly influenced the overall summary ES and contributed to its heterogeneity. After removing this outlier, the ES dropped to $g = -0.35$ (-0.59 to -0.11) but was still significant ($p = 0.004$).

Publication Bias

Visual inspection of the funnel Plot (Fig. 3) revealed a slight asymmetry, which was not significant according to the standard Rank Correlation Test (Kendall's $\tau = -0.36$; $p = 0.06$). We also conducted an Egger's Regression Test that was not significant

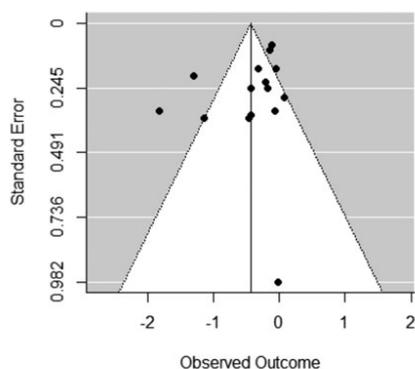


Fig. 3. Funnel Plot. Publication bias visualisation.

($z = -0.71$; $p = 0.47$). Finally, a normal Q-Q plot did not identify any outlier study (online Supplementary Material S3).

Moderators analysis

The high heterogeneity of the overall summary ES ($I^2 = 84.69\%$) warranted the examination of potential moderators.

Meta-regression did not reveal any effect of age ($\beta_1 = -0.21$, $p = 0.63$) and type of subclinical population ($\beta_{\text{hallucination-prone}} = -0.53$; $\beta_{\text{unaffected first-degree relatives}} = -0.32$; $\beta_{\text{ARMS}} = -0.34$; $\beta_{\text{ARMS+unaffected first-degree relatives}} = -0.67$, $p = 0.07$) on self-recognition accuracy. No significant effect of the quality of studies on self-recognition scores was observed ($\beta_{\text{quality}} = -0.46$; $p = 0.72$). The Wald-type test for subgroup analyses indicated that studies using a self-monitoring task ($\beta_{\text{self-monitoring}} = -0.47$; $\text{s.e.} = 0.35$) showed similar ES than studies using a source-monitoring task ($\beta_{\text{source-monitoring}} = -0.42$; $\text{s.e.} = 0.38$). The difference between the two summaries ES was not significant ($z = -1.33$; $p = 0.89$). Thus, as pictured in the boxplot (online Supplementary Material S4), self- and source-monitoring paradigms had a similar effect on the overall summary ES.

Given the high heterogeneity across studies and the absence of any significant effect from investigated moderators (age, type of subclinical group, quality of studies and type of task), a second subgroup analysis was carried out to compare between-group and correlation design subsets. Given that the experiment that mostly contributing to heterogeneity used a correlation design (Szöke et al., 2009) (online Supplementary Material S3), we suspected that type of study design may account as a significant moderator. The Wald-type test indicated that between-group ($\beta_{\text{between-group}} = -0.54$; $\text{s.e.} = 0.191$) showed larger negative ES than correlation studies ($\beta_{\text{correlation}} = -0.15$; $\text{s.e.} = 0.06$). The difference between the two ES was significant ($z = -2.52$; $p = 0.04$). As pictured in the boxplot (online Supplementary Material S4), the type of study design strongly influenced the overall summary ES, and its magnitude was mostly driven by between-groups studies.

Discussion

To the best of our knowledge, this is the first meta-analysis investigating self-recognition ability in populations with no full-blown psychotic symptoms represented across the continuum of

psychosis. The main finding is that these individuals display significant self-recognition deficits compared to healthy controls, with a small-to-moderate magnitude effect size. The deficit was not influenced by age, type of population (ARMS, hallucination-prone individuals, unaffected first-degree relatives), or type of self-recognition paradigm (self-monitoring v. source-monitoring tasks).

Self-recognition deficits across the continuum of psychosis

Regarding the type of population, the deficit in the included subjects with an ARMS (here, APS and BLIPS) intimates that a failure in recognizing self-generated information is associated with attenuated psychotic symptoms. Additionally, the deficit observed in unaffected first-degree relatives suggests that self-recognition impairment may be associated with an increased risk of familial liability to psychosis, independently from the presence of psychotic symptoms. Finally, we replicated previous findings of self-recognition deficits in hallucination-prone individuals (Brookwell et al., 2013), which suggest that self-recognition deficit may also serve as a potential marker of risk for hallucinations. Regarding the type of self-recognition paradigm, we observed that the magnitude of the deficit was similar in both self-monitoring and source-monitoring tasks. Although source-monitoring tasks present a memory component missing in self-monitoring paradigms, this observation confirms that both experimental paradigms may index a common cognitive process that is affected in populations with no full-blown psychotic symptoms. By contrast, a previous meta-analysis (Brookwell et al., 2013) failed to associate hallucinatory experiences with self-recognition deficit within a subset of studies using a self-monitoring paradigm. Nevertheless, the negative result may be explained by the small number of included studies using a self-monitoring experimental paradigm (two studies out of 27).

More broadly, our findings are consistent with previous results demonstrating additional cognitive impairments in unaffected relatives of patients with schizophrenia (Faraone et al., 1995; Green, Nuechterlein, & Breitmeyer, 1997; Saoud et al., 2000), hallucination-prone individuals (Alderson-Day et al., 2019) and subjects with an ARMS (Eisenacher et al., 2018; Ohmuro et al., 2018). Since many studies have shown large self-recognition impairments in patients with schizophrenia (reviewed in Brookwell et al., 2013; Waters et al., 2012), the present analysis argues for a cognitive continuum regarding self-recognition abilities from non-clinical subjects to full-blown psychosis. As compared to the moderate-to-large self-recognition deficit described in patients with schizophrenia ($ES = -0.73$ in Waters et al., 2012), the present small-to-moderate effect ($ES = -0.44$) suggests this deficit to vary from less to more across non-clinical and clinical subjects. Future studies are warranted to directly compare self-recognition performances between patients with diagnosed schizophrenia and subjects with no full-blown psychotic symptoms represented across the continuum for psychosis.

Although self-recognition deficits have been associated with positive symptoms of schizophrenia, an inverse correlation has also been reported between source-monitoring errors and negative symptoms (Brébion, Gorman, Amador, Malaspina, & Sharif, 2002; Brébion, Ohlsen, Bressan, & David, 2012). However, investigating correlations between the severity of negative dimension and source-monitoring performances in first-degree relatives of patients with schizophrenia led to non-significant results (Szöke et al., 2009). Otherwise, this study did

not find any correlation between positive dimension and source-monitoring scores. It would be fruitful to examine potential relationships between positive and negative dimensions and self-recognition scores in various subclinical and non-clinical populations represented across the continuum for psychosis.

Neurobiological substrates

Self-recognition deficits observed in individuals with an ARMS, hallucination-prone individuals and unaffected first-degree relatives suggest that these populations may share neural alterations with patients with diagnosed psychosis.

In healthy subjects, frontotemporal connectivity is thought to underpin self-recognition processes. On the one hand, activation of the prefrontal cortex (PFC) has been associated with correct attributions of internally produced information (Mitchell & Johnson, 2009; Sugimori, Mitchell, Raye, Greene, & Johnson, 2014). On the other hand, activation of the superior temporal gyrus (STG) has been associated with the perception of externally produced but not internally produced information (Allen *et al.*, 2007; Simons, Davis, Gilbert, Frith, & Burgess, 2006; Sugimori *et al.*, 2014). In patients with schizophrenia, the main hypothesis for the self-recognition deficit involves a defective prefrontal lobe activation that fails to inhibit the temporal lobe and lead, in turn, to an external misattribution of self-generated materials (Ford & Mathalon, 2005; Frith, 1996). The relationship between self-recognition deficits and frontotemporal functional disruption in patients with schizophrenia is supported by imaging studies demonstrating a significant association between auditory hallucinations, source-monitoring errors and STG hyperactivity (Jardri, Pouchet, Pins, & Thomas, 2011; Sugimori *et al.*, 2014). Furthermore, repeated sessions of non-invasive electrical brain stimulation applied over the STG and the PFC have been shown to induce a significant increase of source-monitoring performance, as well as a reduction of auditory hallucination in patients (Brunelin, *et al.*, 2006b; Mondino, Haesebaert, Poulet, Suard-Chagny, & Brunelin, 2015).

Even it remains speculative, one can hypothesize that the significant self-recognition deficit in individuals with no full-blown psychosis is associated with the comparable frontotemporal functional alteration. However, at present, only one study assessed neurobiological correlates of source-monitoring deficit in ARMS. This study demonstrated activation in anterior PFC during source-monitoring but less activation in subjects with higher schizotypal traits (Lagioia *et al.*, 2011). Toward a better characterization of self-recognition processes, future studies are warranted to investigate the neural mechanisms associated in these individuals.

Limitations

Several limits should be acknowledged. First, our main outcome was the number of correct responses at self- and source-monitoring tasks. This did not allow investigating the directionality of the recognition bias, *i.e.* whether individuals misattribute internal information as external (externalization bias) or misattribute external information as internal (internalization bias). Consequently, while we reported a failure in self-recognition in ARMS, hallucination-prone individuals and unaffected first-degree relatives, we were not able to conclude if one bias over another is more specific to these populations. Additionally, since Brookwell *et al.* (2013) concluded about a specific externalization bias in patients with schizophrenia and hallucination-

prone subjects, our analysis involved scores indexing both misattribution biases, which may account for the small overall effect.

Second, the analyses reported a large heterogeneity in the aggregated analysis that was not explained by between-population (*i.e.* ARMS, hallucination-prone individuals, unaffected first-degree relatives) differences. Between-tasks analysis only showed a trend for a significant difference between self and source paradigms. However, the low number of studies included involved an imbalance across groups in the task used (*e.g.* there is no 'hallucination-prone group' with task 'self'), which represents a potential bias to the negative results on between-populations and between-tasks differences. The analyses rather indicate a large amount of heterogeneity to be explained by the type of design used across studies (between-groups *v.* correlation designs). We observed that the magnitude of the deficit was mostly driven by between-groups studies. Thus, the inclusion of four correlations studies in the meta-analysis may represent a potential limitation. However, by assessing correlations between self-recognition measures and psychometric scale scores, these studies establish a more detailed description of the relationship between the psychometric parameter and the self-recognition deficit.

Third, two studies included medicated subclinical individuals (Gawęda *et al.*, 2018; Johns *et al.*, 2010) and three studies did not provide information on subjects' medication status (Aldebot Sacks *et al.*, 2012; Versmissen *et al.*, 2007a, 2007b). The medication status seems particularly important since antipsychotic medication has been associated with improvement of self-recognition abilities in patients with schizophrenia (Keefe, Poe, McEvoy, & Vaughan, 2003). Further studies are required to investigate the effects of psychotropic medication on self-recognition performance.

Fourth, this meta-analysis included studies with different task designs including words, actions, drawings and voices items. This experimental diversity may participate in the large heterogeneity between effect-sizes. However, a previous meta-analysis revealing a significant self-recognition impairment in patients with schizophrenia included studies using a wide variety of paradigms, including action, words or speech recognition tasks (Waters *et al.*, 2012). This indicates that the requirement to make a self-recognition judgment underscores the deficit, regardless of the experimental paradigm.

Finally, the inclusion of three different subgroups may represent a potential limitation in this study. Indeed, self-recognition seems significant for the single ARMS group, whereas the other groups display negative non-significant effect-sizes. Nevertheless, meta-regression showed a lack of significant effect of the type of subgroup, arguing for continuity between subgroups regarding self-recognition deficit.

Conclusion

Several populations with no full-blown psychotic symptoms represented across the continuum of psychosis display similar deficits for multiple self-recognition experimental paradigms. Future studies involving subclinical and non-clinical subjects across the continuum, patients with first-episode of psychosis and patients with schizophrenia are warranted to compare such deficit in different stages of the continuum. In the context of growing interest for early intervention, we recommend 2-years follow-up studies (Nelson, Yuen, & Yung, 2011) to address whether early self-recognition deficit could predict potential transition to psychosis in subclinical and non-clinical populations. Furthermore, developing remediative approaches that specifically target self-

recognition abilities might be relevant for these individuals. In addition, future studies may benefit from assessing directional source-recognition inversion scores to increase their statistical power and may also benefit from including drug-naïve subclinical individuals, which may provide more reliable measures of self-recognition performances. Finally, neuroimaging and neurostimulation studies are required to explore the neurobiological correlates of self-recognition deficit across multiple in populations with no full-blown psychotic symptoms represented across the continuum.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/S003329172000152X>.

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Supplementary material

Source-monitoring tasks	Studies
<u>Imagine hearing vs. hear words:</u> Participants had to either <u>hear</u> or imagine hearing words. Then, during the test phase, they had to recognize whether the word was heard, imagined or new.	Brunelin et al., 2007
<u>Word pair completion:</u> Participants are presented with a list of partially completed words phrases. They had to either listen the experimenter completing phrases or complete and read out words by themselves. Then, during the test phase, participants had to recognize whether the word was generated by the experimenter, by themselves or new.	Garrison et al., 2017 Alderson-Day et al., 2019
<u>Self-generated vs. read aloud vs. silently read vs. heard words:</u> The material includes a list of semantic categories as well as words belonging to each category. For each category, participants had to: generate words examples, read the words out loud, read the words silently or listen the experimenter read out the words. Then, during the test phase, participants had to recognize whether words were generated by themselves, read aloud or silently by themselves, read by the experimenter or new.	Szoke et al., 2009
<u>Self-generated vs. experimenter-generated words:</u> Participants are presented with a list of words and had to generate some other words by themselves. Then, during the test phase, participants had to recognize whether the word was generated by themselves, by the experimenter or new.	Aldebot Sacks et al., 2012 Laroi et al., 2004
<u>Imagine performing vs. perform actions:</u> Participants had to either perform or imagine performing actions. Then, during the test phase, participants had to recognize whether the action was performed or imagined.	Gaweda et al., 2018 Peters et al., 2017
<u>Perform vs. watch performing actions:</u> Participants had to either perform or watch performing actions. Then, during the test phase, they had to recognize if actions were performed by themselves, by the experimenter or new.	Humpston et al., 2019
<u>Imagine performing vs. perform vs. watch performing vs. imagine watching performing actions:</u> Participants had to imagine performing action, perform actions by themselves, watch the experimenter performing actions or imagine themselves watching the experimenter performing actions. Then, during the test phase, participants had to recognize whether actions were performed by themselves or by the experimenter, or whether they imagined themselves or the experimenter performing the actions.	Laroi et al., 2005
<u>Self vs. other-generated drawings:</u> Participants had to generate drawings. Then, during the test phase, they had to identify their own drawings from drawings generated by other people.	Marjoram et al., 2006
Self-monitoring tasks	
<u>Self vs. other words:</u> Participants are presented with a list of words they have to read aloud in a microphone. The speech was fed back though headphones. In some of the trials, the pitch were unchanged or distorted with various levels of distortion. In other trials, participants heard someone else' voice instead of their voice. Participants had to indicate if the speech they heard was generated by themselves or by someone else.	Versmissen et al., 2007a Versmissen et al., 2007b Johns et al., 2010
<u>Self vs. other pre-recorded words:</u> Subjects had to listen pre-recorded words with varying source (self/other) and acoustic quality (distortion level). Subjects had to indicate if the words were spoken in their own or another voice.	Allen et al., 2006

Supplementary material 1: Description of the experimental paradigms of the included studies

	1	2	3	4	8	9	10	11	12	13	14		
Studies (yes:2, partial:1, no:0)	Question/ objective sufficiently described?	Study design evident and appropriate?	Method of subject/ comparison group selection or source of information/ input variables described and appropriate?	Subject characteristics sufficiently described?	Outcome well defined and robust to measurement / misclassification on bias? Means of assessment reported?	Sample size appropriate?	Analytic methods described/ justified and appropriate?	Some estimate of variance is reported for the main results?	Controlled for confounding ?	Results reported in sufficient detail?	Conclusions supported by the results?	Total sum	Summary score
Brunelin et al., 2007	2	2	2	2	2	1	2	2	0	1	2	18	0.82
Marjoram et al., 2006	1	2	2	2	2	0	2	2	2	1	2	18	0.82
Szoke et al., 2009	2	2	2	2	2	2	2	2	2	2	2	22	1
Garisson et al., 2017	2	2	1	2	0	2	2	2	1	2	2	18	0.82
Aldebot et al., 2012	2	2	2	1	1	2	2	0	1	1	2	16	0.73
Laroi et al., 2005	2	2	2	2	2	1	2	2	2	1	2	20	0.91
Laroi et al., 2004	2	2	2	2	2	2	1	0	2	1	2	18	0.82
Johns et al., 2010	2	2	2	2	2	1	2	2	2	2	2	21	0.95
Allen et al., 2006	2	2	2	2	2	1	2	2	2	1	2	20	0.91
Gaweda et al., 2018	2	2	2	2	2	2	2	0	2	1	2	19	0.86
Versmissen et al., 2007a	2	2	2	1	1	1	0	2	0	2	2	15	0.68
Versmissen et al., 2007b	2	0	2	1	2	1	0	2	2	1	2	15	0.68
Alderson-Day et al., 2019	2	2	2	0	1	1	2	2	0	1	2	15	0.68
Peters et al., 2007	2	2	2	2	2	1	2	2	2	2	2	21	0.95
Humpston et al., 2017	2	2	2	2	2	2	2	2	0	2	2	20	0.91

Supplementary Material S2: Rating scores calculated for each study using the Standard Quality Assessment (QualSyst tool¹⁴). Three domains relative to clinical intervention were not applicable and thus removed from the table.

Supplementary Material S3

Cohen's d calculation for between-group studies:

Cohen's d and variance have been calculated using *mes* function from the *compute.es* package.

$$d = \frac{\bar{X}_1 - \bar{X}_2}{sd_{pooled}} \quad \text{with} \quad sd_{pooled} = \sqrt{\frac{(n_1 - 1)S_1^2 + (n_2 - 1)S_2^2}{n_1 + n_2 - 2}}$$

Cohen's d calculation for correlation studies:

Correlation coefficients (*Pearson's r*) and variance (*Vr*) were transformed into Cohen's d and variance (*Vd*) using *res* function (*compute.es* package).

$$d = \frac{2r}{\sqrt{1 - r^2}}$$

To transform Pearson's r variances to Cohen's d variances:

$$V_d = \frac{4V_r}{(1 - r^2)^3}$$

Cohen's d conversion into Hedges' g:

$$g = J \cdot d \quad \text{and} \quad V_g = J^2 \cdot V_d \quad \text{with} \quad J = 1 - \frac{3}{4 \cdot df - 1}$$

Wald-Type test for subgroup analysis:

A random-effect omnibus test was conducted using the *mareg* function of the MAd package (an implementation of the *metafor* package's *rma* function).

$$z = \frac{\mu_1 - \mu_2}{\sqrt{SE[\mu_1]^2 + SE[\mu_2]^2}}$$

Plots:

Meta-analysis's plots were constructed using *metafor* and *ggplot2* packages.

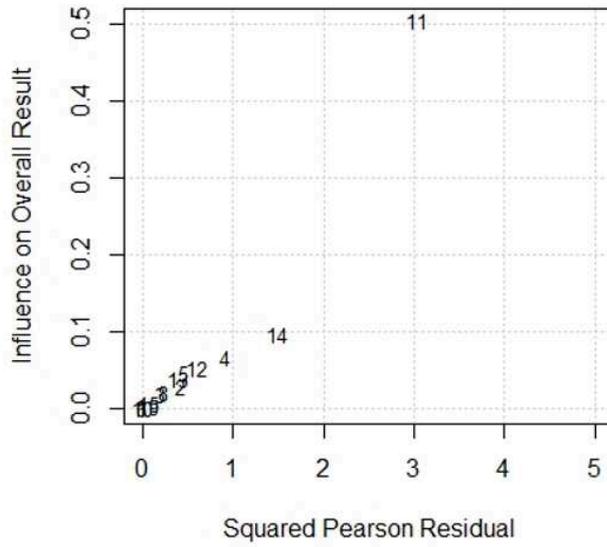
Meta-regressions:

Meta-regressions were conducted using the *mareg* function of the *metafor* package.

Subgroup analysis:

Subgroup analyses were conducted using *rma* function of the *metafor* package.

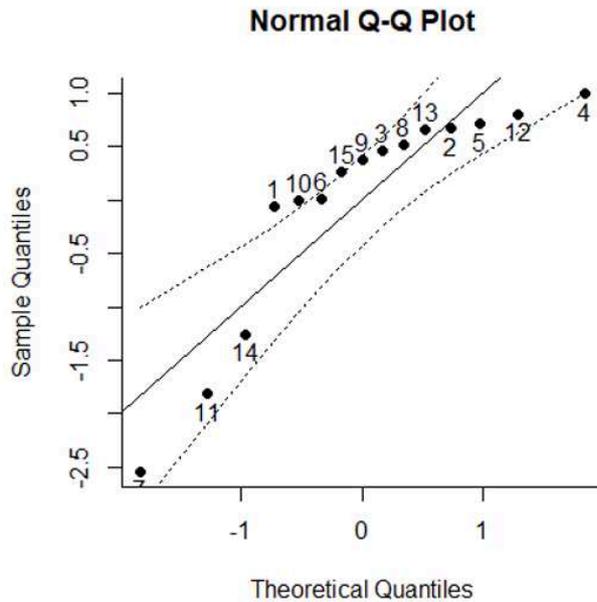
Supplementary Material S4



Baujat Plot: Studies influence on the summary effect size and their contribution to the heterogeneity.

¹Brunelin et al., 2007; ²Marjoram et al., 2006; ³Szoke et al., 2009; ⁴Garisson et al., 2017; ⁵Aldebot et al., 2012; ⁶Laroi et al., 2005; ⁷Laroi et al., 2004; ⁸Johns et al., 2010; ⁹Allen et al., 2006; ¹⁰Gaweda et al., 2018; ¹¹Versmissen et al., 2007; ¹²Versmissen et al., 2007; ¹³Alderson-Day et al., 2019; ¹⁴Peters et al., 2007; ¹⁵Humpston et al., 2017.

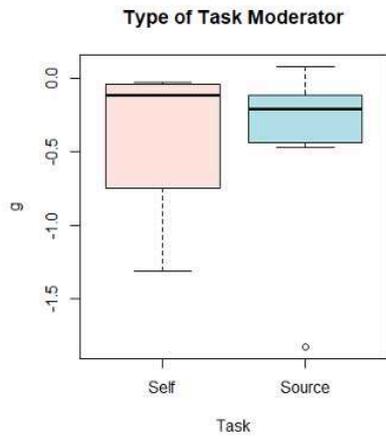
Supplementary Material S5



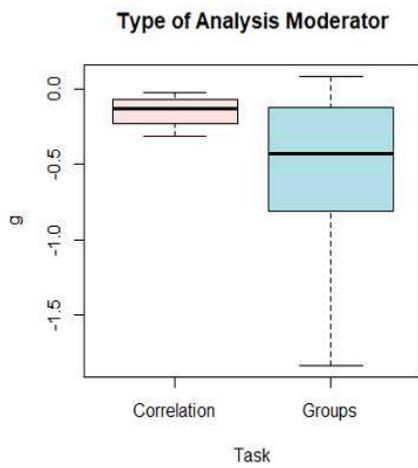
QQ Plot: Potential outliers visualisation.

¹Brunelin et al., 2007; ²Marjoram et al., 2006; ³Szoke et al., 2009; ⁴Garisson et al., 2017; ⁵Aldebot et al., 2012; ⁶Laroi et al., 2005; ⁷Laroi et al., 2004; ⁸Johns et al., 2010; ⁹Allen et al., 2006; ¹⁰Gaweda et al., 2018; ¹¹Versmissen et al., 2007; ¹²Versmissen et al., 2007; ¹³Alderson-Day et al., 2019; ¹⁴Peters et al., 2007; ¹⁵Humpston et al., 2017.

Supplementary Material S6



Boxplot: Type of Task Moderator visualisation.



Boxplot: Type of Analysis Moderator visualisation.

3.3. Conclusion and perspectives

This meta-analysis aimed to determine whether self-recognition is affected in individuals with no full-blown psychosis symptoms across the continuum of psychosis. We included eleven studies that compared self-recognition between three populations, i.e., people with an at-risk mental state for psychosis, unaffected relatives of patients with schizophrenia and hallucination-prone individuals ($n = 386$) and healthy controls ($n = 315$) and four studies that used a correlational approach to estimate comparable effects ($n = 629$). The included studies used either reality-monitoring or self-monitoring experimental paradigms. This meta-analysis demonstrated that self-recognition accuracy was significantly reduced in these populations compared to controls, with a small-to-moderate magnitude effect-size. This deficit was not influenced by age, type of population (i.e., at-risk mental state, unaffected relatives, hallucination-prone individuals), or type of self-recognition (i.e., reality-monitoring, self-monitoring).

Our results in ARMS and unaffected relatives of patients with schizophrenia suggests that self-recognition deficits may be a marker of increased risk for psychosis in individuals without full-blown symptoms. We also replicated Brookwell's findings of self-recognition deficits in hallucination-prone individuals (Brookwell et al., 2013), suggesting that self-recognition deficits may also serve as a potential marker for hallucinations. Finally, we observed a similar magnitude of deficit in both tasks. This result is consistent with a previous meta-analysis demonstrating that patients with schizophrenia have impaired reality-monitoring and impaired self-monitoring, with no difference in magnitude (Waters et al., 2012). More importantly, this result is consistent with a recent experimental study showing a specific correlation between self-monitoring performance and accuracy of internal source recognition during reality-monitoring (Subramaniam et al., 2018). Although reality-monitoring presents a memory

component absent in the self-monitoring paradigm, this observation confirms that both experimental paradigms may index a common cognitive process that is impaired in the context of psychosis.

With respect to hallucination-prone individuals, our results should be taken with caution due to more recent large-scale publications. The largest included 1375 healthy volunteers in a multi-site study who completed assessments of hallucinatory experiences and various cognitive tasks, including reality-monitoring. The authors reported no significant correlation between hallucination-proneness and reality-monitoring accuracy or externalization bias (Moseley et al., 2021).

Our results highlight self-recognition deficits in populations genetic or clinical at-risk for psychosis. Future studies 2-years follow-up studies should address whether early self-recognition deficit could predict the transition to psychosis. Furthermore, it remains unclear whether the self-recognition deficit is a stable factor in the individual's life or whether it worsens with the onset of the disease. Finally, a computer-based training intervention could improve reality-monitoring in patients with schizophrenia (Subramaniam et al., 2012). Interestingly, Subramaniam et al. used intensive training of lower-level processes, including component aspects of auditory/verbal, visual and social cognitive processes. Reality-monitoring has previously been linked to basic auditory processes by our team, who demonstrated that source-monitoring performance can be predicted by pitch discrimination in healthy individuals and patients with schizophrenia (Dondé et al., 2019). These findings suggests that low-level cognitive mechanisms associated with basic auditory features discrimination may underlie impaired source-monitoring in patients with schizophrenia.

Further studies should examine the impact of cognitive training specifically targeting these basic features on reality-monitoring performance and transition in at-risk populations.

4. Third Chapter: Examining the neurobiological substrates of reality-monitoring

4.1. Introduction

Reality-monitoring is the cognitive process by which we distinguish between information that originates from external sources and information that is generated internally. Impaired reality-monitoring is a common feature of schizophrenia, particularly in patients who experience hallucinations. In the second chapter of this manuscript, we demonstrated that non-clinical individuals on the continuum of psychosis, i.e., people with an at-risk state for psychosis and healthy individuals with hallucination-proneness, also exhibit such impaired reality-monitoring.

Previous meta-analyses have shown that patients with schizophrenia also have impairments in self-monitoring, that is, in their ability to distinguish actions or thoughts that they generate themselves from those generated by others. Based on these studies, we also explored self-monitoring in individuals along the continuum of psychosis with no full-blown diagnosis of schizophrenia, and found that they also had significant impairment in self-monitoring. Similar to Waters et al. in patients with schizophrenia, we found no significant difference between deficits in reality-monitoring and self-monitoring in nonclinical individuals on the continuum of psychosis. These results are highly consistent with a recent study showing a correlation between the accuracy of recognition of self-generated information during reality-monitoring and during self-monitoring. Altogether, these results suggest that reality monitoring and self-monitoring are at least partially underpinned by a common mechanism.

Reality-monitoring has been primarily associated with modulation of activity of amPFC activity in healthy individuals (see section 1.2.3.1). Studies in schizophrenia patients supported the key involvement of this brain region located in the anterior part of the medial prefrontal cortex and have associated impaired reality-monitoring with altered function and structure of the amPFC (see section 1.2.3.2). The purpose of the current meta-analysis was to determine whether reality-monitoring and self-monitoring recruit overlapping brain regions, thereby furthering our understanding of their common underlying cognitive processes: 1. We meta-analyzed the functional substrates of reality-monitoring, 2. We meta-analyzed the functional substrates of self-monitoring, 3. We performed a conjunction analysis between these two processes.

4.2. The neural signature of reality-monitoring: a meta-analysis of functional neuroimaging studies [Article 4]

Article 4: The neural signature of reality-monitoring: A meta-analysis of functional neuroimaging studies. In revision with Human Brain Mapping. Lavallé L., Brunelin J., Jardri R., Haesebaert F., Mondino M.

TAKE HOME MESSAGE

- **The process of identifying the source of our memories is called reality-monitoring.**
- **This meta-analysis investigated the brain regions involved in reality-monitoring and the common brain activations with self-monitoring, a process consisting of distinguishing self-generated actions or thoughts from actions or thoughts generated by others.**
- **Reality-monitoring is associated with modulation of activity in the lobule VI of the cerebellum, the right amPFC and anterior thalamic projections.**
- **Self-monitoring is associated with modulation of activity in the lobule VI of the left cerebellum and fronto-temporo-parietal regions.**
- **The lobule VI of the cerebellum is consistently engaged in both reality- and self-monitoring.**

THE NEURAL SIGNATURE OF REALITY-MONITORING: A META-ANALYSIS OF FUNCTIONAL NEUROIMAGING STUDIES

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Abstract

Distinguishing imagination and thoughts from information we perceived from the environment is important in the daily life situations. The process of identifying the source of our memories is called reality-monitoring. We adopted a metanalytic approach to investigate the brain regions that are involved in reality-monitoring and explored the common brain activations with self-monitoring, a process consisting of distinguishing self-generated actions or thoughts from actions or thoughts generated by others. We conducted a coordinate-based meta-analysis of reality-monitoring meta-analysis (172 healthy subjects) revealing clusters including the lobule VI of the cerebellum, the right amPFC and anterior thalamic projections. The self-monitoring neuroimaging studies (192 healthy subjects) highlighted the involvement of a set of brain regions including the lobule VI of the left cerebellum and fronto-temporo-parietal regions. Our results finally suggest that the lobule VI of the cerebellum is consistently engaged in both reality- and self-monitoring. Overall, the current findings offer new insights into the common brain regions underlying reality-monitoring and suggest that the neural signature of the self that may occur during self-production should persist in memories.

Keywords

Reality-monitoring; Self-monitoring; fMRI; coordinate-based meta-analysis

Highlights

- Fronto-thalamic structures are involved in reality-monitoring.
- Anterior medial prefrontal cortex is a key structure of reality-monitoring.
- Fronto-temporal regions are involved in self-monitoring.
- The lobule VI of the cerebellum constitutes the shared neural basis of reality- and self-monitoring.

4.2.1. Introduction

How can we determine that memories come from real perceptions and not from imagination? The process of making attributions about the source of memories between internal sources (such as imagination) and external sources (such as perception) is called reality monitoring. Strong reality-monitoring capacities are necessary in everyday life, for instance to distinguish our mental imagery, or the events that we daydream about, from the events that actually occurred.

Reality monitoring has been theorized into the “source-monitoring framework” by Johnson et al. (Johnson et al., 1993), who suggested that memories did not come with a label indicating their source; but that the source is rather determined based on several cues associated with the event such as the amount of perceptual details, contextual information and cognitive operations. According to the source-monitoring framework, veridical perceptions include more and stronger sensory details, whereas imagination is under more top-down cognitive control signals due to the rich cognitive operations involved in generating the mental experience. A higher-order reality monitoring mechanism is then supposed to integrate information about sensory signals and cognitive control to make source attributions (Garrison et al., 2017a; Johnson, 1997; Johnson et al., 1993).

Reality monitoring seems intrinsically tied to self-monitoring, i.e., the ability to distinguish self-generated actions or thoughts from actions or thoughts generated by others, and more broadly to the concept of self-agency, i.e., the experience of being the agent of one’s action or thought and the feeling that self-productions are intentional and associated with a cognitive experience of voluntary control (Haggard, 2017). However, only few studies investigated the relationship between the two processes. In one of them, Subramaniam et al. showed that the reality-monitoring imagination/perception decision was correlated with self-monitoring measures,

which provides support for a unitary experience of self-agency resulting from the ability to reliably predict the outcome of self-generated actions (Subramaniam et al., 2018). Where and to what extent reality monitoring and self-monitoring processes overlap in the brain remains unknown.

Several neuroimaging studies have tried to identify the neural substrates of reality-monitoring. A qualitative review of imaging studies highlighted the crucial role of the medial prefrontal cortex (mPFC) and especially its anterior part (amPFC) in distinguishing between the imagined or perceived origin of a signal (Simons et al., 2017). Activity in this area, localized at the anterior portion of the medial prefrontal cortex, was observed regardless of the stimulus type (*i.e.*, voice, faces, objects). Any interpretation of the amPFC as the key structure for reality-monitoring needs to be cautious because most of the included studies reported results that were bound to the scope of an a priori defined region of interest (ROI) in the amPFC. However, a causal role for the mPFC has also been established by using noninvasive brain stimulation to target the mPFC and improve reality-monitoring performances (Subramaniam et al., 2020).

Regarding self-monitoring, two previous meta-analyses have revealed converging activations in the left inferior parietal lobule (IPL) and the right temporoparietal junction (TPJ), including the supramarginal gyrus, the angular gyrus, and the superior temporal gyrus, when confronted with externally-derived information (Seghezzi et al., 2019; Sperduti et al., 2011). Their results when facing self-generated information were more heterogeneous: Seghezzi et al. revealed activations in the left supplementary motor area, left posterior insula, right calcarine scissure and right cerebellum while Sperduti et al. revealed activations in the bilateral postcentral gyrus, left precentral gyrus and insula. These conflicting findings can be due to common methodological issues, such as the inclusion of small-volume corrected analyses that violate the assumption that all included experiments should be based on the same search and whole-brain

coverage. Moreover, their use of the *activation likelihood estimation* (ALE) approach led them to analyze activations and deactivations in two separate analyses, which may lead to statistical bias because positive and negative differences could not counteract each other.

The current study aimed to determine whether reality-monitoring and self-monitoring recruit overlapping brain regions, thereby allowing to deepen our understanding of their common underlying cognitive processes. Specifically, this study had three aims:

1. For the first time, we meta-analyzed the neural substrates of reality-monitoring. We expected that distinguishing imagination- from perception-derived information would activate the amPFC.
2. We also updated the current knowledge regarding the substrates of self-monitoring using a relatively unbiased meta-analytic approach and strict inclusion criteria. Based on the two previous coordinate-based meta-analyses, we expected modulation of activity in the bilateral temporo-parietal regions.
3. Third, we aimed to determine whether reality-monitoring and self-monitoring are associated with similar activations. Based on previous behavioral studies showing strong correlation between reality-monitoring and self-monitoring behavioral scores, we argue that observing such spatial overlap would support the hypothesis of partially shared cognitive mechanisms between these two processes.

4.2.2. Methods

This systematic review was performed according to the recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). The protocol was registered in PROSPERO (Chien et al., 2012) (*registration number: CRD42020204113*).

4.2.2.1. Search strategy

The articles included in the meta-analyses were retrieved using a systematic search strategy. We searched for articles published up until May 2022 without any starting date in the PubMed and ScienceDirect databases. We used the following terms for the reality-monitoring meta-analysis: (“source-monitoring” OR “reality-monitoring” OR “self-related”) AND (“fMRI” OR “functional magnetic resonance imaging” OR “PET” OR “positron emission tomography” OR “neuroimaging”) and the following search terms for the self-monitoring meta-analysis: (“self-monitoring” OR “agency” OR “self-related”) AND (“fMRI” OR “functional magnetic resonance imaging” OR “PET” OR “positron emission tomography” OR “neuroimaging”). We identified a total of 253 overlapping papers between these two searches. Additional relevant articles were retrieved by up and down ancestry search across all the selected articles. The “similar articles” function of PubMed was also employed, although no additional references were identified in this manner. Finally, we manually searched through review articles on reality-monitoring, agency, self-judgment and self-referential thinking to find additional topics falling into our inclusion criteria (Denny et al., 2012; Morin and Hamper, 2012; Seghezzi et al., 2019; Simons et al., 2017; Sperduti et al., 2011; van der Meer et al., 2010; van Veluw and Chance, 2014).

The detailed process of article selection and the reasons for exclusions are depicted in the PRISMA flowcharts presented in *Figure 1 and Figure 2*.

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources

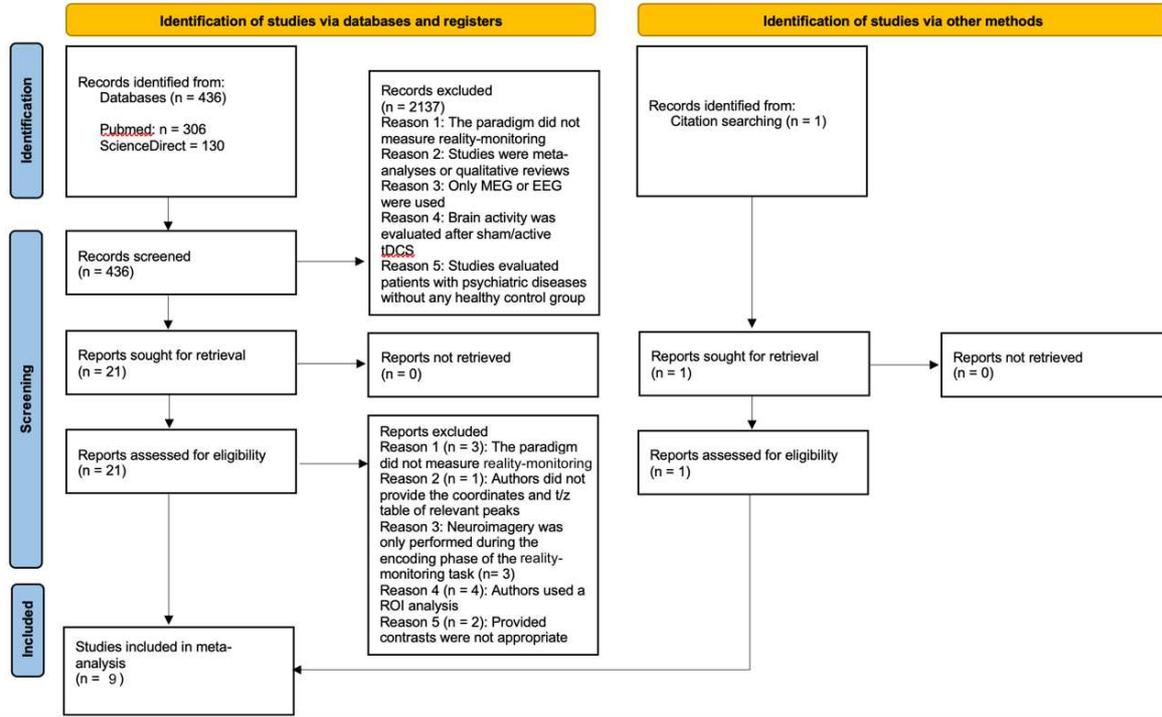


Figure 20. PRISMA flow diagram of the literature search for the reality-monitoring meta-analysis.

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources

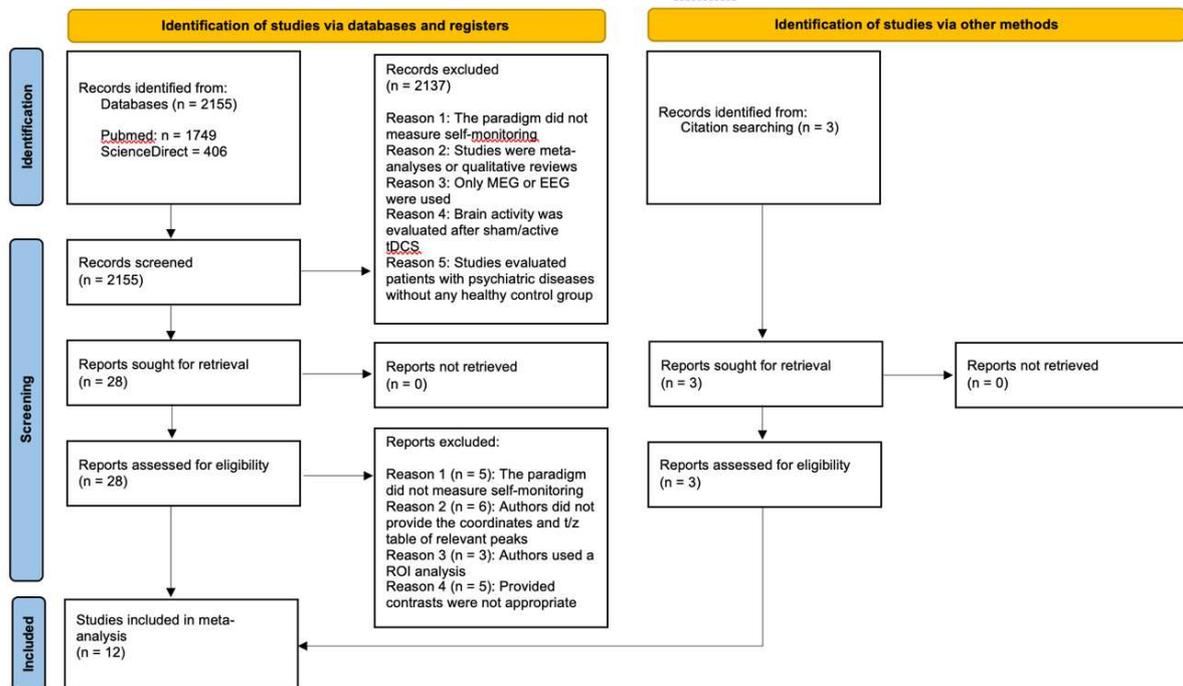


Figure 21. PRISMA flow diagram of the literature search for the self-monitoring meta-analysis.

4.2.2.2. *Eligibility*

The inclusion criteria were as follows: i) original articles were written in the English language and published in peer-reviewed journals, ii) healthy volunteers without any established clinical diagnosis of neurological or psychiatric disease were included, iii) task-related fMRI or PET contrasts were reported, iv) studies provided clear information regarding the task and used either the reality-monitoring paradigm (i.e., a paradigm eliciting subjects to judge whether information was previously self-generated or derived from the outside) or a self-monitoring paradigm (i.e., a paradigm eliciting subjects to make comparisons between sensory predictions and continuous sensory feedback), v) concerning the reality-monitoring meta-analysis, neuroimaging explored brain activity during the retrieval phase of the task, vi) studies conducted direct statistical comparisons between self- and nonself-conditions (self > nonself; self < nonself), vii) studies reported results from whole-brain analyses with full-brain coverage), viii) studies reported x/y/z coordinates in either standard space, Talairach space or Montreal Neurological Institute (MNI) spaces, and ix) studies reported Z-statistics, t-statistics or uncorrected p-values.

The exclusion criteria were as follows: i) studies explored brain activity only during the encoding phase of the reality-monitoring paradigm, ii) studies used small volume corrected analyses (SVCs), iii) studies only reported ROI analysis, iv) studies used data from subjects already included in other studies, v) studies included fewer than 5 healthy subjects and vi) studies reporting other statistical comparisons (e.g., misattribution of the source vs. correct attribution).

Decisions on inclusion and data extraction were made independently by two authors (LL and MM).

4.2.2.3. Data extraction

For each selected article, the following demographic and task-related information was extracted: sample size, gender and age of the subjects, imaging modality (fMRI or PET), detailed description of the design and the task used, and pertinent contrasts (*see Table 1, Supplementary Table 1*). Regarding gender information, it may be mentioned that several studies did not clearly report the number of male and female after exclusion of participants. For each dataset, we extracted x/y/z coordinates and Z- or t-statistics or uncorrected p-values (*see Supplementary Table 2*). We also reported several MRI-related acquisition and analysis parameters: the fMRI design (event-related or block), the magnetic field strength, the number of acquired slices, slice thickness and gap, the field of view, the matrix size, the software used for analysis (SPM, FSL or other) and its version, the reference space (MNI or TAL), smoothing kernel, and the statistical threshold used (*see Supplementary Table 3*).

Author, year	<i>n</i>	Sex (%M)	Age (range)	Neuroimaging	Analysis software	Paradigm	Stimuli	Contrast of interest	Quality
Takahashi et al. 2002	13	78.6*	(19-30)	fMRI	SPM99	reality-monitoring	verbal	self > nonself; self < nonself	0.69
Turner et al. 2008	16	31.2*	26.2 (19-36)	fMRI	SPM2	reality-monitoring	verbal	self > nonself	0.78
King et al. 2014	20	45	28.1 (20-51)	fMRI	SPM5	reality-monitoring	verbal	self > nonself; self < nonself	0.53
Subramaniam et al. 2012	15	68.7*	45	fMRI	SPM2	reality-monitoring	verbal	self > nonself	0.84
Lundstrom et al. 2003	21	52.3	24 (20-28)	fMRI	SPM99	reality-monitoring	verbal	self > nonself	0.56
King et al. 2017	28	48.5*	21 (19-32)	fMRI	SPM8	reality-monitoring	verbal + image	self < nonself	0.91
King et al. 2015	27	62.8*	26.4 (20-34)	fMRI	SPM8	reality-monitoring	verbal + image	self < nonself	0.91

Vinogradov et al. 2008	8	50	28 (25-33)	fMRI	SPM2	reality-monitoring	verbal	self > nonself	0.53
Stephan-Otto et al. 2017	24	38.7*	37.3	fMRI	SPM8	reality-monitoring	verbal + image	self < nonself	0.71
Tsakiris et al. 2010	19	60*	24.8 (18-36)	fMRI	SPM5	self-monitoring	action	self > nonself; self < nonself	0.80
Uhlmann et al. 2020	23	47.8	26.4 (20-35)	fMRI	SPM12	self-monitoring	action	self > nonself; self < nonself	0.56
Renes et al. 2015	23	52.1	21.7	fMRI	SPM5	self-monitoring	action	self > nonself	0.87
Farrer et al. 2002	12	66.7	29	fMRI	SPM99	self-monitoring	action	self > nonself; self < nonself	0.67
Kontaris et al. 2009	11	18.2	24	fMRI	BVQX 1.9	self-monitoring	action	self > nonself; self < nonself	0.60
Sasaki et al. 2018	24	54.2	24.8	fMRI	SPM8	self-monitoring	action	self > nonself	0.77
Schnell et al. 2007	15	100	29.49	fMRI	SPM2	self-monitoring	action	self < nonself	0.67
Jardri et al. 2007	12	50	(25-29)	fMRI	BVQX 1.7.9	self-monitoring	verbal	self < nonself	0.40
Jardri et al. 2011	15	66.7	30.1	fMRI	BVQX 1.9	self-monitoring	verbal	self < nonself	0.80
Balslev et al. 2008	15	46.7	(20-28)	fMRI	SPM2	self-monitoring	action	self < nonself	0.86
Farrer et al. 2008	15	73.3	20.7	fMRI	SPM99	self-monitoring	action	self < nonself	0.60
Farrer et al. 2003	8	100	34	PET	SPM99	self-monitoring	action	self > nonself; self < nonself	0.72

*Table 3. Characteristics of the studies included in the reality-monitoring (upper panel) and self-monitoring (lower panel) meta-analyses. Abbreviations: BVQX: BrainVoyager QX; fMRI: functional magnetic resonance imaging; PET: positron emission tomography; M/F: Male/Female. *studies mentioning the number of male and female before removal of participants from the fMRI analyses. Range of Quality score : 0-1*

4.2.2.4. Seed-based d mapping

The data were analyzed using seed-based d mapping software (formerly *Signed Differential Mapping*) with Permutation of Subject Images (SDM-PSI, version 6.21, <https://www.sdmproject.com/>). This voxel-based method allowed us to summarize peak coordinates and statistical t-maps from the multiple included studies to produce a whole-brain summary of brain activity associated with self-agency and had been extensively validated by previous meta-analyses (Albajes-Eizagirre et al., 2019a, 2019b; Radua et al., 2012b, 2014b; Radua and Mataix-Cols, 2009).

SDM-PSI imputes the brain maps of statistical effects for each included study to conduct a standard random-effect meta-analysis that tests whether the effects are different from zero. This method was mainly chosen in the current study because it offers the key advantages of accounting for effect sizes and analyzing both positive and negative peaks to counteract positive and negative differences. These properties have previously been shown to enhance the balance between the false and positive rate and increase reliability, particularly with a small number of included studies in the meta-analysis (Bossier et al., 2018).

The procedure includes 4 main steps: data preparation, preprocessing, mean analysis, and complementary analyses (heterogeneity and publication bias analyses).

- 1) During data preparation, Z-values were first converted into t-values with the SDM statistics converter (<https://www.sdmproject.com/utilities/?show=Statistics>). Then, coordinates and t-values were written in separate text files to be extracted by SDM. The t-values obtained from the analysis of the “self < nonself” contrast were added with a negative sign corresponding to deactivation.

- 2) Then, data were preprocessed to convert t-values for each peak of activation into Hedges' *g* effect size and their associated variance, thereby obtaining the maximum likely maps of the lower and upper bounds of potential effect sizes for each study.
- 3) During the main analysis, SDM allowed us to calculate the mean of the voxel values in the different studies. Hedge's *g*-corrected effect sizes were calculated at the group level, and a random model was run with each study weighted by its variance and between-study heterogeneity. Finally, the familywise error (FWE) rate was applied to correct for multiple comparisons. The default setting of 1000 permutations has been kept. The distribution of the maximum statistics obtained was then used to threshold the meta-analysis images, resulting in a corrected p-value map.
- 4) Finally, heterogeneity was studied by analyzing a map of I^2 statistics and potential publication bias was evaluated using funnel plots and Egger's tests. I^2 values are typically categorized as low, moderate, and high for values of 25%, 50% and 75%, respectively.

We reported results using an uncorrected $p < 0.005$ threshold with a cluster extent = 20 voxels, since it was found to be optimally balance sensitivity and specificity (Lieberman and Cunningham, 2009; Radua et al., 2012b, 2012a). We also reported using FWE-corrected $p < 0.05$ using the threshold-free cluster enhancement (TFCE) approach (Dugré et al., 2020; Smith and Nichols, 2009). All activations/deactivations were reported in the MNI space. The regions listed in the tables of results were labeled using the SDM stereotactic space (Radua et al., 2014a; Thiebaut de Schotten et al., 2011a, 2011b) and the SPM12 Anatomy Toolbox v3.0 (Eickhoff et al., 2007).

Based on our aims and predictions, we carried out two sets of analyses:

1. We performed separate meta-analyses to examine the neural substrate of both reality-monitoring and self-monitoring paradigms.
2. Using the SDM-PSI tool for overlap analyses, we conducted a conjunction analysis between the meta-analytical map of reality-monitoring and that of self-monitoring to investigate their overlap.

4.2.2.5. Complementary analyses

Reliability

To test the robustness of the results, a jackknife sensitivity procedure was conducted (Radua and Mataix-Cols, 2009). This analysis was carried out by successively repeating the mean analysis as many times as studies were included but discarding one different individual study at a time. Findings were considered highly replicable when significant brain regions remained significant in all the included studies.

Quality assessment

A quality assessment score was also computed based on the criteria used in the study of Tian et al. (Tian et al., 2020) and the guidelines for reporting a fMRI study from Poldrack et al. (Poldrack et al., 2008). The final checklist included 18 items evaluating, among other things, the subject sample, design specification, data acquisition, data preprocessing, statistical analyses, and reporting of conclusions (*see Supplementary Table 4*).

Controlling the potential confounding

The potential influence of age and study quality on estimated activations/deactivations was further explored by meta-regression using a linear random-effect model. Results were considered statistically significant at FWE-corrected a conservative threshold of $p = 0.005$ to reduce the risk of type 1 error related to multiple testing and minimize the detection of spurious relationships. Only brain regions also found in the main meta-analyses were considered.

4.2.3. Results

After the selection process and removal of duplicates, 9 studies met the criteria for inclusion in the reality-monitoring meta-analysis, including a total of 172 subjects. Twelve studies met the criteria for inclusion in the self-monitoring meta-analysis, including a total of 192 subjects.

4.2.3.1. Brain responses associated with reality-monitoring

The SDM meta-analysis revealed significant activations associated with reality-monitoring (self > nonself) in the lobule VI of the left cerebellum, the right medial superior frontal gyrus (BA 10, amPFC) and the left supramarginal gyrus (BA 48) (*see Table 2, Figure 3*). Results also revealed significant deactivations in the right anterior thalamic projections, the left median cingulate gyrus (BA 23), the right inferior frontal gyrus (BA 45), the left precuneus (BA 7), the left caudate nucleus, the left supplementary motor area (BA 6) and the left fusiform gyrus (BA 37). Only the deactivation in the right anterior thalamic projections survived to FWE-correction. This peak was associated with low between-study heterogeneity ($I^2 = 0.62\%$). Egger's test results and funnel plot observations suggested that none of results were driven by publication bias ($p = 0.53$) (*see Supplementary Figure 1*). Finally, no significant effect was observed between our results and moderators (age, quality of the study, *see Supplementary Table 7*).

Robustness analyses indicated that these findings were consistent in most studies (*see Supplementary Table 5*).

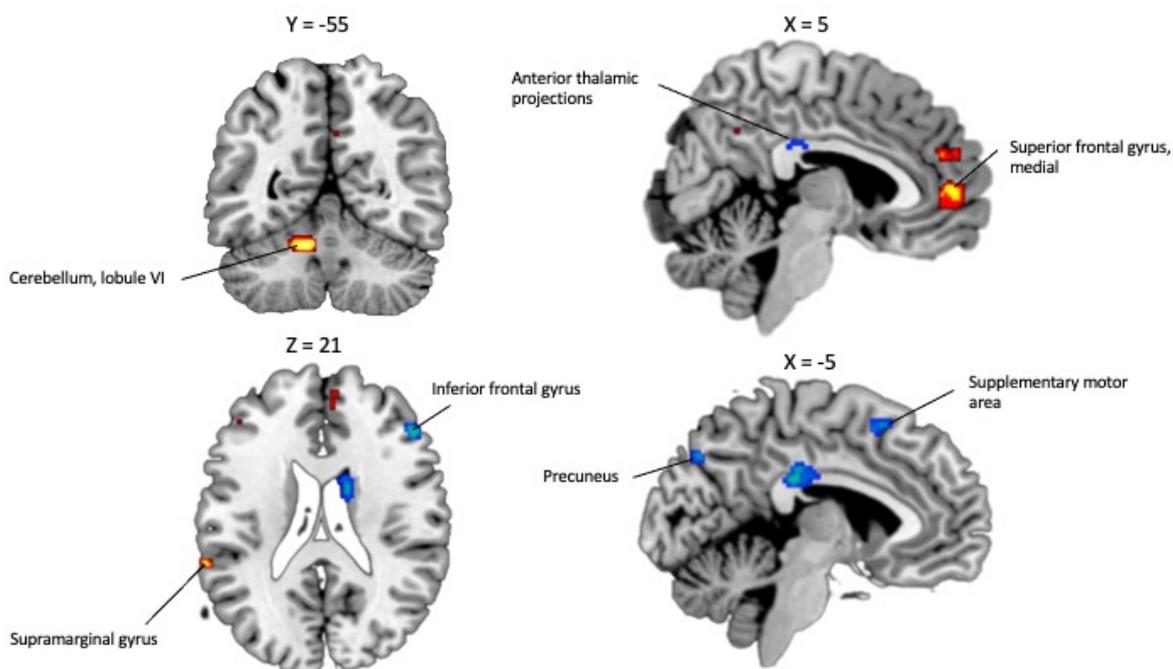


Figure 22. Significant brain functional activations and deactivations associated with reality-monitoring (self > nonself) estimated by a whole-brain meta-analysis. The results are displayed based on the uncorrected threshold of $p < 0.005$ (minimum cluster size = 20 voxels) and overlaid on sagittal and axial sections of a normalized canonical template brain (ch2better) using MRIcron software. Coordinates are reported in Montreal Neurological Institute (MNI) space. The intensity color scale indicates Z-score values. (colors should be used for Figure 3 to print)

Cluster description							
Macroanatomical label	Cytoarchitec tonic label	Number of voxels	of p- value	I^2 (%)	Egger test p- value	MNI	SD M- Z
<i>self > nonself (activation)</i>							
Left cerebellum, hemispheric lobule VI		135	0.000	8.3	0.563	-14,- 50,- 26	3.72 0

Right superior frontal gyrus, medial, BA 10	Area p32	54	0.000	4.2	0.211	6,52,6	3.16
			77				7
Left supramarginal gyrus, BA 48 / Left superior temporal gyrus	Area PFem	21	0.001	15.8	0.519	-60,-	3.05
			14			40,24	2
<i>self < nonself (deactivation)</i>							
Right anterior thalamic projections		285	0.000	0.6	0.922	10,8,8	-
			11*				4.44
							8
Left median cingulate, BA 23		135	0.000	3.6	0.932	-2,-	-
			30			24,30	3.70
							1
Right inferior frontal gyrus, triangular part	Area 45	40	0.000	1.4	0.956	50,32,	-
			76			20	3.43
							0
Left precuneus, BA 7	Area 7P	26	0.000	12.4	0.978	-8,-	-
			40			76,40	3.16
							9
Left caudate nucleus		22	0.001	1.2	0.563	-	-
			07			12,2,1	3.35
						8	1
Left supplementary motor area, BA 6	Area 6mr	23	0.001	2.9	0.988	-	-
			53			6,14,5	3.07
						6	1

Table 4. Significant activation/deactivation for the reality-monitoring meta-analysis.

Regional differences in activation are based on the uncorrected threshold of $p < 0.005$, minimal cluster > 20 . Coordinates are reported in the standardized Montreal Neurological Institute (MNI) space. *Survived to the familywise error rate correction threshold of $p < 0.05$.

Abbreviations: SDM-Z: Seed-based d Mapping Z-value; BA: Broadman area; I^2 : Percentage of variance attributable to heterogeneity.

4.2.3.2. Brain responses associated with self-monitoring

The SDM meta-analysis revealed significant activations associated with self-monitoring (self > nonself) in the bilateral cerebellum, hemispheric lobule VI, the left supramarginal and postcentral gyrus (BA 48), the corpus callosum, the right supplementary motor area (BA 6), the right caudate nucleus and the left thalamic projections (*see Table 3*). Results also revealed significant deactivations in the right supramarginal gyrus (BA 40), the right precuneus, the left anterior cingulate and medial superior frontal gyrus (BA 32), the left inferior parietal gyrus (BA 40), the right inferior frontal gyrus (BA 48), the left inferior frontal gyrus (BA 44), the right anterior cingulate and paracingulate gyri (BA 11) and the right middle temporal gyrus (BA 48) (*see Figure 4*). The activation in the left cerebellum, hemispheric lobule VI, and the left postcentral gyrus (BA 48) survived to FWE-correction, as well as the deactivation in the right supramarginal gyrus (BA 40), the left anterior cingulate and medial superior frontal gyrus (BA 32), the right precuneus and the left inferior parietal gyrus (BA 40).

Low between-study heterogeneity has been associated with each significant peak ($I^2 = 3.23\% - 6.71\%$). Egger's test results and funnel plot observations suggested that none of results were driven by publication bias ($p = 0.14 - 0.52$) (*see Supplementary Figure 2*). No significant effect was observed between our results and moderators (age and quality of the study, *see Supplementary Table 8*). Robustness analyses indicated that these findings were consistent in most studies (*see Supplementary Table 6*).

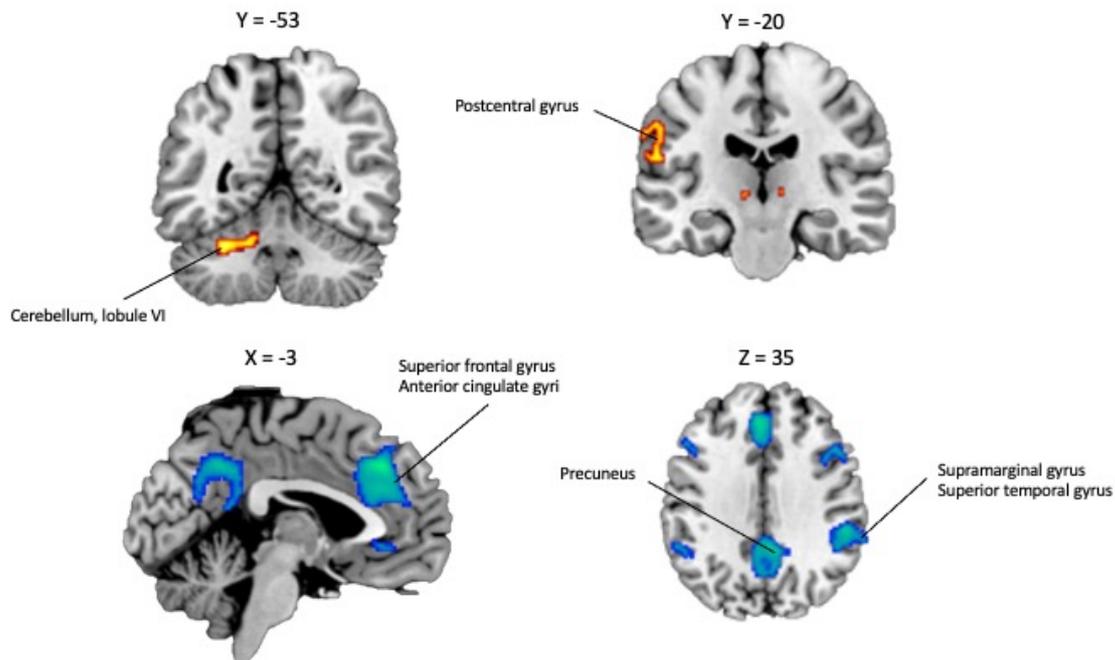


Figure 23. Significant brain functional activations and deactivations associated with self-monitoring (*self* > *nonself*) estimated by a whole-brain meta-analysis. The results are displayed based on the uncorrected threshold of $p < 0.005$ (minimum cluster size = 20 voxels) and overlaid on sagittal and axial sections of a normalized canonical template brain (ch2better) using MRIcron software. Coordinates are reported in Montreal Neurological Institute (MNI) space. The intensity color scale indicates Z-score values. (*colors should be used for Figure 4 to print*)

Cluster description							
Macroanatomical label	Cytoarchitectonic label	Number of voxels	p-value	I ² (%)	Egger test p-value	MNI	SDM-Z
<i>self</i> > <i>nonself</i> (activation)							
Left cerebellum, hemispheric lobule VI		347	0.00001*	6.7	0.381	-28,-58,-26	4.169
Left postcentral gyrus, BA 48	Area OP1	288	0.00017*	3.2	0.364	-56,-18,18	3.583
Corpus callosum	Area hPO1	175	0.00010	5.5	0.764	22,-76,32	3.707

Right supplementary motor area, BA 6	Area 6d1	60	0.00148	9.1	0.511	16,0,62	2.971
Corpus callosum	Area hOc2	42	0.00094	11.5	0.574	20,- 94,10	3.108
<i>self < nonself (deactivation)</i>							
Right supramarginal gyrus, BA 40 / Right superior temporal gyrus, BA 22	Area hIP2	1229	< 0.00001*	3.3	0.486	48,- 42,42	- 5.223
Right precuneus		887	< 0.00001*	4.3	0.137	4,-52,40	- 4.869
Left superior frontal gyrus, BA 32 / Left anterior cingulate gyri, BA 32	Area p32	844	< 0.00001*	5.6	0.520	-4,34,38	- 5.002
Left inferior parietal gyri, BA 40	Area hIP2	412	0.00002*	5.8	0.340	-44,- 52,52	- 4.130
Right inferior frontal opercular part, BA 48	Area 45	216	0.00027	4.8	0.279	48,18,30	- 3.463
Left inferior frontal triangular part, BA 48	Area 45	102	0.00044	20.3	0.211	- 52,22,30	- 3.327
Right anterior paracingulate gyri, BA 11	Area p24ab	58	0.00125	7.9	0.468	4,34,-6	- 3.126
Right middle temporal gyrus, BA 48		52	0.00125	10.2	0.648	50,-16,- 10	- 3.296
Right middle temporal gyrus, BA 21		21	0.00305	15.6	0.301	58,-44,- 4	- 3.024

Table 5. Significant activation/deactivation for the self-monitoring meta-analysis.

Regional differences in activation are based on the uncorrected threshold of $p < 0.005$, minimal cluster > 20 . Coordinates are reported in the standardized Montreal Neurological Institute (MNI) space. *Survived to the familywise error rate correction threshold of $p < 0.05$.

Abbreviations: SDM-Z: Seed-based d Mapping Z-value; BA: Broadman area; I²: Percentage of variance attributable to heterogeneity.

4.2.3.3. *Overlap between reality-monitoring and self-monitoring brain reactivity*

We finally performed a conjunction analysis to identify the overlapping brain regions between both self-monitoring and reality-monitoring meta-analytic statistical maps. Results revealed significant activation of the left cerebellum, lobule VI in the self > nonself contrast in both paradigms of self-agency (*see Table 4, Figure 5*). This finding was not detectable after TWE-correction. The coordinates of this part of the cerebellum were used to extract a mask from the two main analyses. Activation in this region was associated with similar effect size and low heterogeneity in both self-monitoring and reality-monitoring (Hedge's $g = 0.36$ and 0.40 , $I^2 = 1.08\%$ and 19.17% , respectively).

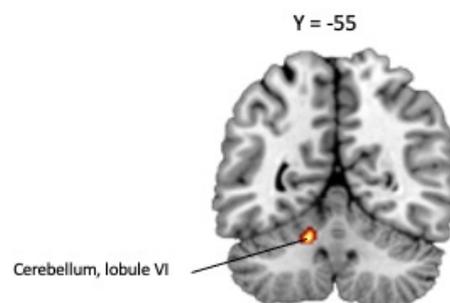


Figure 24. Significant brain functional activations reflecting the overlap between reality-monitoring and self-monitoring whole-brain meta-analyses. The results are displayed based on the uncorrected threshold of $p < 0.005$ (minimum cluster size = 20 voxels) and overlaid on sagittal and axial sections of a normalized canonical template brain (ch2better) using MRIcron software. Coordinates are reported in Montreal Neurological Institute (MNI) space. The intensity color scale indicates Z-score values. (colors should be used for Figure 5 to print)

Macroanatomical label	Number of voxels	p-value	MNI	SDM-Z
<i>self > nonself (activation)</i>				
Left cerebellum, hemispheric lobule VI	53	0.00046	-14,-52,-26	3.310
<i>self < nonself (deactivation)</i>				

Table 6. Significant activation/deactivation for the conjunction meta-analysis between reality-monitoring and self-monitoring. Regional differences in activation are based on the uncorrected threshold of $p < 0.005$, minimal cluster > 20 . Coordinates are reported in the standardized Montreal Neurological Institute (MNI) space. *Survived to the familywise error rate correction threshold of $p < 0.05$. *Abbreviations:* SDM-Z: Seed-based d Mapping Z-value.

4.2.3.4. Supplemental analysis results

Controlling for confounders

The study quality had no significant influence on the functional results in either self-monitoring or reality-monitoring. Higher age was significantly associated with activation in the left inferior frontal gyrus (BA 44) and right supplementary area during the self-monitoring paradigm. None of these brain regions overlapped with areas that survived to FWE-correction. Finally, age had no significant influence on the reality-monitoring results.

4.2.4. Discussion

While self- and reality-monitoring conceptually overlaps in the sense that they both involve distinguishing self from nonself origins of information, the two concepts remain largely separate cognitive fields; moreover, their common brain substrates have received relatively

little attention. Using a coordinate-based meta-analysis, we compiled and analyzed results from imaging studies investigating the brain correlates of either reality-monitoring and self-monitoring and examined their overlapping neural responses. We identified specific brain regions involved in reality-monitoring and confirmed the central role played by the bilateral IPL in self-monitoring (Seghezzi et al., 2019; Sperduti et al., 2011). Importantly, our findings suggest consistent activation of the lobule VI of the left cerebellum in both reality-monitoring and self-monitoring.

Brain areas involved in reality-monitoring

Our meta-analysis revealed that the right amPFC is consistently activated during reality-monitoring. Its activation has been shown using a liberal statistical threshold (i.e., $p < 0.005$, uncorrected, minimal cluster size > 20) but not when using a conservative one (i.e., $p < 0.05$ FWE-corrected). That being said, this activation is highly consistent with a large corpus of studies showing that the amPFC exhibits differential activity during the retrieval of internally vs. externally-generated information using a ROI approach (for review (Simons et al., 2017)). All the studies that were bound to the scope of an a priori ROI were excluded from the present meta-analysis. However, these studies demonstrated that the amPFC modulates its activity during a more diverse range of reality-monitoring tasks than those we included, using verbal items but also faces and objects (Dobbins and Wagner, 2005; Kensinger and Schacter, 2006; Simons et al., 2005b, 2005a). Our findings are also in line with interventional studies using neurofeedback or brain stimulation that have shown the causal involvement of amPFC in reality-monitoring (Garrison et al., 2021; Subramaniam et al., 2020). Here, the activation of the amPFC during reality-monitoring but not self-monitoring suggests its specific role in attributing the source of memories through the distinction between the retrieval of their internal and external features. These findings are consistent with the hypothesis that the amPFC plays a

higher-order role of evaluation of low-level sensory signals and cognitive control aspects of perception and imagination in order to make a source attribution (Dijkstra et al., 2022). At the structural level, the reduction in length in the paracingulate sulcus (PCS), a tertiary sulcus surrounding the ACC, is associated with reduced reality-monitoring performance (Buda et al., 2011; Fornito et al., 2008). The pathological implication of this structural variability has been shown in patients with schizophrenia, for whom the reduction in PCS length is associated with hallucinations (Garrison et al., 2015) and deficits of reality monitoring (Perret et al., 2021). If the relationship between brain morphometry and functional activity remains unclear, one may suggest the cortical folding to influence the functional involvement of the amPFC and ACC during reality-monitoring. Our meta-analysis also identified a specific activation in the left SMG. However, this activation was associated with 16% of heterogeneity, only concerned a small number of voxels and did not survive to FWE-correction. Finally, the only cluster surviving to FWE-correction has peaks in the right anterior thalamic projections. Its specific role in self vs. nonself distinction should be further explored. Given the crucial projection from the anterior thalamus to the anterior cingulate cortex within the Papez circuit supporting the neural substrates of memory (O'Mara, 2013; Papez, 1937), future studies should pay particular attention to their functional connectivity during reality-monitoring.

Brain areas involved in self-monitoring

Concerning self-monitoring, we identified activations in the left cerebellum and postcentral gyrus and deactivations in the right supramarginal gyrus and left anterior cingulate and medial superior frontal gyrus. The deactivation of the right SMG corroborates the findings of Seghezzi et al. and Sperduti et al. (Seghezzi et al., 2019; Sperduti et al., 2011). Substantiating its pivotal role in self vs. nonself distinction, hyperactivity of the right IPL in response to self-generated events is correlated with symptoms that include delusion of alien control, insertion-of-thought

experiences and hallucinations in schizophrenia patients (Jardri et al., 2011b; Spence et al., 1997). Furthermore, a distinct sulcal pattern distribution of the Sylvian fissure, a sulcus surrounding the right IPL, has been observed in patients with schizophrenia who misattribute their hallucinations to an external source compared to patients who recognize that they originate from their own thoughts (Plaze et al., 2015). One can assume that such anatomical variability in pathological condition gives an indication as to the functional role of the right IPL in disentangling the origin of online information. But how would the deactivation of the right IPL participate in self-monitoring? Interestingly, the right IPL is involved in various tasks, such as go/no go, false-belief reasoning and theory of mind, which also require online comparison between internal predictions and external perceived events (Decety and Lamm, 2007; Rothmayr et al., 2011). As a core region of the ventral frontoparietal network, the right SMG is indeed engaged in attention reorienting from an internal model to externally directed information in the context of a violation of expectations (Corbetta et al., 2008). Moreover, as a part of the secondary somatosensory cortex, the right SMG receives strong connections from sensory and motor areas such as the left postcentral gyrus and has specifically been involved in attentional modulation of somatosensory stimuli (Chen et al., 2008; Fujiwara et al., 2002; Hämäläinen et al., 2002). Hence, the right SMG deactivation during self-monitoring could reflect the sensory dampening observed in the context of self-generated action and lead to maintaining or redirecting attention toward internally generated stimuli. Our meta-analysis also confirms the findings of Sperduti et al. and Seghezzi et al. about the left IPL key role for external agency during self-monitoring. This region has previously been associated with detection of incongruent feedback during action execution (Balslev et al., 2006). In schizophrenia patients, hyperactivation of the left IPL during self-monitoring is associated with false signaling of incongruence and passivity symptoms, characterizing the experience of believing that one's thoughts or actions are controlled by an external agent (Frith, 2005; Schnell et al., 2008). One

could then assume that the left IPL deactivation reflects the absence of conflict in the event of congruence between the predicted and actual feedback of self-generated action. Our cytoarchitectonic analysis further specified the localization of this deactivation in the hIP2 region of the left IPL, displaying strong functional connectivity with the right SMG and the left superior frontal gyrus (Uddin et al., 2010) which also deactivate during the self vs. nonself distinction. The latter is also involved in conflictual decision making: the left superior frontal gyrus and ACC are specifically associated with confusion between imagined and perceived pictures (Gonsalves et al., 2004; Stephan-Otto et al., 2017a) and their disruption is associated with deficits in error-monitoring in schizophrenia patients (Alain et al., 2002; Mathalon et al., 2002). In the context of self-agency, this suggests that the left superior frontal gyrus and ACC act conjointly with the left IPL in monitoring the conflicts between predicted and observed stimuli.

Functional convergence between reality-monitoring and self-monitoring: is the lobule VI of the cerebellum a key structure for self-agency?

The conjunction analysis between reality-monitoring and self-monitoring has revealed robust common activation of left lobule VI of the cerebellum. This activation further corroborates the *cerebellar forward model*, indicating that self-generated productions lead the cerebellum to generate sensory predictions (Pineiro et al., 2020; Sokolov et al., 2017). After finding a selective response of the lobule VI when tactile stimuli were self-produced, Blakemore et al. assumed for the first time that the cerebellum receives an efference copy of motor commands to build the prediction of their somatosensory consequences (Blakemore et al., 1998). The generation of the expected sensory outcome has been hypothesized to then reduce the activity of the implicated sensory areas. For instance, amplitude reduction of the N1 event-related

response (ERP) and reduced BOLD activity of the auditory cortex after voice onset seem to reflect a match between self-generated motor-to-auditory prediction and actual sensory feedback (Baess et al., 2011, 2009; Christoffels et al., 2007; Numminen et al., 1999; Sato and Shiller, 2018). Such a role of cerebrocerebellar pathways has been demonstrated by studies reporting patients with cerebellar lesions to not display any N100 suppression after a self-generated sound (Knolle et al., 2013, 2012). In the same way, actions with predictable visual consequences are associated with BOLD suppression in visual cortices and greater cerebellar-visual cortex connectivity than actions with unpredictable visual consequences (Straube et al., 2017). Furthermore, several fMRI studies highlighted the role of the cerebellum during language prediction (Lesage et al., 2017; Moberget et al., 2014) and used neurostimulation to demonstrate causality between the activation of the cerebellum and the ability to anticipate words in a sentence (D’Mello et al., 2017; Lesage et al., 2012; Miall et al., 2016). In a subsequent study, Blakemore et al. also found the lobule VI to modulate its activity when increasing the delay between a hand’s movement and the resulting tactile stimulation of a passive hand, suggesting that this region should constantly compare expected and actual sensory feedback to detect potential discrepancies (Blakemore et al., 2001). In response to mismatches, an error signal from the cerebellum would update the *forward model* by reducing the sensory suppression of the implicated sensory areas (Pinheiro et al., 2020). If the activation of lobule VI of the cerebellum during online self-agency is highly coherent with the cerebellum forward model, our results suggest that this region reactivates when remembering the self-provenance of information during the reality-monitoring retrieval phase. Previous studies implicated the cerebellum in both encoding and retrieval aspects of episodic memory (*i.e.*, the ability to recollect a specific personal experience, including the context) and in acquisition and retention of motor memories (Herzfeld et al., 2014) using plasticity mechanisms (Andreasen et al., 1999; D’Angelo, 2014; Fliessbach et al., 2007; Fossati et al., 2004; Hirano, 2013; Ito, 2001).

The cerebellum has been more specifically identified as a part of a neural network activated during source memory relative to object memory (Hawco et al., 2015), and lesions in this structure are associated with repeated misattributions between the self and the external origin of a memory (Tamagni et al., 2010). Based on its overlapping activation in self-monitoring and reality-monitoring, the cerebellum may be both considered for its role in the feed-forward model and as a “cognitive cue” to identify the self-origin of stored information.

Integrating the cerebellar forward model and the reality-monitoring framework

The feed-forward model accounting for the recognition of self-generated productions proposes that the outgoing motor signal is accompanied by a replicate called the efference copy, and the integration of this replicate results in building a prediction of the sensory feedback. This prediction minimizes the sensory perception of our own actions or speech. In addition, a constant comparison between the prediction and the actual sensory input would allow the detection of potential discrepancies to update the forward model. What would be the neurobiological substrates of such a model? First, our results lend support to the claim that the lobule VI of the cerebellum is a pivotal neural locus for recognizing self-produced behaviors. According to this view, the cerebellum might integrate the efference copy of self-productions to generate an expectation of sensory feedback, which would then transit by cerebello-cortical connections to prepare the sensory areas for incoming sensory feedback. This sensory attenuation would be underpinned by deactivation of somatosensory regions such as the left postcentral gyrus and right SMG. In this way, the connectivity between lobule VI of the cerebellum and the right SMG has been suggested to support somatosensory attenuation in the context of a self-generated action (Kilteni and Ehrsson, 2020). Moreover, deactivation in the right TPJ would in turn lead to alleviate the accuracy of future expectations by maintaining or reallocating attention to internally generated stimuli. In the event of a mismatch between the

expected and actual sensory feedback, an error signal would transit again from the cerebellum to the primary sensory cortices and motor areas to reduce the sensory attenuation and update the motor command, respectively. The difference between expected and actual sensory feedback would then be propagated to other hierarchical levels such as the left IPL and ACC, involved in error processing and contributing to altered sense of agency. Within the *reality-monitoring framework*, our meta-analysis finally advocates for a reactivation of the lobule VI cerebellum during the retrieval phase of reality-monitoring to reinstate the encoding context in collaboration with the amPFC. The amPFC would then integrate and evaluate the retrieved markers of the cognitive operations associated with thought, speech, and other actions to attribute its source.

Several limitations of this study should be acknowledged. First, even with a total of 172 individuals, we could only include 9 reality-monitoring studies. Most of the studies mentioned in the Simons et al. review (Simons et al., 2017) have not been included in this quantitative meta-analysis. Several of these studies have only reported ROI-based analyses in the amPFC (Brandt et al., 2014; Simons et al., 2008, 2006; Vinogradov et al., 2008). The inclusion of experiments from different original search coverage would lead to inflate significance for the amPFC (Müller et al., 2018). Another portion of these studies reported the involvement of the amPFC in reality-monitoring using heterogeneous contrasts that we excluded from the present meta-analysis (e.g., misattributions of the source vs. correct attribution (Kensinger and Schacter, 2006), correct recognition of the source status vs. baseline (Simons et al., 2008)). Of note, Simons et al. paper is not a systematic review and most of the studies of reality-monitoring in healthy subjects using fMRI that we included in the present meta-analysis are not mentioned in their review. Second, due to the number of included studies, we were not able to subcategorize the experiments according to the modality of the stimulus (i.e., action, imagery,

verbal tasks). Regarding the amPFC, previous studies adopting an ROI approach have shown a similar activation of the amPFC in imagery and verbal studies, suggesting that this region is involved in reality-monitoring regardless of the modality. In the self-monitoring meta-analysis, only 2 studies used verbal tasks (Jardri et al., 2011a, 2007). However, heterogeneity tests did not reveal any significant between-study variance that could have indicated a verbal versus action difference. Nonetheless, comparing subgroups according to the stimulus dimension is certainly the most thorough way of controlling this potential confounder. Currently, the complete lack of whole-brain fMRI reality-monitoring contrasts using action stimuli and the small number of neuroimaging studies using verbal self-monitoring contrasts prevent us from employing this kind of rigorous standard. A third limitation of the current study is the uncertainty about the inclusion of the cerebellum in whole-brain analyses. Out of the 16 included studies, 4 did not reveal activation in this structure or specify whether their whole-brain analysis covered the structure (Lundstrom et al., 2003; Renes et al., 2015; Subramaniam et al., 2012; Takahashi et al., 2002). Consequently, for these 4 studies, the lack of signal in the cerebellum may be considered a potential false negative. However, our meta-analysis showed that the most substantial and consistent activation in the cerebellum occurred in response to self-generated information; therefore, the only risk of bias might be a slight underestimation of the effect size. Nevertheless, further studies are needed to investigate self-agency by systematically including the cerebellum in their whole-brain coverage, and these works should specify whether the structure is included in the analyses. Fourth, we reported results with a statistical threshold of $p < 0.005$ (uncorrected, minimal cluster size > 20). Although the SDM developers demonstrated that the liberal threshold of $p < 0.005$ optimally balances sensitivity and specificity (Radua et al., 2012b) and this threshold has been mostly used in meta-analyses of neuroimaging studies, it remains an approximation of the corrected results. When using a more conservative threshold of $p < 0.05$ (FWE-corrected), the amPFC activation did not survive

in the reality-monitoring meta-analysis and the conjunction meta-analysis yielded no significant results. This could be due to several reasons: a) even with a total number of 172 subjects included in the reality-monitoring meta-analysis, only 9 studies were included, b) the heterogeneity between verbal reality-monitoring studies and action self-monitoring studies could have reduced our ability to observe results surviving conservative thresholding, c) coordinate-based meta-analyses are susceptible to threshold bias (we were not able to ask for unthresholded maps because most of the included studies were published more than 10 years ago). We reported results with both thresholded and unthresholded p-values to move beyond p-value and discussed the amPFC activation in the light of the converging evidence from numerous ROI studies showing its consistent involvement in reality-monitoring. Concerning the conjunction meta-analysis, we supplemented the unthresholded p-values by extracting masks that allowed us to report similar moderate effect-sizes in the cerebellum peak for both self-monitoring and reality-monitoring meta-analyses. A last caveat of this study is the inclusion of slightly heterogeneous contrasts in the reality-monitoring meta-analysis. Seven over nine studies reported a self vs. nonself contrast regardless the correct identification of the source. Two studies (Stephan-Otto et al., 2017b; Takahashi et al., 2002) however reported the contrast between correctly remembered self-generated items and correctly remembered nonself-generated items. We tested the robustness of our results by replicating our meta-analysis while excluding these studies and showed no difference with the original meta-analysis.

Conclusions

Based on the common cognitive substrate of reality- and self-monitoring, we adopted a metanalytic approach to investigate the brain regions that are involved in either of these two paradigms and performed conjunction analysis to highlight their overlaps. Our results suggest

that the lobule VI of the cerebellum is consistently engaged in both reality- and self-monitoring. This finding is highly consistent with the *cerebellar forward model*, in which the cerebellum has a key role in generating the predicted feedback of our own actions and producing an error signal in the event of a mismatch with the actual sensory feedback. During self-monitoring, the cerebellum would act together with cerebral regions including the right TPJ and left IPL and ACC. When remembering the self-origin of information at the retrieval phase of reality-monitoring, the cerebellum would reactivate within a set of brain regions including the right amPFC and anterior thalamic projections. Because the exact functions of these structures remain highly speculative, our results set the rationale for future imaging and brain stimulation studies that may explore their contribution to self-agency. Finally, this study has far-reaching implications for a better understanding of altered reality-monitoring in the context of schizophrenia, in which patients experience a severe blurring of the self/nonselves distinction and confusion between self-generated stimuli and those they perceive from the environment (Brookwell et al., 2013; Waters et al., 2012).

Author contribution

LL: Conceptualization, Methodology, Formal analysis, Visualization, Writing – original draft, Writing – review and editing. MM: Conceptualization, Methodology, Writing – review and editing. JB: Conceptualization, Methodology, Writing – review and editing. FH: Writing – review and editing. RJ: Writing – review and editing.

Declaration of competing interest

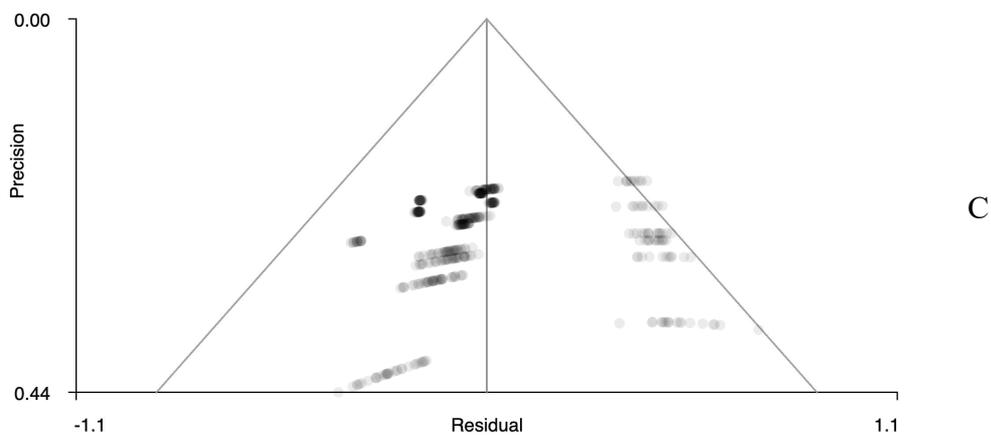
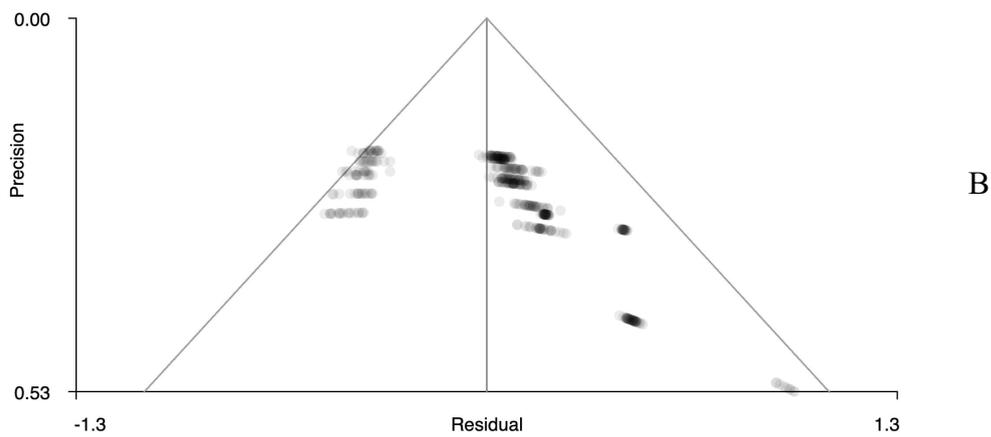
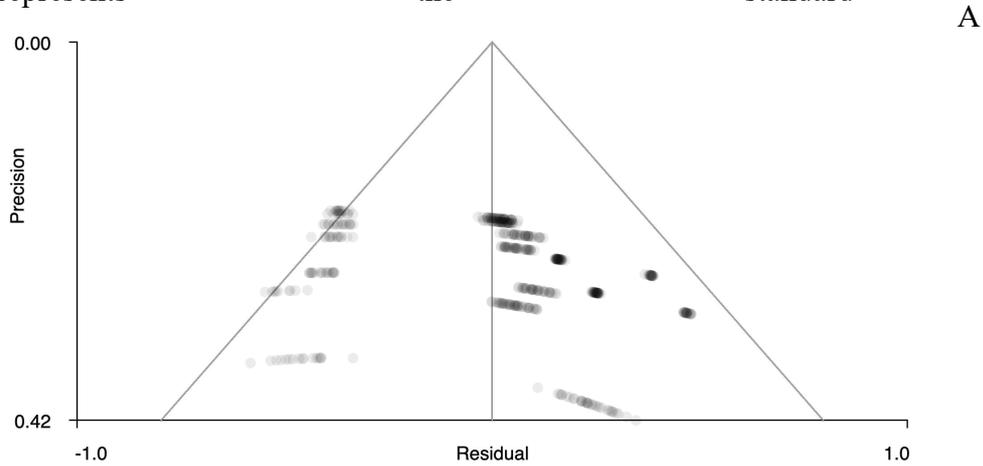
The authors declare no competing financial interests.

Data and code availability statement

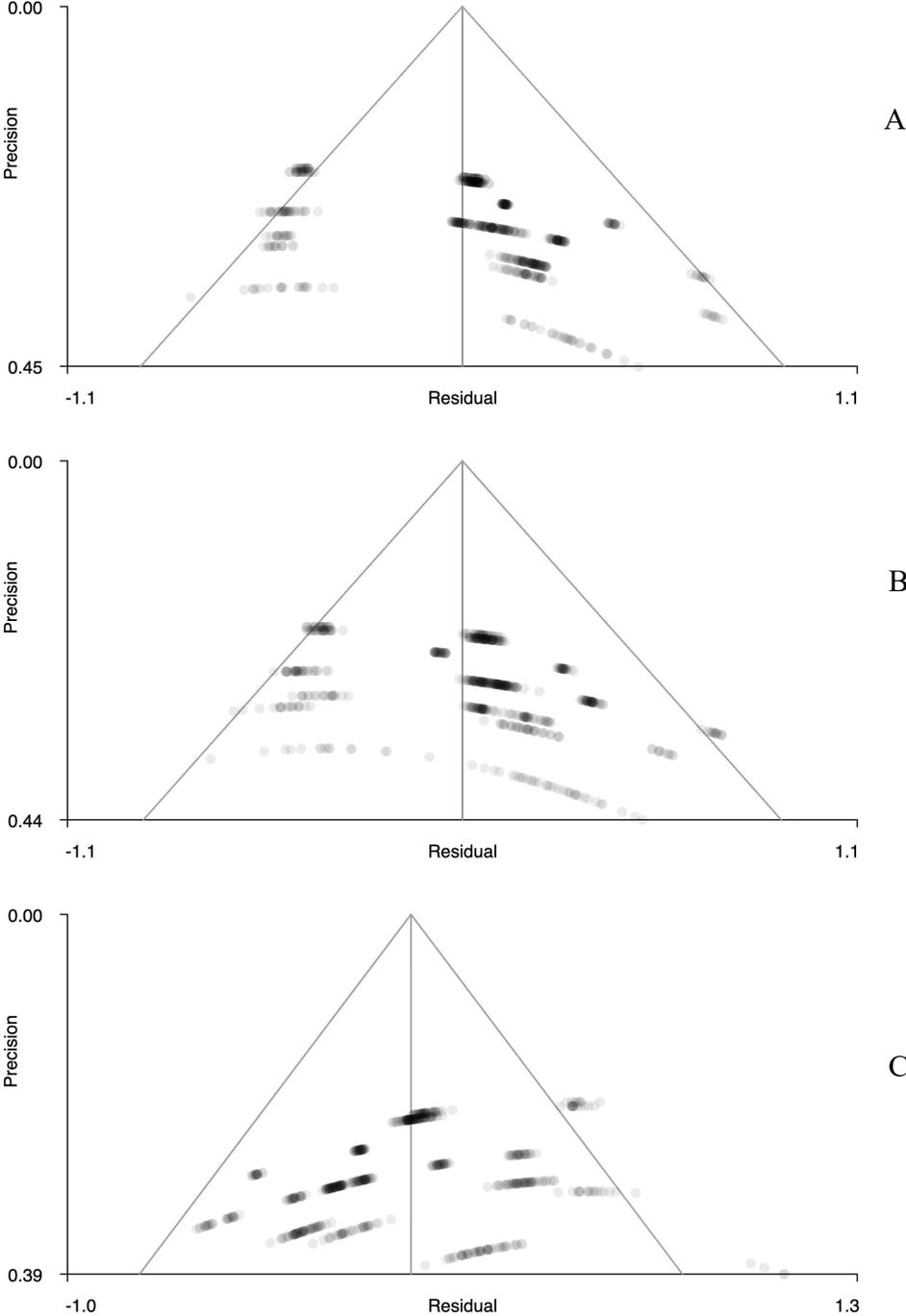
All data used in this study were obtained from original publications. Meta-analyses that we used in this study were achieved via the software SDM-PSI (<https://www.sdmproject.com/>). The unthresholded maps from meta-analyses are publicly available at: <https://neurovault.org/collections/12882/>.

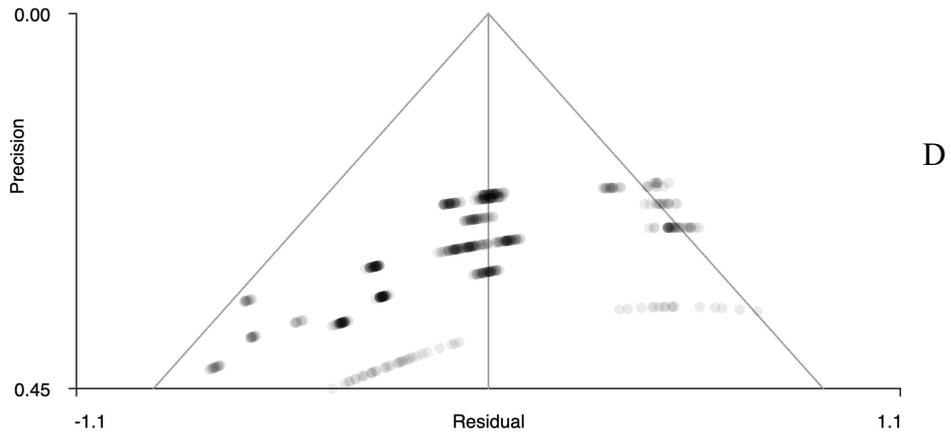
APPENDIX

Supplementary Figure 1: Funnels plots of the activation and deactivation effect-sizes in the reality-monitoring meta-analysis (A: Left cerebellum, Eggers' test p-value = 0.563, B: Right superior frontal gyrus, Eggers' test p-value = 0.211, C: Right anterior thalamic projections, Eggers' test p-value = 0.922). The horizontal axis represents the effect-size. The vertical axis represents the standard error.

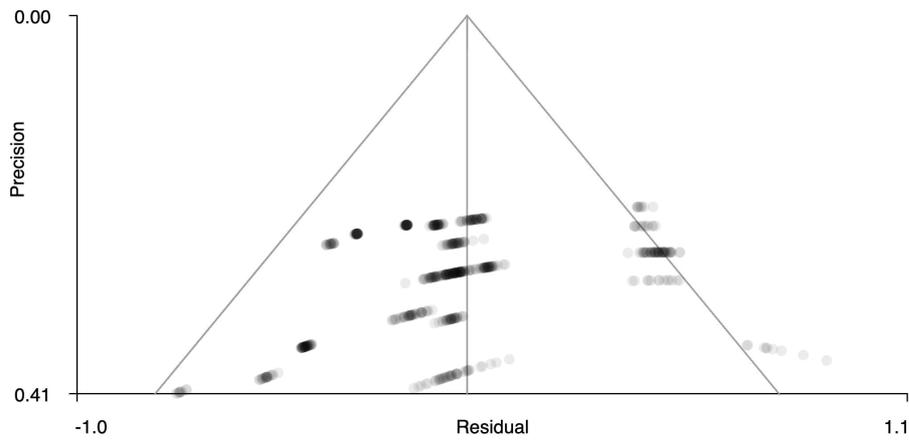


Supplementary Figure 2: Funnels plots of the activations and deactivations effect-sizes in the self-monitoring meta-analysis (A: Left cerebellum, Eggers' test p-value = 0.381, B: Left postcentral gyrus, Eggers' test p-value = 0.364, C: Right supramarginal gyrus / Right superior temporal gyrus, Eggers' test p-value = 0.486, D: Right precuneus, Eggers' test p-value = 0.137, E: Left superior frontal gyrus / Left anterior cingulate gyri, Eggers' test p-value = 0.520, F: Left inferior parietal gyri, Eggers' test p-value = 0.340). The horizontal axis represents the effect-size. The vertical axis represents the standard error.

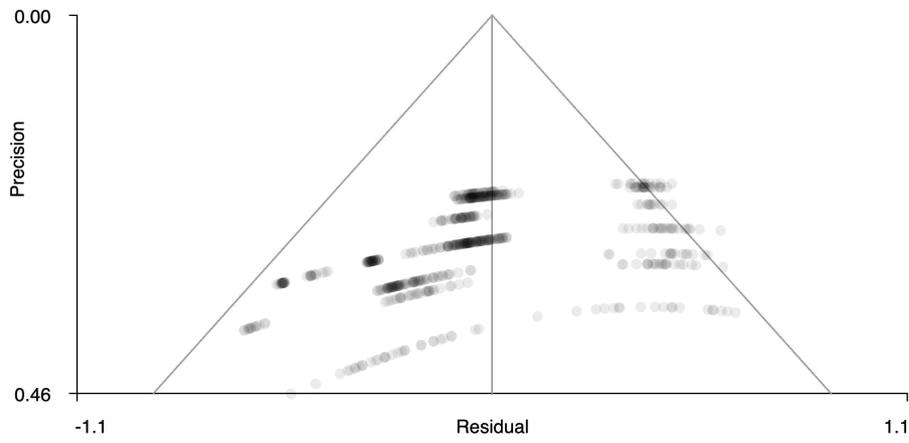




D



E



F

Supplementary Tables

Supplementary Table 1: Details of the tasks and selected contrasts for each included study.

Study	Task	Selected contrast	Stimuli	Category
Takahashi et al., 2002	1) Chinese characters were either pronounced but not presented visually or pronounced and presented visually; 2) During the scan, subjects judged whether the characters were perceived or imagined	imagined vs. perceived	verbal	Reality-monitoring
Turner et al., 2008	1) Subjects were presented with either a clue and target word or a clue and a target question mark prompting them to imagine the target word; 2) During the scan, subjects indicated whether words had been perceived or imagined	imagined vs. perceived	verbal	Reality-monitoring
King et al., 2014	1) Subjects were presented with either a word followed with a corresponding picture or a word followed with a black rectangle; 2) During the scan, subjects indicated whether the words corresponded to pictures that were perceived, imagined or new	imagined vs. perceived	verbal picture	+ Reality-monitoring
Subramaniam et al., 2012	1) Subjects were shown sentences for which the final word was presented by the experimenter or left blank; 2) During the scan, subjects indicated whether words were externally presented or self-generated	self-generated perceived	vs. verbal	Reality-monitoring
Lundstrom et al., 2003	1) Subjects viewed either a word with a corresponding picture or a word followed by a blank screen; 2) During the scan, subjects indicated whether the words corresponded to pictures that were perceived or imagined	imagined vs. perceived	verbal	Reality-monitoring
King et al., 2017	1) Subjects viewed either a word with a corresponding picture or a word followed by a blank screen; 2) During the scan, subjects indicated whether the words corresponded to pictures that were perceived or imagined	imagined vs. perceived	verbal picture	+ Reality-monitoring
King et al., 2015	1) Subjects viewed either a word with a corresponding picture or a word followed by a blank screen; 2) During the scan, subjects indicated whether the words corresponded to pictures that were perceived or imagined	imagined vs. perceived	verbal picture	+ Reality-monitoring
Vinogradov et al., 2008	1) Subjects were shown sentences for which the final word was presented by the experimenter or left blank; 2) During the scan, subjects indicated whether words were externally presented or self-generated	self-generated perceived	vs. verbal	Reality-monitoring
Stephan-Otto et al., 2017	1) Subjects viewed either a word with a corresponding picture or a word followed by a blank screen; 2) During the scan, subjects indicated whether the words corresponded to pictures that were perceived or imagined	imagined vs. perceived	verbal picture	+ Reality-monitoring
Tsakiris et al., 2010	Subjects viewed a video image of their right hand that was covered with a woolen glove. This image was either direct or delayed. In the passive condition, an experimenter lifted and lowered the index finger up and down. In the active condition, the subject actively lifted and lowered his/her finger.	synchronous asynchronous	vs. action - visual feedback	Self-monitoring

Uhlmann et al., 2020	Subjects held the handle of a device to perform movements. Subjects were presented with visual feedback on a screen. Subject's own hand or someone else's hand was displayed on the screen. Movements could either be self-generated or generated by the device. Videos were either presented in real time or delayed. Subsequently, subjects were required to indicate whether they detected a delay or not.	self-generated externally generated	vs.	action - visual feedback	Self- monitoring
Renes et al., 2015	Subjects performed a computerized task in which the color of a square was changed. They were required to indicate whether this change of color was computer-generated or self-generated.	self-generated externally generated	vs.	action - visual feedback	Self- monitoring
Farrer et al., 2002	Subjects traced a circle along a T-shaped path with a joystick. They were told that the circle would be drawn by either themselves or the experimenter.	self-generated externally generated	vs.	action - visual feedback	Self- monitoring
Kontaris et al., 2009	Subjects performed hand actions when receiving a visual feedback. The feedback was either compatible or incompatible from the actions they were executing. During the incompatible condition, subjects viewed a record of the movements generated by their hand in the preceding block when they performed a different sequence of movements.	synchronous asynchronous	vs.	action - visual feedback	Self- monitoring
Sasaki et al., 2018	Subjects performed finger movements while receiving visual feedback. The feedback varied in 3 factors: action kinematics, body identity and feedback timing. Subjects were instructed to judge the degree of congruity.	self-generated externally generated	vs.	action - visual feedback	Self- monitoring
Schnell et al., 2007	Subjects played a racing video game in which a car had to be kept on a racing track. Incongruity was artificially generated by intermittent takeover of the controls by the computer acting as an autopilot. Subjects were instructed to abstain from their own actions as soon as the computer took over control.	self-generated externally generated	vs.	action - visual feedback	Self- monitoring
Jardri et al., 2007	Subjects either listened to their own voice when whispering or listened to another person's voice.	self-generated externally generated	vs.	verbal - verbal feedback	Self- monitoring
Jardri et al., 2011	Subjects either listened their own voice when whispering or listened to another person's voice.	self-generated externally generated	vs.	verbal - verbal feedback	Self- monitoring
Balslev et al., 2006	Subjects held a joystick to execute some random movements. They were presented with visual feedback about their own movements, which was either vertical or distorted to a variable degree. During the passive condition, an experimenter moved the subject's fingers. During each session, subjects were asked to indicate if the movements they saw were synchronous, asynchronous, or actively or passively provoked.	synchronous asynchronous	vs.	action - visual feedback	Self- monitoring
Farrer et al., 2008	Subjects continuously performed finger movements. They were led to believe that they were watching alternating depictions of their own movements with a delay and those of another agent. They were asked to indicate whether they thought the observed movement was their own or belonged to another agent.	self-generated externally generated	vs.	action - visual feedback	Self- monitoring
Farrer et al., 2003	Subjects executed movements with a joystick. They were presented with either the actual feedback of their movement, the distorted feedback or the movement	Conjunction: synchronous	vs.	action - visual feedback	Self- monitoring

of the joystick controlled by another agent. Subjects were instructed to judge in asynchronous and self-generated vs. externally generated the movement was their own movement, their own movement distorted or the movement of another agent. generated

Supplementary Table 2: Activation/deactivation peaks for the included studies in both meta-analyses (n = 21).

Authors	Coordinate system	ACTIVATIONS						DEACTIVATIONS								
		x	y	z	Z (peak)	t (peak)	F (peak)	p-value	x	y	z	Z (peak)	t (peak)	F (peak)	p-value	
Takahashi et al., 2002	TAL	42	-60	56	4.37											
Turner et al., 2008	MNI	-39	45	24	3.48											
		12	48	27	3.76											
		-33	27	42	4.28											
		45	15	12	4.31											
		57	12	42	3.76											
		33	39	45	4.53											
		-30	-6	57	3.97											
		-9	-18	-51	3.62											
		36	-9	36	3.82											
		-51	-36	9	4.12											
		-63	-45	-6	3.66											
		57	-57	-12	3.63											
		60	-27	15	4.01											
		-39	-36	54	4.14											
		-63	-33	24	3.63											
		-42	-63	42	4.5											
		-3	-54	27	4.1											
		42	-81	33	4.24											
		6	-84	42	3.62											
		18	-69	-30	4.47											
King et al., 2014	MNI	-15	-57	-27	3.56											
		45	-21	57		6.98										
		30	42	27		3.56										
		-9	-45	15		3.84										
		-57	-63	6		4.19										
		45	3	-18		4.02										
		-63	-42	24		3.9										
		54	-66	3		3.86										
		15	-27	48		3.74										
		30	-12	0		4.17										
		-15	-54	-21		4.92										
		-30	-45	-30		4										
		12	-54	-15		5.4										
Subramaniam et al., 2012	MNI	10	52	2												

Lundstrom et al., 2003	TAL	-48	26	24	3.96					
		-18	-66	40	3.93					
King et al., 2017	MNI					-48	-52	28		22.47
						60	-25	28		21.17
King et al., 2015	MNI					-39	-58	52	5.21	
						33	-67	46	4.81	
						-9	-70	43	4.72	
						-30	26	-2	4.42	
						33	29	4	4.13	
						-3	14	61	3.96	
						51	29	25	3.92	
						-3	-28	31	4.15	
						-9	-19	-2	4.50	
						12	8	13	4.41	
						-12	2	10	4.02	
Vinogradov et al., 2008		-10	48	18	4.5					
		-4	57	19	4.08					
		-4	49	12	3.87					
		2	40	20	3.74					
		8	59	19	3.63					
		6	52	21	3.61					
		-8	-56	36	4.3					
Stephan-Otto et al., 2017						-16	3	23		0.001
						10	2	13		0.001
						-7	-91	-1		0.021
Tsakiris et al., 2010	MNI	-22	-54	-24	4.44	52	-38	38	4.53	
		24	-40	54	4.15	40	-58	26	4.82	
		38	-42	58	3.72	-38	20	2	4.01	
		12	-48	-20	3.69	-16	-84	-26	3.88	
		-44	-18	18	3.56	-12	-62	-38	3.85	
		24	-72	36	3.46	40	52	14	3.8	
						24	48	-14	3.56	
						50	-46	-2	3.51	
						60	20	6	3.5	
Uhlmann et al., 2020	MNI	10	-94	10	6.63	18	-48	42	6.79	
		-6	-66	6	6.1	-8	34	44	6.57	
		-12	-80	10	5.03	18	-46	58	6.41	
						44	-16	-6	5.51	
						52	0	-8	4.12	

								20	-58	-50		4.07
								62	-8	22		3.78
								62	-10	32		3.65
								54	-10	36		3.52
Renes et al., 2015	MNI	-52	-68	32		5.08						
		-20	52	40		5.13						
		20	36	52		5.67						
		8	64	4		4.88						
Farrer et al., 2002	TAL	40	8	2	4.55		44	-58	32	4.86		
		-36	-2	2	4.21		-48	-52	40	4.04		
							-6	-58	50	4.62		
							2	-50	44	3.76		
							-38	28	48	3.65		
Kontaris et al., 2009	TAL	24	-85	1	9.21		57	-55	19			7.8
		24	-76	16	5.72		60	-46	-5			9.59
							45	12	22			6.65
							48	17	2			6.04
							9	-55	34			6.2
							42	5	34			6.17
							0	38	43			6.94
							-54	-52	16			8.81
							-6	8	55			5.22
							-45	11	31			6.21
							-42	-46	-8			8.86
							-42	20	2			6.1
Sasaki et al., 2018	MNI	62	-14	36	4.66		-6	32	34	3.8		
		26	-68	38	5.95							
Schnell et al., 2007	TAL						42	20	-14	5.19		
							45	46	-10	4.27		
							53	20	-11	3.97		
							42	5	38	4.64		
							50	19	32	3.87		
							50	21	21	3.57		
							56	21	10	4.41		
							48	24	7	3.74		
							56	-39	41	5.48		
							56	-51	36	4.48		
							62	-48	25	4.12		
Jardri et al., 2007	TAL	58	-15	28	8.6		4	48	25			6.6

		-58	-15	28	8.6			-4	48	25		6.6
		-57	-6	23	13			-32	36	8		7.8
		4	-8	55	12.3			1	-55	19		7.6
		2	46	42	8.3			-1	-55	19		7.6
		-2	46	42	8.3			3	33	10		7.6
		-32	23	1	9.2			-3	33	10		7.6
		-57	8	11	7.6			23	-13	-16		7.3
		11	-55	-29	12.3			0	-54	25		8.2
		-11	-55	-29	12.3			1	28	33		7.6
		17	-4	23	8.5			-1	28	33		7.6
		-17	-4	23	8.5			45	-61	20		5.7
		10	-18	9	7.1			-45	-61	20		5.7
		-10	-18	9	7.1			43	-33	44		7.6
Jardri et al., 2011	TAL	58	-16	26	8.5			3	-54	20		8
		-58	-16	26	8.5			-3	-54	20		8
		-57	-8	22	11.8			2	-54	26		8.3
		3	-5	56	10.9			3	32	12		7.6
		3	46	39	7.9			-3	32	12		7.6
		-3	46	39	7.9			3	34	18		9.2
		-57	7	11	7.8			-3	34	18		9.2
		19	-53	-33	10.3			47	-54	12		5.9
		-19	-53	-33	10.3			-47	-54	12		5.9
		17	-1	22	7.9			44	-38	40		7.8
		-17	-1	22	7.9							
		10	-18	10	7.6							
Balslev et al., 2006	MNI							54	-42	33		7.09
								-42	-51	45		7.1
								-54	-48	27		5.71
								51	-24	-12		7.04
Farrer et al., 2008	MNI							58	-46	48	4.36	
								44	-50	60	3.19	
								-48	-46	56	3.97	
								-48	28	30	4.5	
								-44	22	36	3.81	
								28	54	-2	3.34	
								46	30	42	3.51	
								-54	18	20	4.33	
								38	50	-2	3.89	
Farrer et al., 2003	MNI	56	-56	36	4.72			40	-10	16	4.42	

-64	-58	32	4.43
0	14	54	4.27
50	10	58	4.20
12	30	42	4.07

20	-38	-28	4.38
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Abbreviations: MNI: Montreal Neurological Institute, TAL: Talairach

Supplementary Table 3: Imaging parameters and statistical threshold of each included study.

Authors	Magnetic field	Slice thickness, gap	Smoothing kernel	Number of slices	FOV	matrix	Threshold	design
Balslev et al., 2006	1.5T	3 mm, NR	8 mm	42	NR	64x64	$p_{\text{uncorr}} < 0.001$	block
Farrer et al., 2002	2T	3 mm, NR	8 mm	26	192	64x64	$p_{\text{uncorr}} < 0.0001$	event-related
Farrer et al., 2003	Siemens CTI	NA	NA	63	15.2	NA	$p_{\text{uncorr}} < 0.0001$	block
Farrer et al., 2008	1.5T	4.5 mm, 1 mm	8 mm	25	NR	NR	$p_{\text{uncorr}} < 0.002$	block
Jardri et al., 2007	1.5T	4 mm, NR	4 mm	30	240	64x64	NR	block
Jardri et al., 2011	1.5T	4 mm, NR	5 mm	30	240	64x64	NR	block
King et al., 2014	3T	3 mm, NR	8 mm	37	NR	64x64	$p_{\text{corr}} < 0.05$	event-related
King et al., 2015	3T	3 mm, NR	8 mm	37	NR	64x64	$p_{\text{corr}} < 0.05$	event-related
King et al., 2017	3T	3 mm, NR	8 mm	37	NR	64x64	$p_{\text{corr}} < 0.05$	event-related
Kontaris et al., 2009	3T	3 mm, NR	no smoothing	34	NR	64x64	$p_{\text{uncorr}} < 0.005$	block
Lundstrom et al., 2003	1.5T	3 mm, 0.4 mm	12 mm	42	NR	64x64	$p_{\text{uncorr}} < 0.001$	event-related
Renes et al., 2015	3T	4 mm, NR	8 mm	30	256x208	64x51	$p_{\text{uncorr}} < 0.001$	event-related
Sasaki et al., 2018	3T	3 mm, NR	8 mm	39	192x192	64x64	$p_{\text{uncorr}} < 0.001$	block
Schnell et al., 2007	1.5T	4 mm, 0.2 mm	9 mm	30	192	64x64	$p_{\text{corr}} < 0.01$	event-related
Stephan-Otto et al., 2017	1.5T	4 mm, 1 mm	8 mm	26	240	64x64	$p_{\text{corr}} < 0.05$	event-related
Subramaniam et al., 2012	3T	6 mm, NR	10 mm	14	220	64x64	$p_{\text{uncorr}} < 0.001$	event-related
Takahashi et al., 2002	1.5T	6 mm, NR	8 mm	20	256	64x64	$p_{\text{corr}} < 0.05$	event-related
Tsakiris et al., 2010	1.5T	3 mm, NR	8 mm	48	NR	NR	$p_{\text{uncorr}} < 0.001$	block
Turner et al., 2008	3T	2 mm, 1 mm	8 mm	36	NR	64x64	$p_{\text{uncorr}} < 0.001$	event-related
Uhlmann et al., 2020	3T	4 mm, 0.6 mm	8 mm	34	192	64x64	$p_{\text{uncorr}} < 0.001$	block
Vinogradov et al., 2008	1.5T	5 mm, 1mm	8 mm	19	26x26	128x128	$p_{\text{uncorr}} < 0.001$	event-related

Abbreviations: FOV: Field of view; NR: Not Reported; T: Tesla.

Supplementary Table 4: Quality assessment checklist. Score 0/0.5/1 for each item (0.5 points were given for criteria partially met).

Subjects

1. The sample size was appropriate
2. Subjects were evaluated prospectively, demographic data were reported (age (mean and SD/range), sex, and handedness), and psychiatric and medical illnesses were excluded
3. If any subject was scanned but then rejected from the analysis, withdrawals from the study were explained

Methods for self-recognition tasks

4. All participants went through a training session outside the scanner
5. The design was clearly described so that it could be reproduced (number of blocks or trials per subject, length of each trial and ISI, block or event-related design)
6. The stimuli and the number of repetitions were sufficient and clearly described
7. If applicable, the baseline condition was defined as almost the same as the task condition except for the self-recognition

Methods for image acquisition and statistical analysis

8. MRI slice thickness ≤ 3 mm
9. 3T MRI was used
10. The imaging technique used for data acquisition was clearly described so that it could be reproduced (e.g., MRI system used, field strength, pulse sequence type, number of volumes per session, field of view, matrix size, slice thickness, interslice skip, acquisition orientation, TE/TR/flip angle)
11. Preprocessing operations were clearly described and detailed so that it could be reproduced (e.g., software used, order of preprocessing operations, slice-timing, motion correction, coregistration and normalization (linear/affine or nonlinear), smoothing)
12. Adjustments were made for multiple statistical comparisons
13. Appropriate design and/or analytical methods to control confounding
14. Appropriate use of statistics for primary analysis effect (excluding control of confounders)

Results, conclusions and conflicts of interest

15. Statistical parameters for significant and important nonsignificant differences were provided
 16. Conclusions were consistent with the results obtained and the limitations were discussed
 17. Declarations of conflicts of interest or identification of funding sources
-

Supplementary Table 5: Sensitivity analysis for the reality-monitoring meta-analysis

Study	Activation				Deactivation								
	Left cerebellum, hemispheric lobule VI	Right superior frontal gyrus, medial (BA10)	Left supramarginal gyrus (BA 48)		Right anterior thalamic projections	Left medial cingulate (BA 23)	Right inferior frontal gyrus, triangular part	Left precuneus (BA 7)	Left nucleus caudate	Left supplementary motor area (BA 6)			
King et al., 2014	n	y	n		y	n	n	n	y	n			
King et al., 2015	y	y	y		y	n	n	n	n	n			
King et al., 2017	y	y	y		y	y	y	y	y	y			
Stephan-Otto et al., 2017	y	y	y		y	y	y	y	y	y			
Subramaniam et al., 2012	y	y	y		y	y	y	y	y	y			
Takahashi et al., 2002	y	y	y		y	y	y	n	y	y			
Turner et al., 2008	n	y	n		y	y	y	y	y	y			
Lundstrom et al., 2003	y	y	n		y	y	y	y	y	y			
Vinogradov et al., 2008	y	n	y		y	y	y	y	y	y			
Total	7/9	8/9	6/9		9/9	7/9	7/9	6/9	8/9	7/9			

Supplementary Table 6: Sensitivity analysis for the self-monitoring meta-analysis

Study	Activation				Deactivation									
	Left cerebellum, hemispheric lobule VI	Left postcentral gyrus (BA 48)	Corpus callosum	Right supplementary motor area (BA 6)	Right supramarginal gyrus (BA 22)	Right precuneus	Left superior frontal gyrus (BA 32)	Left inferior parietal gyri (BA 40)	Right inferior frontal opercular part (BA 48)	Left inferior frontal gyrus, triangular part (BA 48)	Right anterior cingulate / paracingulate gyri (BA 11)	Right middle temporal gyrus (BA 48)	Right middle temporal gyrus (BA 21)	
Balslev et al., 2006	y	y	y	y	y	y	y	y	y	y	n	n	y	
Farrer et al., 2002	y	y	y	y	y	y	y	n	y	y	y	y	y	
Farrer et al., 2003	y	y	y	y	y	y	y	y	y	y	y	y	y	
Farrer et al., 2008	y	y	y	y	y	y	y	y	n	y	y	y	y	
Jardri et al., 2007	y	y	y	n	y	y	y	y	y	y	n	y	n	
Jardri et al., 2011	y	y	y	n	y	y	y	y	y	y	n	y	y	
Kontaris et al., 2009	y	y	y	y	y	y	y	n	y	y	n	y	n	
Renes et al., 2015	y	y	y	y	y	y	y	n	y	y	n	y	y	
Sasaki et al., 2018	y	y	y	y	y	y	y	y	y	y	y	n	y	
Schnell et al., 2007	y	y	y	y	y	y	y	n	n	n	y	n	y	
Tsakiris et al., 2010	y	y	y	y	y	y	y	n	y	y	y	n	y	
Uhlmann et al., 2020	y	y	y	y	y	y	y	y	y	y	y	n	y	
Total	12/12	12/12	12/12	10/12	12/12	12/12	12/12	7/12	10/12	7/12	7/12	7/12	10/12	

Supplementary Table 7: Results of meta-regression for the reality-monitoring meta-analysis.

Variable	Brain region	BA	Number of voxels	p-value	MNI	SDM-Z
<i>Age, increase</i>	ns					
	ns					
<i>Age, decrease</i>	ns					
Quality score, increase	ns					
Quality score, decrease	ns					

The results are displayed based on the familywise error rate correction threshold of $p < 0.005$. Coordinates are reported in Montreal Neurological Institute (MNI) space. *Abbreviations:* SDM-Z: Seed-based d Mapping Z-value; BA: Broadman Area; and I^2 : Percentage of variance attributable to heterogeneity

Supplementary Table 8: Results of meta-regression for the self-monitoring meta-analysis.

Variable	Brain region	BA	Number of voxels	p-value	MNI	SDM-Z
<i>Age, increase</i>	Left inferior frontal gyrus, opercular part	44	116	0.00199	-54, 14, 12	3.142
	Right supplementary motor area		11	0.00400	4, 12, 54	3.117
<i>Age, decrease</i>	ns					
Quality score, increase	ns					
Quality score, decrease	ns					

The results are displayed based on the familywise error rate correction threshold of $p < 0.005$. Coordinates are reported in Montreal Neurological Institute (MNI) space. *Abbreviations:* SDM-Z: Seed-based d Mapping Z-value; BA: Broadman Area; and I^2 : Percentage of variance attributable to heterogeneity

4.3. Conclusion

In this study, we adopted a meta-analytic approach to investigate the brain regions involved in reality-monitoring. We also examined the common brain activation between reality-monitoring and self-monitoring, based on studies that have shown correlated performance between reality-monitoring and self-monitoring in healthy individuals and their similar magnitude alteration in patients with schizophrenia and at-risk individuals (Lavallé et al., 2020b; Subramaniam et al., 2018; Waters et al., 2012). We demonstrated that reality-monitoring is associated with activations in the lobule VI of the cerebellum, the right amPFC and anterior thalamic projections. We also demonstrated that self-monitoring is associated with modulations of activity in the lobule VI of the left cerebellum and fronto-temporo-parietal regions. Finally, our results suggest that the lobule VI of the cerebellum is consistently engaged in both reality-monitoring and self-monitoring.

4.4. Immediate perspectives: Looking for the neural correlates of the reality-monitoring impairment in patients with schizophrenia

4.4.1. Introduction

Schizophrenia is a chronic mental disorder characterized by a wide range of symptoms, including hallucinations, delusions, and disordered thinking. One of the major cognitive deficits associated with schizophrenia is a dysfunction in reality-monitoring, that is, the ability to distinguish between internally and externally generated information. Research has shown that this reality-monitoring dysfunction is strongly related to the experience of hallucinations in

individuals with schizophrenia. Specifically, people with schizophrenia who have difficulty distinguishing between internally generated thoughts and external reality, referred to as "reality-monitoring externalizations", are more likely to experience hallucinations.

Studies using neuroimaging techniques such as fMRI and PET have identified the involvement of specific brain regions such as the amPFC in reality-monitoring in healthy individuals. Its activity and connectivity with other brain regions are disrupted in patients with schizophrenia who have a reality-monitoring deficit. In order to verify which brain regions are functionally implicated in reality-monitoring, we performed a coordinate-based meta-analysis of studies evaluating reality-monitoring performances in healthy individuals. Our results confirmed the involvement of the amPFC in this process and revealed the involvement of the lobule VI of the left cerebellum in healthy individuals (*Lavallé et al., submitted in Human Brain Mapping, see Chapter 3*).

Understanding the neural substrates of the reality-monitoring deficit in schizophrenia may provide important insights into the underlying mechanisms of the disease and contribute to the development of more effective treatments. To determine the relationship between reality-monitoring performances, clinical characteristics and functional and structural connectivity in patients with schizophrenia, we are conducting a study in patients with schizophrenia who completed various clinical and demographic assessments, source-monitoring evaluation, including reality-monitoring and internal source-monitoring (i.e., the ability to distinguish between two internally-generated information, such as thoughts and speech), and MRI acquisitions, including T1, fMRI and DTI.

4.4.2. Material and Methods

4.4.2.1. *Participants*

A total of 95 patients with schizophrenia were recruited from several different centers in France: CH Le Vinatier in Lyon, University Hospital Center in Saint-Etienne, University Hospital Center in Lille, CH Saint-Anne in Paris, University Hospital Center in Tours, University Hospital Center in Nice and University Hospital Center in Caen. All assessments were standardized across sites. Inclusion criteria for patients to enter this study were as follows: (1) they fulfilled the diagnostic criteria for SZ in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), (2) Age between 18 and 65 years old, (3) they were fluent in French. A patient was excluded if any of the following conditions was met: (1) Refusal to participate, (2) History of serious medical or neurological disorder that would affect cognition functioning, (3) Presence of other neuropsychiatric disorders, including bipolar disorders and mood depression disorders, (4) Any contraindication or incompatibility for MRI. All participants provided written consent in accordance with the Declaration of Helsinki. Of the 95 included subjects, 87 had MRI acquisitions. We used data from 78 patients after quality control. For the full demographic and clinical characteristics of the sample are in *Table 7*.

4.4.2.2. *Clinical and demographic assessment*

Clinical symptoms were quantified with the Positive and Negative Syndrome Scale (PANSS). Hallucinations characteristics were quantified using the Auditory Hallucinations Rating Scale (AHRS) and the Psycho-Sensory Hallucination Scale (PSAS). Age and chlorpromazine equivalent were also reported.

	Mean (SD)
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Age (years)	37.99 (10.90)
PANSS (total score)	
PANSS positive	18.95 (4.87)
PANSS negative	23.73 (6.29)
PANSS general	39.13 (8.66)
PANSS total	81.81 (14.47)
AHRS (total score)	21.07 (11.87)
PSAS (total score)	27.19 (16.95)
Chlorpromazine equivalent	822.35 (611.98)

Table 7. Demographic and clinical information of the participants.

4.4.2.3. Cognitive assessment

Patients completed a sensory gating assessment using the Sensory Gating Inventory (SGI) (Hetrick et al., 2012). The participants were individually tested with two source-monitoring tasks presented in a randomized order: one internal source-monitoring task and one reality-monitoring task (Brunelin et al., 2008). The testing procedure took approximately 15 min to complete. Each source-monitoring task was divided into two phases, an encoding phase and a memory retrieval phase, which were preceded by a short practice trial. As displayed in Figure 1, during the encoding phase, 16 words were sequentially presented in a randomized order. Each word was preceded by an instruction. During the memory retrieval phase, 24 words were presented, including the 16 words that were presented during the encoding phase and 8 new words. Our stimulus materials were similar to those described by Lavallé et al. in [Article 2]. In the internal source-monitoring task, the verbal list included eight words with the “imagine saying” encoding condition and eight other words with the “say aloud” encoding condition. Then, internal source-monitoring abilities were assessed by asking subjects to identify whether each word was said aloud, imagined or new (*see Figure 25A*). In the reality-monitoring task,

the verbal list included eight words with the “imagine hearing” encoding condition and eight other words with the “listen to” encoding condition. Then, reality-monitoring abilities were assessed by asking subjects to identify whether each word was heard, imagined or new (*see Figure 25B*).

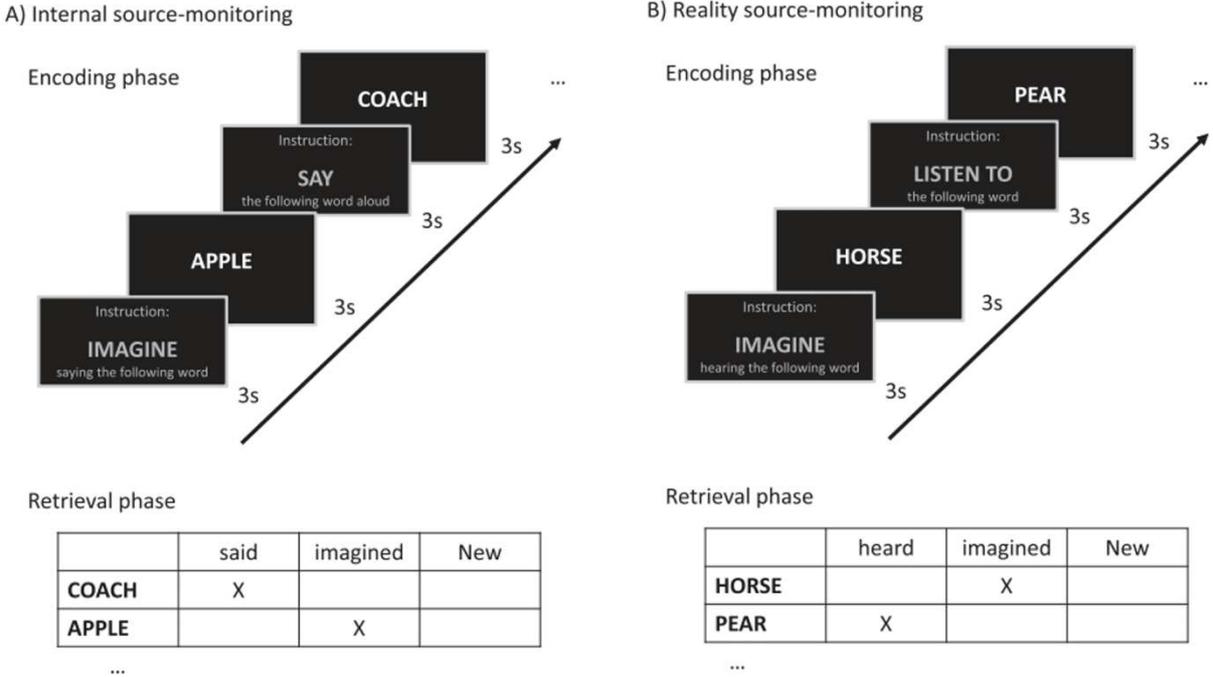


Figure 25. Experimental procedures for reality-monitoring (right panel) and internal source-monitoring (left panel) assessments.

4.4.2.4. Neural data acquisition and pre/postprocessing

Participants completed a neural magnetic resonance imaging (MRI) scan at 3T including resting-state blood-oxygene-level-dependent (BOLD), magnetization-prepared rapid gradient echo (MP-RAGE) sequence for T1 weighted data and 2D echo planar imaging sequence to obtain diffusion-weighted MRI data. A head-stabilizer was used to reduce head motion.

Full details on the acquisition parameters for each center are reported in Table 8.

	Center	Lyon	Tours	Saint- Etienne	Clermont	Paris, Saint-Anne	Nice	Caen	Lille
Machine		Siemens Prisma	Siemens Verio	Siemens Prisma	Siemens Magnetom Vida	GE discovery	GE discovery	Philips Achieva	Philips Achieva
3DT1	Echo time (TE, ms)	2.98	2.98	2.98	2.98	3.19	3	3.3	3.3
	Repetition time (TR, ms)	2300	2300	2300	2300	8.18	6.95	7.19	7.19
	Slice thickness (mm)	1	1	1	1	1	1	1	1
	Field of View (FOV, mm)	240x256	240x256	240x256	240x256	256	256	240x256x176	240x256x176
	Reconstruction matrix	240x256	240x256	240x256	240x256	256	256	256x256	256x256
	Number of slices	176	176	176	176	176	176	176	176
fMRI	Echo time (TE, ms)	30	30	30	30	27	27	30	30
	Repetition time (TR, ms)	2400	2460	2380	2440	2500	2500	2400	2400
	Slice thickness (mm)	3	3	3	3	3	3	3	3
	Field of View (FOV, mm)	1344x1344	1344x1344	192x192	192x192	192	192	192x135x192	192x135x192
	Reconstruction matrix	64x64	64x64	64x64	64x64	64	64	64	64
	Number of slices	45	45	45	45	42	46	45	45
DTI	Echo time (TE, ms)	102	102	102	102	91	104	75	75
	Repetition time (TR, ms)	14700	14700	14700	14400	14000	17000	14000	14000
	Slice thickness (mm)	2	2	2	2	2	2.5	2	2
	Field of View (FOV, mm)	2304x2304	256x256	2304x2304	256x256	218	218	256x140x256	256x140x256
	Reconstruction matrix	128x128	128x128	128x128	128x128	128	128	128	128
	Number of directions / of sequences	60(15*4)	60(15*4)	60(15*4)	60(15*4)	60(15*4)	60(15*4)	60(15*4)	60(15*4)
	b values (s/mm ²)	[0,1500]	[0,1500]	[0,1500]	[0,1500]	[0,1500]	[0,1500]	[0,1500]	[0,1500]
	Number of slices	70	70	70	70	1120	1008	70	70

Table 8. Acquisition parameters of T1-weighted, BOLD and DTI data for each center.

Neuroimaging data were preprocessed using the Quantitative Neuroimaging Environment & Toolbox (QuNex) (Ji et al., 2022), that is an open-source software suite supporting an extensible framework for data organization, preprocessing, quality assurance and analyses across various neuroimaging modalities (see Figure 26, Figure 27).

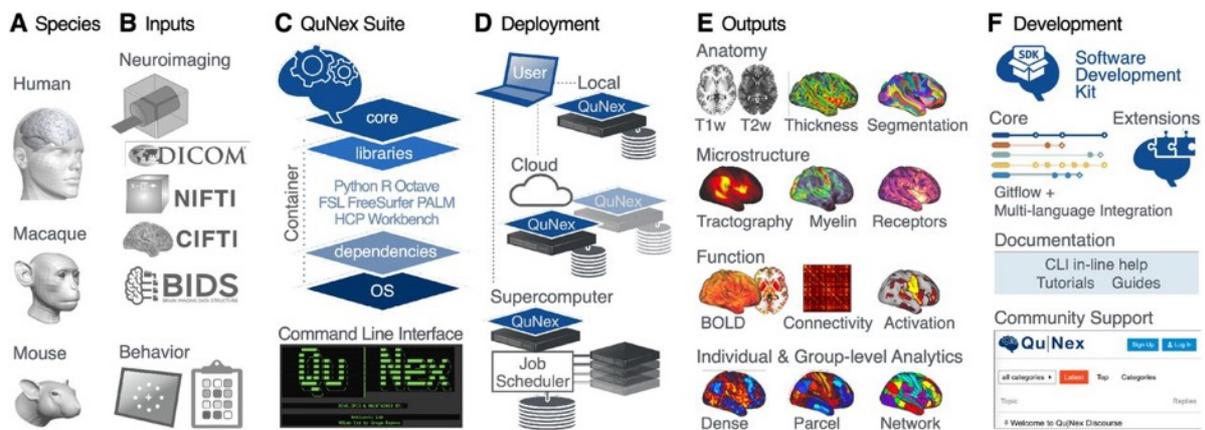


Figure 26 from Ji et al. (Ji et al., 2022). QuNex provides an integrated, versatile and flexible neuroimaging platform. A) QuNex supports processing of input data from multiple species, including human, macaque and mouse. B) Additionally, data can be onboarded from a variety of popular formats, including neuroimaging data in DICOM, PAR/REC, NifTI formats, a full BIDS dataset, or behavioral data from task performance or symptom assessments. C) The QuNex platform is available as a container for ease of distribution, portability and execution. The QuNex container can be accessed via the command line and contains all the necessary packages, libraries and dependencies needed for running processing and analytic functions. D) QuNex is designed to be easily scalable to accommodate a variety of datasets and job sizes. From a user access point (i.e. the user’s local machine), QuNex can be deployed locally, on cloud servers, or via job schedulers in supercomputer environments. E) QuNex outputs multi-modal features at the single subject and group levels. Supported features that can be extracted from individual subjects include structural features from T1w, T2w and dMRI (such as myelin, cortical thickness, sulcal depth and curvature) and functional features from BOLD imaging (such as functional connectivity matrices). Features can be extracted at the dense, parcel, or

network levels. F) Importantly, QuNex also provides a comprehensive set of tools for community contribution, engagement and support. A Software Development Kit (SDK) and GitFlow-powered DevOps framework is provided for community-developed extensions. A forum (<https://forum.qunex.yale.edu>) is available for users to engage with the QuNex developer team to ask questions, report bugs and/or provide feedback.

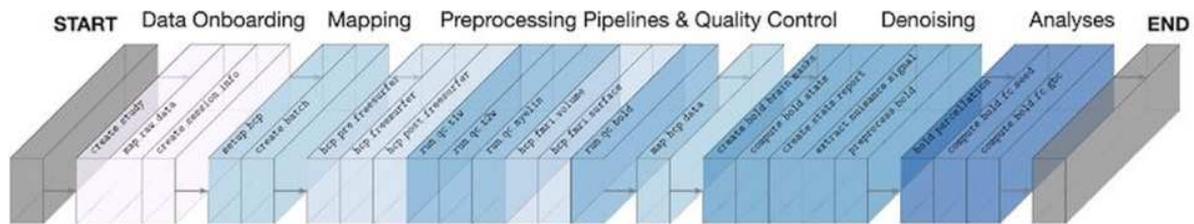


Figure 27 adapted from from Ji et al. (Ji et al., 2022). The QuNex toolbox supports data onboarding, mapping, preprocessing, quality control, postprocessing and analyses.

The first steps of preprocessing were based on the Human Connectome Project (HCP) minimal processing pipeline (Glasser et al., 2013) adapted for compatibility with legacy data through the QuNex toolbox. First, the *qunex hcp_pre_freesurfer* function was used to align the T1-weighted structural images by warping them to the standard Montreal Neurological Institute-152 (MNI-152) brain template, through a combination of linear and non-linear transformations via the FMRIB Software Library (FSL) linear image registration tool (FLIRT) and non-linear image registration tool (FNIRT) (Jenkinson et al., 2002). Second, the *qunex hcp_freesurfer* function was used to segment gray and white matter and produce cortical and subcortical anatomical segmentations through the FreeSurfer’s recon-all pipeline (Reuter et al., 2012). Third, the *qunex hcp_postfreesurfer* function was used to define a ‘cortical ribbon’ was defined from the pial and white matter surface boundaries along with corresponding subcortical voxels, which were combined to generate the neural file in the Connectivity Informatics Technology Initiative (CIFTI) volume/surface ‘grayordinate’ space for each subject (Glasser et al., 2013).

Finally, the structural quality control (*see Figure 28*) was checked by two independent persons (Layla Lavallé, Marine Mondino).

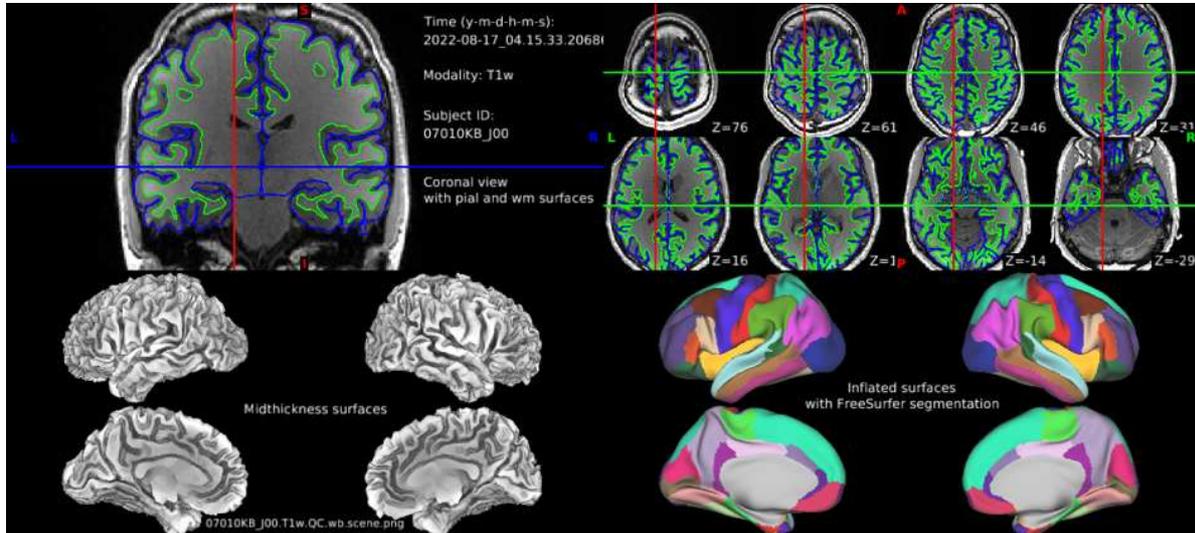


Figure 28. Output obtained by the first three minimal preprocessing pipelines applied on T1-weighted structural image for one subject. Upper left panel: coronal view of the white-gray matter segmentation. Upper right panel: axial view of the white-gray matter segmentation. Lower left panel: Midthickness surfaces, that are the average of the white and pial surfaces. Lower right panel: Inflated surfaces with FreeSurfer segmentation.

The *qunex_fmri_volume* function was used to perform a motion-correction of the BOLD data by aligning to the middle frame of every run in the initial NIFTI volume space via FLIRT. A brain mask was then applied to exclude signal from non-brain tissue. Then, the *qunex_fmri_surface* function was used to convert cortical BOLD data to the CIFTI format and to align them to the HCP atlas using surface-based nonlinear deformation. After the HCP minimal preprocessing pipelines, movement scrubbing was performed by computing statistics that reflect movement and its artifactual properties using the *qunex_compute_bold_stats* and *qunex_create_stats_report* functions. All BOLD image frame with possible movement-induced artifactual fluctuations in intensity were flagged using two criteria: frame displacement

exceeding 0.5 mm and/or the normalized root mean square (RMS) exceeding 1.6 times the median across scans. Any frame that met any of these criteria, as well as the frame immediately preceding and immediately following, were discarded from further analyses. Then, the *qunex extract_nuisance_signal* function was used to extract nuisance signal to be regressed out. Finally, the *qunex preprocess_bold* function was used to smooth, to apply a high-pass filter to the BOLD data to remove low-frequency signals and to regress out nuisance signal. Finally, the functional quality control (see Figure 29) was checked by two independent persons (Layla Lavallé, Marine Mondino).

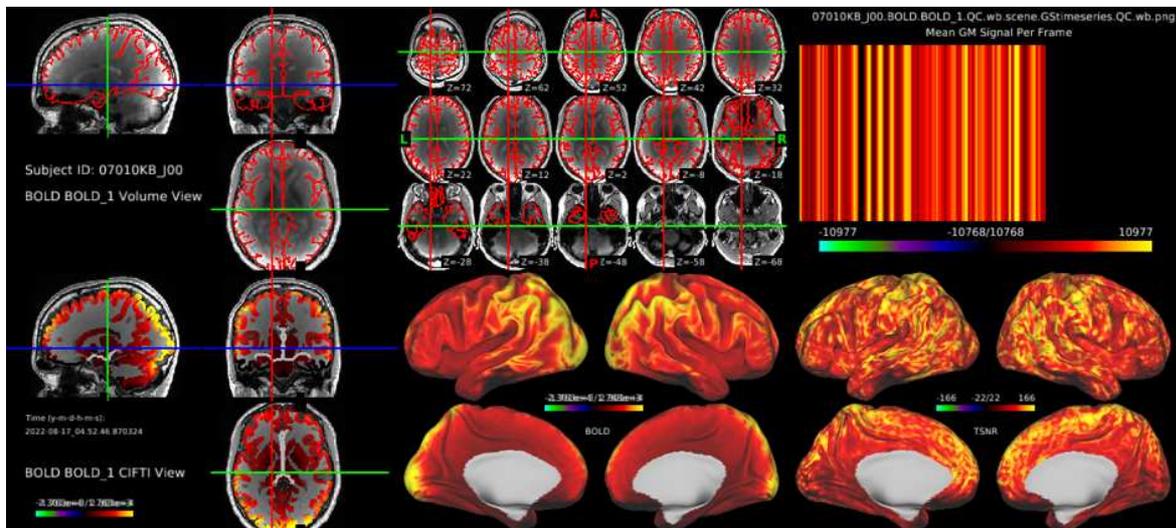


Figure 29. Output obtained by the first two last minimal preprocessing pipelines and the denoising pipelines applied on BOLD images for one subject. Upper left and middle panels: Volume view of the BOLD data with the corresponding pial surface of the subject. Upper right panel: Mean gray-matter signal per frame. Lower left panel: CIFTI view including BOLD signal overlying the gray-matter ribbon. Lower middle panel: BOLD signal on the inflated surface of the brain. Lower right panel: Temporal Signal-to-Noise Ratio (TSNR).

Diffusion data were preprocessed using the *qunex hcp_diffusion* *qunex* function which is a modified version of the diffusion minimal preprocessing pipeline (Glasser et al., 2013) that runs

the FSL *eddy* tool to correct for eddy-current induced field inhomogeneities and head motion and registers diffusion with the structural data. After preprocessing, the *dwi_bedpostx* function was used to model crossing fibers within each voxel. The probability of diffusion from each voxel in every direction versus all other directions was estimated, building the distributions that are needed to run probabilistic tractography. Then, the *dwi_pre_tractography* function performed pretractography dense trajectory space generation. Finally, the *dwi_probtrackx_dense* function was used to sample the distribution results and generate a whole-brain connectome showing the probability of streamline connections from every voxel to every other voxel.

4.4.2.5. Neural data reduction via functional brain-wide parcellation

Using the *bold_parcellate* function for BOLD data and the *dwi_parcellate* function for diffusion, a parcellation was implemented on the dense connectome using a whole-brain parcellation file. The recently developed Cole-Anticevic Brain Network Parcellation (CAB-NP, *see Figure 30*) was used (Ji et al., 2019). This partition has been built on previous network partitions (Glasser et al., 2016) and includes several high-order cognitive networks such as the left-lateralized language network. In addition, the CAB-NP partition expands these cortical networks to subcortex, “placing all brain structures across both cortex and subcortex into a single large-scale functional framework” (Ji et al., 2019).

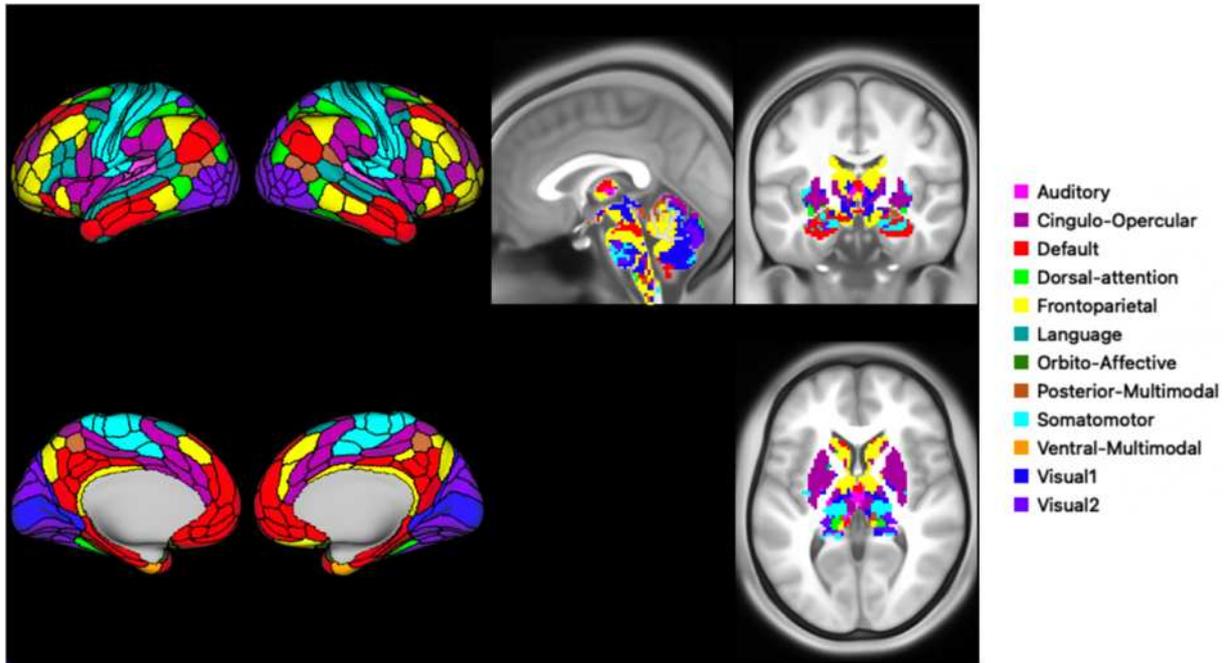


Figure 30. Illustration of the network partition using the CAB-NP partition. The cortical parcellation contains 180 bilateral cortical parcels and 358 subcortical parcels that take part in forming whole brain functional networks.

4.4.2.6. Global brain connectivity calculation

Global brain connectivity (GBC) is a summary functional connectivity (FC) metric also known as functional connectivity strength. GBC is a correlation-based connectivity approach that is calculated by correlating the time series of every gray-matter voxel with every other gray-matter voxel and transforming correlations to Fisher Z-scores (Cole et al., 2010). As for Ji et al., we mainly opted to use GBC because i) it yields an interpretable dimensionality-reduction of the full FC matrix, ii) unlike the full FC matrix, GBC produces a neural map which can be related to other independent neural maps, iii) GBC is sensitive to altered patterns of connectivity in psychosis (Ji et al., 2021). GBC was calculated on parcellated BOLD data using the *compute_bold_fc* function.

4.4.2.7. Behavioral data reduction using principal component analysis (PCA)

A PCA performed a dimension-reduction of the behavioral scores: age of participants, items of the PANSS, items of the AHRS, items of the PSAS, items of the SGI and composite scores of reality-monitoring and internal source-monitoring, including 92 symptoms or cognitive variables (see Figure 31). To this end, we used the Neuro-Behavioral Relationships In Dimensional Geometric Embedding (N-BRIDGE) suite (Anticevic, 2019; Ji et al., 2021), that is a computation neuroinformatics platform which is optimized for integration with the QuNex suite and provides a mapping between complex data-driven neuroimaging maps of the human brain and latent behavioral features. The *prep* N-BRIDGE function was used to run the PCA. Significance of the derived principal components (PCs) was computed via permutation testing. For each permutation, patient order was randomly shuffled for each variable before re-computing PCA. This permutation was repeated 5000 times to establish the null model. PCs which accounted for a proportion of variance that exceeded chance ($p < 0.05$ across all 5000 permutations) were retained for further analysis.

two PCA solutions were then evaluated for reproducibility. This process was repeated 1000 times. Next, a leave-one-out cross-validation was performed to evaluate the reliability of the PCA solution. For this analysis, a PCA was computed using all patients except one held-out patient ($n = 77$). The derived loadings were then used to compute the predicted PC scores for the left-out patient. This process was repeated until predicted PC scores were calculated for each patient. Then, the predicted score for each patient was evaluated for reproducibility relative to the observed score obtained from the PCA solution computed using the full sample of patients.

4.4.2.8. Mass univariate behavioral-neural mapping

A mass univariate behavioral-neural mapping was performed to quantify the relationship between the symptom/cognitive scores and individual parcellated GBC variation (*see Figure 32, Figure 33*). The *gatherneural* N-BRIDGE function was used to prepare a concatenated parcellated neural data series file from individual data files in subject-specific directories. Then, the *initialize* function was used to set-up the univariate mapping of behavior to neural data and perform the canonical correlation analysis.

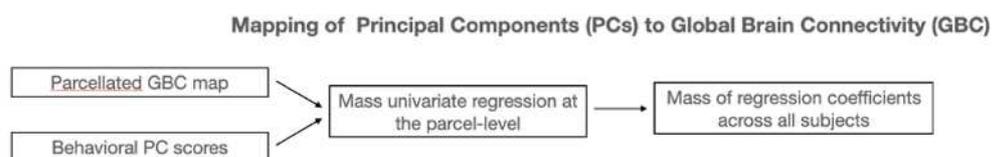


Figure 32. Schematic representation of the mass univariate behavioral-neural mapping. BOLD data is parcellated and a global brain connectivity (GBC) map is computed. Behavioral data is also reduced, using a principal component analysis (PCA). Then, a mass univariate regression is calculated at the parcel-level and across all subjects.

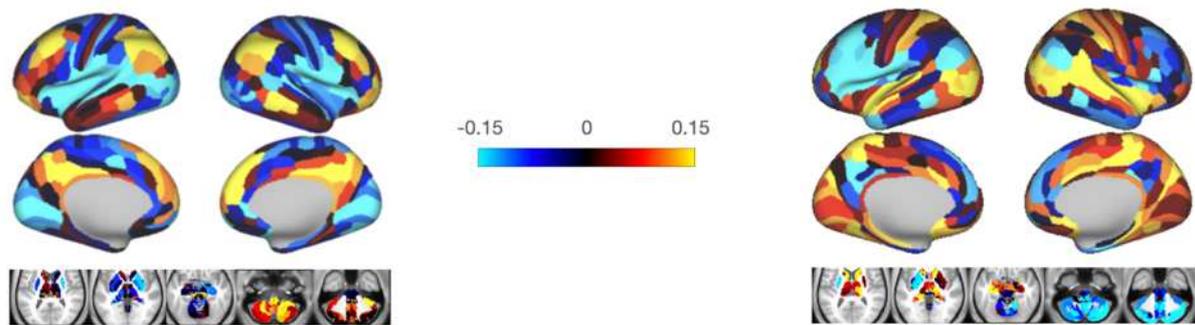


Figure 33. Example of output of the whole-brain behavioral-GBC mapping from parcellated neural data.

The univariate behavioral mapping was performed at the whole-brain level and from seeds localized in two region-of-interest (ROI) in the right amPFC and left lobule VI of the cerebellum based on the results of our coordinate-based meta-analysis in healthy individuals (see section 3.1.1, see Figure 34). The ROI localized in the left lobule VI of the cerebellum was generated using the cerebellar atlas in MNI152 space after normalization with FLIRT (Diedrichsen et al., 2009) in FSL (see Figure 10.A). The ROI localized in the right amPFC was generated using the Sallet Dorsal Frontal connectivity-based parcellation (Sallet et al., 2013) in FSL (see Figure 10.B).

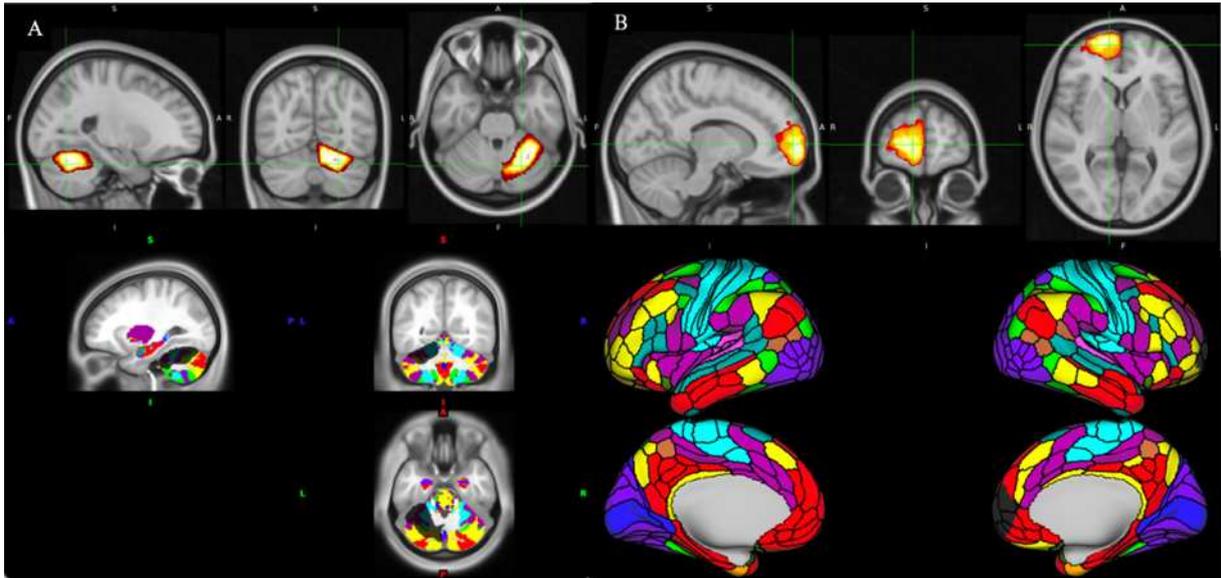


Figure 34. Seed regions generated for the ROI-based behavioral-GBC mapping from parcellated neural data. A. Seed region in the left lobule VI of the cerebellum. Upper panel: FSL view, from the cerebellar atlas in MNI152 space after normalization with FLIRT. Lower panel: Workbench view of the seed (appears in darker) overlaid on the CAB-NP parcellation. B. Seed region in the right amPFC. Upper panel: FSL view, from the Sallet Dorsal Frontal connectivity-based parcellation. Lower panel: Workbench view of the seed (appears in darker) overlaid on the CAB-NP parcellation.

4.4.2.9. Joint inference from multi-modal data

Non-parametric combination tests between functional connectivity and probabilistic tractography have been performed using the `run_palm` `qunex` function via Permutation Analysis of Linear Models (PALM) (Winkler et al., 2014). The relationship between reality-monitoring externalizations and right amPFC / left lobule VI of the cerebellum functional connectivity and structural connectivity have been assessed using a Hotelling's T^2 test. The resulting map has been thresholded ($p < 0.05$ familywise error protection (FWEP), 10 000 permutations) and shows the relationship between age and both neural modalities for each seed (see Figure 35).

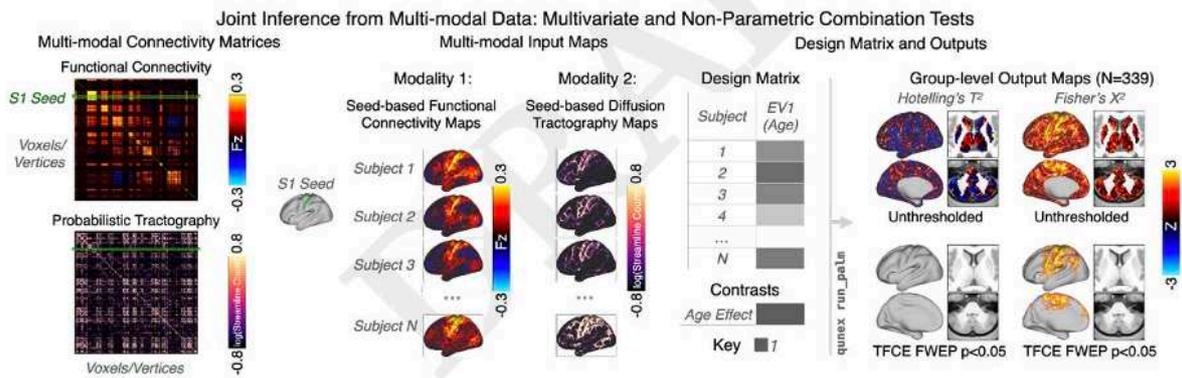


Figure 35 from Ji et al. (Ji et al., 2022). Example of workflow and outputs for joint inference testing from multimodal data. Functional connectivity and probabilistic tractography maps have been entered in a group-level analysis with a group-level design matrix and contrasts using the `run_palm` function. In this example, the relationship between age and S1-seeded functional connectivity and structural connectivity is assessed using a Hotelling's T^2 test and Fisher's X^2 test. The resulting output maps show the unthresholded and thresholded (p<0.05 familywise error protection (FWE), 10 000 permutations) relationship between age and both neural modalities.

4.4.3. Hypotheses

4.4.3.1. Behavioral data reduction using principal component analysis (PCA)

We performed a dimension-reduction of the behavioral scores using a PCA on the age of participants, the items of the PANSS, the items of the AHRs, the items of the PSAS and the items of the SGI and composite scores of reality-monitoring and internal source-monitoring, including 92 symptoms or cognitive variables. Our first hypothesis is that a PC component will include hallucination-related scores, sensory gating scores and will discriminate source-monitoring composite scores by including only reality-monitoring externalizations. Our second hypothesis is that a more general PC component will index the severity of schizophrenia by including scores like age, equivalent chlorpromazine, high positive and negative PANSS, and low reality-monitoring and internal source-monitoring performance, with especially high reality-monitoring externalization bias.

4.4.3.2. Mass univariate behavioral-neural mapping

First, we performed a mass univariate behavioral-neural mapping to quantify the relationship between the symptom/cognitive PCs and individual parcellated GBC variation at the whole-brain level. We expect that the hallucinations / sensory gating / reality-monitoring externalizations PC will be particularly correlated with GBC of the DMN, including the amPFC, as defined in the functional network parcellation from the CAB-NP. We also expect this PC to be highly correlated with GBC of the lobule VI of the cerebellum. According to the CAB-NP parcellation, the left lobule VI of the cerebellum is included in three functional networks: the somatomotor, the opercular, and the frontoparietal networks (*see Figure 9*). Thus, we expect this PC to be correlated with variation of GBC in these three networks.

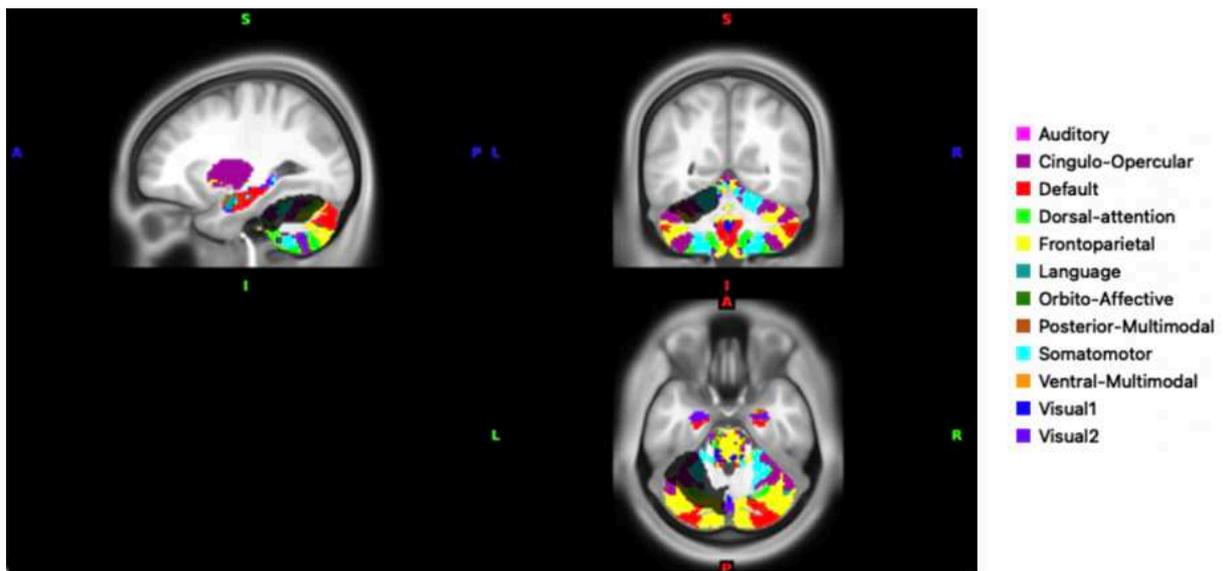


Figure 36. Workbench view of the CAB-NP parcellation in subcortical regions with a darker overlay of the lobule VI of the left cerebellum.

We also performed a mass univariate behavioral-neural mapping to quantify the relationship between the symptom/cognitive PCs and individual parcellated GBC variation at the ROI level.

We expect a correlation between the hallucinations / sensory gating / reality-monitoring externalizations PC and GBC in the amPFC and lobule VI of the left cerebellum.

4.4.3.3. Joint inference from multi-modal data

Finally, we tested the relationship between reality-monitoring externalizations and amPFC / left lobule VI of the cerebellum – seeded functional connectivity and probabilistic tractography. We expect that the resulting thresholded map will reveal a significant relationship between reality-monitoring externalization and both modalities.

4.4.4. Perspectives

Analyses of this study are still in progress.

One aspect of schizophrenia that is often discussed is its impact on the individual's sense of self. People with schizophrenia may experience disturbances in their sense of identity and self-awareness, resulting in a sense of disconnection from themselves and their surroundings. This phenomenon is often referred to as a "self-disorder" in the literature on schizophrenia (*see section 1.2.1*). According to this model, people with schizophrenia experience a breakdown in the normal functioning of the self-system. The self-disorder model is highly consistent with the theory of schizophrenia that positive symptoms emerge from an impairment of the distinction between imagination and reality, between endogenous and exogenous stimuli. This impairment, also referred to as reality-monitoring impairment, has been repeatedly identified in patients with schizophrenia, and particularly in those suffering from hallucinations. In the second chapter, we also demonstrated that individuals across the continuum of psychosis with no full-blown

diagnosis of schizophrenia, including individuals with hallucination-proneness, have impaired reality-monitoring.

In healthy subjects, reality-monitoring has been mainly associated with modulation of activity in the amPFC. In the third chapter, we confirmed the key involvement of the amPFC and highlighted the involvement of the lobule VI of the left cerebellum in this process. In patients with schizophrenia, previous studies have associated impaired reality-monitoring with reduced activity and altered structure of the amPFC. Studies in patients with schizophrenia using NIBS and fMRI to investigate reality-monitoring in various sensory modalities have also highlighted altered connectivity between the amPFC and corresponding sensory areas (*see section 1.2.3.2*). However, the relationship between clinical characteristics of schizophrenia, reality-monitoring, and functional and structural brain connectivity is still unclear.

To clarify this relationship, this study adopts a comprehensive approach including clinical, cognitive and neuroimaging assessments. We first performed a dimension-reduction of the symptoms scores and composite scores of source-monitoring to identify whether specific symptoms of schizophrenia are associated with impaired reality-monitoring. Next, we performed mass univariate behavioral-neural mapping to determine whether this symptoms-source-monitoring aggregates are associated with altered GBC. We particularly looked for GBC in the 2 seeds identified in the chapter 3: the right amPFC and the lobule VI of the left cerebellum. Finally, we tested whether impaired reality-monitoring is associated with common modulations of the seed-based functional connectivity and probabilistic tractography.

5. Conclusion and perspectives

5.1. Summary of findings

The goal of this thesis has been to advance our understanding of the reality-monitoring deficit in schizophrenia. To do so, we explored the specificity of impaired reality-monitoring in different clinical and nonclinical populations. We also investigated the functional bases of reality-monitoring in healthy individuals and patients with schizophrenia. In this work, we placed great emphasis on the cognitive models that have been proposed to underlie reality-monitoring. To this end, we considered reality-monitoring as a component of source-monitoring, and compared this performance with that of internal source-monitoring. We also proposed several studies that include assessments of both reality-monitoring and self-agency performances. In this way, we have argued for a reconciliation between the source-monitoring framework and the forward model and for establishing continuity between these two models.

We achieved this by first seeking to determine the specificity of reality-monitoring impairment in schizophrenia. In a first paper, we published a qualitative review reporting mixed results in patients with OCD, including studies demonstrating significant reality-monitoring impairment, studies demonstrating significant internal source-monitoring impairment, and studies reporting nonsignificant results. The presence of source-monitoring abnormalities in this population remained an open question. Therefore, in a second paper, we compared source-monitoring performances of patients with OCD with that of patients with schizophrenia and healthy controls. We demonstrated that only patients with schizophrenia show a significant deficit in reality-monitoring, while both groups of patients displayed a significant deficit in internal

source-monitoring. In the perspectives of this first chapter, we described a new study we designed to further our understanding of the specificity of the reality-monitoring deficit. This study aims to compare reality-monitoring between different neuropsychiatric diseases with psychotic features.

Secondly, in a third paper, we investigated the specificity of the reality-monitoring impairment in the continuum of psychosis. We adopted a meta-analytical approach to examine potential deficits of reality-monitoring and self-agency in several populations along the continuum of psychosis with no full-blown diagnosis of schizophrenia, i.e., individuals with a clinical at-risk state for psychosis, individuals with a genetic risk state for psychosis and individuals with nonclinical hallucinations. We demonstrated that all these populations exhibited both impaired reality-monitoring and impaired self-agency compared to controls.

Thirdly, in a recently submitted fourth paper, we sought to better understand the functional correlates of reality-monitoring in healthy individuals. We adopted a coordinate-based meta-analytic approach to investigate the brain regions involved in reality-monitoring and explore the functional substrates shared with self-monitoring. Our analysis revealed that reality-monitoring is associated with activations in clusters including the lobule VI of the cerebellum, the right amPFC and anterior thalamic projections. Neuroimaging studies of self-monitoring revealed the involvement of a set of brain regions including the lobule VI of the left cerebellum and fronto-temporo-parietal regions. Finally, our results suggest that the lobule VI of the cerebellum is consistently engaged in both reality-monitoring and self-monitoring. In the perspectives of this third chapter, we presented a new study that aims to clarify the relationship

between reality-monitoring, clinical characteristics and structural and functional connectivity in patients with schizophrenia.

5.2. General discussion

5.2.1. Is reality-monitoring a marker of schizophrenia?

Reality-monitoring characterizes our ability to determine whether information has been perceived from the environment or imagined, for example whether a sentence has been spoken by someone or simply imagined. In the literature, disturbance in reality-monitoring have been repeatedly demonstrated in patients with schizophrenia, particularly in those who present hallucinations. These patients tend to attribute their internal thoughts and experiences to external sources, which is called externalization bias. Reality-monitoring is a component of a larger cognitive process called source-monitoring, which refers to our ability to remember the source of information. Source-monitoring also includes internal source-monitoring, a process characterizing our ability to distinguish between two internal sources, for example whether a sentence was spoken aloud or internally using inner speech. Patients with schizophrenia have also been found to have impaired internal source-monitoring (*see section 1.2.2*).

This work places particular emphasis on the question of whether impaired reality-monitoring is a marker of schizophrenia. One central issue in schizophrenia is to identify and characterize cognitive and biological markers that could serve as targets for prevention, detection and treatment. A trait marker represents the properties of biological processes that play a role in the pathophysiology of schizophrenia, whereas a state marker represents the status of clinical manifestations in patients (Chen et al., 2006). Impaired reality-monitoring would be a trait

marker if it is specific to patients with schizophrenia, or if it is already present in individuals at-risk of schizophrenia without any clinical manifestation. Impaired reality-monitoring would be a state marker if it is, for example, specific to patients with hallucinations, or also present in healthy individuals with non-clinical hallucinations. A previous work by our team suggested, with a small sample size, that impaired reality-monitoring might be considered as an intermediate trait marker of schizophrenia: this deficit is present in unaffected siblings of patients with schizophrenia, but more pronounced in patients and exacerbated when hallucinatory symptoms are present (Brunelin et al., 2007).

In the first chapter of this manuscript, we asked whether source-monitoring alterations were specific to schizophrenia or whether they might involve other clinical groups. To better understand each subtype of source-monitoring and the consequences of their alterations, we put particular emphasis on distinguishing between alterations of reality-monitoring and internal source-monitoring. First, we explored potential alterations in source-monitoring in patients with OCD. According to the source-monitoring model of OCD, these patients would be more likely to confuse memories of performed and imagined actions (e.g., did I imagined turning off the oven or did I really turn off the oven?). The resulting uncertainty could therefore contribute to obsessive thoughts, which in turn lead to compulsive behaviors aimed at ensuring that the intended actions was indeed performed (Sher et al., 1983). We conducted a review of the literature establishing potential source-monitoring alterations in patients with OCD, giving a special attention to internal source-monitoring, since it seems more related to OCD symptoms than reality-monitoring or external source-monitoring [*article 1*]. This review reported mixed results and mostly highlighted a lack of reproducibility associated with the presence of high methodological heterogeneity across studies. The factors of heterogeneity mainly included

population (i.e., either patients with OCD or individuals with subclinical symptoms of OCD), type of items (i.e., words, actions, drawing, object recognition) and disparities when defining the subtypes of source-monitoring. In a second study, we directly explored differences in reality-monitoring and internal source-monitoring between patients with OCD, patients with schizophrenia and healthy controls [*article 2*]. We demonstrated that patients with OCD and patients with schizophrenia shared impaired internal source-monitoring, whereas only patients with schizophrenia had impaired reality-monitoring. These results suggest that patients with schizophrenia and patients with OCD share a common deficit in the recognition process of what they actually did and imagined doing. As a comorbid diagnosis of schizophrenia was ruled out of our OCD sample, it can be assumed that the observed deficit in internal source-monitoring may similarly contribute to symptoms of OCD and schizophrenia. One of the main similarities between obsessive thoughts of OCD and symptoms of schizophrenia is that they both involve intrusive, unwanted and foreign thoughts. In sum, both conditions are associated with a lack of cognitive control. Along these lines, both diseases have been associated with reduced performances on tasks requiring cognitive control, such as conflict tasks, where subjects must suppress a prepotent response to follow a less intuitive rule. According to the SMF, source attribution is determined by the balance between the strength of perceptual detail and the strength of top-down cognitive control associated with information (*see section 1.2.2.3*). Thus, the common alteration of internal source-monitoring in schizophrenia and OCD could be explained by the weakness of cognitive control cues. Further studies should clarify the relationship between altered internal source-monitoring and specific clinical features of schizophrenia and OCD, such as delusions and obsessional thoughts. In addition, exaggerated sensory signals could participate to the additional impairment of reality-monitoring in patients with schizophrenia.

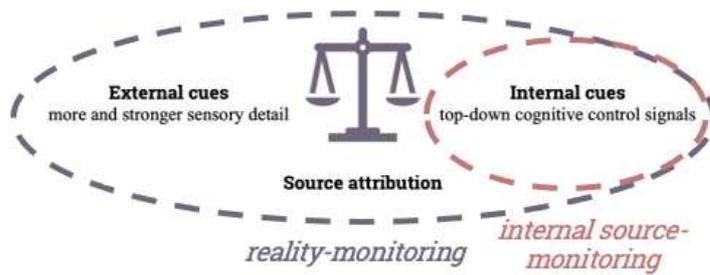


Figure 37. Balance between internal and external cues during source attribution. In the context of source-monitoring framework, the origin of memories is based on the balance between “internal” and “external” cues established during memory acquisition. Veridical perceptions are associated with more and stronger perceptual detail, whereas imagination is subject to more top-down cognitive control signals. We speculate that the common impairment of internal source-monitoring in OCD and schizophrenia may be due to the weakness of cognitive control in these two diseases. The association between weak cognitive control and overemphasis on sensory detail could be responsible for the specific impairment of reality-monitoring in schizophrenia.

Source-monitoring has been studied in other neuropsychiatric diseases than schizophrenia and OCD. First, it seems that individuals with depression (Brunelin et al., 2008) and body dysmorphic disorder (Reese et al., 2011) have no alteration of reality-monitoring, which rather encourages the hypothesis of a specific marker for schizophrenia. In addition, source-monitoring has been specifically examined in patients without schizophrenia who experience hallucinations: patients with Parkinson’s disease with hallucinations exhibit impaired reality-monitoring (Barnes et al., 2003) and patients with Alzheimer’s disease with hallucinations have impaired reality-monitoring, internal source-monitoring and external source-monitoring (El Haj et al., 2020). In the perspectives of this chapter, we presented a larger transdiagnostic study including patients with neuropsychiatric diseases associated with hallucinations and fronto-

temporal alterations. As with OCD and schizophrenia, we expect that these populations will exhibit impaired internal source-monitoring. We also expect these patients will exhibit impaired reality-monitoring, and that this impairment will be exacerbated in those with hallucinations.

The continuum of psychosis refers to the concept that psychosis exists along a spectrum, rather than as a distinct categorical diagnosis. Schizophrenia is generally considered as being a part of a continuum from at-risk state to chronic schizophrenia through FEP. However, the continuum of psychosis can also be viewed phenomenologically, postulating that psychotic experiences lie on a continuum with normal experience and include nonclinical manifestations such as hallucinations. Generalized alterations in cognitive function have been reported in individuals with a clinical and/or genetic at-risk state and in people with hallucination proneness (Bora and Murray, 2014; Brébion et al., 2010; Fusar-Poli et al., 2012; Giuliano et al., 2012; Gupta et al., 2018; Morrison et al., 2000). These findings suggest the existence of a cognitive continuum, that is, a continuum of cognitive impairment from healthy functioning to full-blown psychotic disorder (Johns et al., 2001) that encompasses subclinical alterations and severe clinical manifestations in schizophrenia. In the second chapter of this manuscript, we asked whether impaired reality-monitoring is specific to schizophrenia or whether it might involve populations included in the continuum of psychosis without a diagnostic of psychotic disorder. We demonstrated that individuals included in the continuum of psychosis with no diagnostic of schizophrenia, i.e., individuals with clinical high-risk, individuals with genetic high-risk and healthy individuals with nonclinical hallucinations, also exhibit impaired reality-monitoring. These results suggest that impaired reality-monitoring may represent a marker of risk for schizophrenia. Further studies using longitudinal approaches should examine the relationship between impaired self-recognition and transition to psychosis and explore a potential gradation

of the deficit between individuals who will and will not transit. Furthermore, the deficit observed in unaffected first-degree relatives of patients with schizophrenia suggests that impaired reality-monitoring may be associated with increased risk of familial liability to psychosis, independent of the presence of attenuated/subclinical psychotic symptoms. New studies including at-risk individuals and patients with schizophrenia are needed to better understand the occurrence of reality-monitoring impairment. A gradation of the deficit would be an indication of the degenerative aspect of the impairment of reality control in these patients. On the contrary, if alterations in reality-monitoring of similar magnitude were observed between patients with schizophrenia and at-risk individuals, it could reflect a neurodevelopmental disorder preceding the onset of the disease.

A previous meta-analysis demonstrated that externalization bias was specifically associated with clinical and nonclinical hallucinations (Brookwell et al., 2013). We showed that patients with schizophrenia who have hallucinations in two sensory modalities, i.e., auditory and visual hallucinations, have a more pronounced impairment of reality-monitoring than patients with hallucination in the auditory modality only [*article 7*] (Mondino et al., 2019). This finding reinforces the association between impaired reality-monitoring and hallucinations. In the context of the SMF, one can thus suggest that patients with multimodal hallucinations associate more detail with imagined information, leading to more severe externalization bias and greater confusion when identifying the source of information. Furthermore, the alteration of reality-monitoring we found in the high-risk population was comparable to that observed in healthy subjects with nonclinical hallucinations. Therefore, impaired reality-monitoring could also represent a trait marker of hallucinations, regardless of their clinical status. However, these findings are at odds with the recent large-scale multi-site study by Moseley et al., including

1375 healthy individuals. No significant association was reported between externalization bias and severity of hallucinations. This study used a typical verbal reality-monitoring task asking subjects to hear or imagine words. The main particularity of their experimental protocol is that reality-monitoring was assessed online for half of the participants. However, no difference were reported when the analyses were repeated for laboratory data only and online data only (Moseley et al., 2021). These recent findings call into question the results of our meta-analysis, in which we only included 5 studies evaluating reality-monitoring in healthy individuals with hallucination-proneness, for a total of 123 participants. As suggested by Moseley et al., one potential interpretation is that there is a discontinuity in mechanism between clinical and nonclinical hallucinations. Nonclinical manifestations are generally distinguished from clinical hallucinations on the basis of characteristics such as emotional valence, conviction, control and elicited stress (*see section 1.1.3.2*). Further studies of reality-monitoring accompanied by a comprehensive assessment of the clinical characteristics of hallucinations in clinical and nonclinical groups should provide insight into whether impaired reality-monitoring is a marker of clinically significant hallucinations but not of less controlled or less distressing experiences. Thus, our new study evaluating the neural substrates of impaired reality-monitoring in patients with schizophrenia includes detailed evaluation of hallucinations, e.g., modality, frequency, elicited distress, vividness, insight, loudness using the PANSS, AHRS and PSAS (*see section 4.4*).

5.2.2. Reconciling reality-monitoring and self-monitoring

Reality-monitoring seems intrinsically tied to self-monitoring, i.e., the ability to distinguish self-generated actions or speech from those generated by others (*see section 1.2.2.5*). Reality-monitoring and self-monitoring have been theorized in two different frameworks: the SMF and

the forward model. According to the SMF, the encoding of imagined information is accompanied by strong top-down cognitive signals, whereas perceived information induces bottom-up sensory signals. During the retrieval phase of reality-monitoring, source discrimination is based on the balance between cognitive and sensory cues (*see section 1.2.2.3*). The forward model explains online distinction between self and nonself information. It is used to compare the predicted sensory outcome of an action or speech with the actual sensory outcome and determine whether an event was generated by the self or by an external source. A match between the predicted sensory outcome and the actual outcome induces sensory dampening and the experience of self-agency (*see section 1.2.2.5*).

Both reality-monitoring and self-monitoring involve discrimination between endogenous and exogenous information. Two main features distinguish these two processes: 1. reality-monitoring is memory-based while self-monitoring is online, 2. the internal condition of reality-monitoring is imagination whereas the internal condition of self-monitoring is self-generation (i.e., the action or speech is not simply imagined but performed). However, a recent study in healthy individuals showed that the accuracy of self-recognition judgement in a reality-monitoring task was correlated with performance in a self-monitoring task (Subramaniam et al., 2018). Patients with schizophrenia exhibit both deficits, with no significant difference in magnitude (Waters et al., 2012). Similarly, our meta-analysis demonstrated that healthy individuals of the continuum of psychosis have impaired reality-monitoring and impaired self-monitoring, with no difference in magnitude [*article 3*]. These findings thus suggest a unitary process underlying reality-monitoring and self-monitoring that would be impaired in the context of psychosis. Then, our neuroimaging meta-analysis included studies examining the functional substrates of reality-monitoring and self-monitoring in healthy subjects [*article 4*].

Our results support the claim that the lobule VI of the cerebellum is a pivotal neural locus for the recognition of self-generated behaviors (Pinheiro et al., 2020; Sokolov et al., 2017). According to this view, the cerebellum might integrate the efference copy of self-productions to generate an expectation of the sensory feedback and prepare the sensory areas for incoming sensory feedback. This sensory attenuation would be underpinned by the deactivation of primary and secondary somatosensory regions. Our results also suggest that lobule VI of the left cerebellum reactivates during the memory of the self-provenance of information. Thus, it may be considered both for its role in the forward model and in the SMF as a “cognitive cue” to identify the self-origin of stored information. The role of the cerebellum in schizophrenia has been much less studied than that of cortical areas. For many years, the cerebellum has been only considered for its involvement in motor function. The cerebellar cognitive theory assumes the importance of the cerebellum in cognition. Neuroimaging studies have suggested that the lateral hemispheres of the posterior cerebellum (lobule VI-IX) are associated with cognitive processes while more anterior regions (lobules I-V) are primarily responsible for motor function (Kansal et al., 2017; Schmahmann and Caplan, 2006; Stoodley, 2012). Work suggesting that cerebellar abnormalities occur in schizophrenia has been accumulating for several decades (for review, see (Andreasen and Pierson, 2008; Picard et al., 2008)). The central role of the posterior region highlighted by our convergence analysis between reality-monitoring and self-monitoring is consistent with schizophrenia literature, associating the lobule VI of the left cerebellum with altered structure and function. For instance, this specific region has lower GMV in patients with chronic schizophrenia and FEP (Kim et al., 2018; Moberget et al., 2018; Rasser et al., 2010) and is associated with pronounced decrease in activation in patients with schizophrenia compared to healthy controls (Bernard and Mittal, 2015).

To date, two qualitative reviews highlighted the unique role for the amPFC in reality-monitoring (Dijkstra et al., 2022; Simons et al., 2017). Our neuroimaging meta-analysis confirmed that the right amPFC is consistently activated during the retrieval phase of reality-monitoring [article 4]. This region does not modulate its activity during self-monitoring. Thus, our findings suggest its high-order role of evaluating sensory cues and cognitive control aspects of perception and imagination to attribute the source of memories. Our results on the involvement of the amPFC in reality-monitoring are consistent with previous studies that have revealed alterations in the function and structure of this region in patients with schizophrenia (see section 1.1.3.3). In addition, we demonstrated a correlation between PCS length and impaired reality-monitoring in patients with schizophrenia (see appendix 4, [article 8] (Perret et al., 2021)), and cortical folding in the PCS has previously been directly associated with the experience of hallucinations in patients with schizophrenia (Garrison et al., 2015; Rollins et al., 2020) (see section 1.2.3.2). Finally, abnormalities in the amPFC have been reported already in individuals with high-risk for psychosis (Borgwardt et al., 2008; Cannon, 2015; Pantelis et al., 2003), which is consistent with our findings that individuals on the continuum of psychosis also exhibit impaired reality-monitoring [article 3]. Several studies already demonstrated causality between amPFC activity and reality-monitoring: NIBS targeting the amPFC (Mammarella et al., 2017; Subramaniam et al., 2020) and real-time fMRI neurofeedback that modulates activity the amPFC improve reality-monitoring in healthy individuals (Garrison et al., 2021). Further studies should use such techniques to target the amPFC in patients with schizophrenia and expect improved reality-monitoring and hallucination severity.

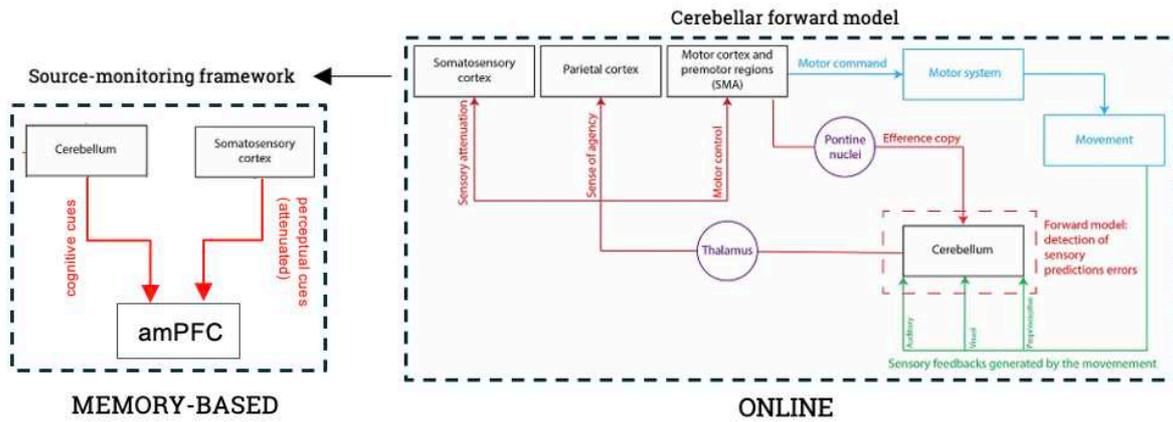


Figure 38, adapted from (Welnarz et al., 2021). Continuity between the cerebellar forward model and the source-monitoring framework. According to the cerebellar forward model, the cerebellum is supposed to integrate the efference copy and the actual sensory feedback generated by movement or speech. The lack of discrepancy would be detected at the level of the cerebellum, which would send signals to different cortical areas to serve different functions: sensory attenuation in the somatosensory cortex, sense of agency in the parietal cortex and motor control signal in the motor cortex and premotor regions. We argue for the existence of a continuity between the cerebellar forward model and the source-monitoring framework. According to this theory, cerebellar reactivation during source attribution would represent the internal/cognitive cues that are specific to self-generated actions or speech. Re-deactivation of the somatosensory cortex during source attribution would represent perceptual cues that are attenuated when there is a match between predicted and actual sensory feedback. The role of the anterior medial prefrontal cortex would be to integrate these cognitive and perceptual cues to make the final source attribution during reality-monitoring.

5.3. Long-term perspectives: Investigating the role of dopamine transmission in reality-monitoring

The presence of hallucinations in schizophrenia has been associated with both dopamine abnormalities and marked reality-monitoring alterations. Furthermore, reality-monitoring impairments have also been observed in PD, another neuropsychiatric disease associated with both hallucinations and alterations of dopamine transmission (Barnes et al., 2003). In PD, hallucinations were initially considered as a side effect of DA drugs. The main hypothesis is that chronic DA stimulation of the DA pathways is responsible for hypersensitivity of striatal D2 receptors, resulting in increased susceptibility to develop psychotic symptoms (Zahodne and Fernandez, 2008). Furthermore, newly diagnosed drug-naïve patients with PD also reported higher frequency of hallucinations than age-paired normal controls (Pagonabarraga et al., 2016), and the dosage of dopaminergic agents is not correlated with the risk of hallucinations (Sanchez-Ramos et al., 1996), suggesting that hallucinations are not only induced by DA replacement but may be part of PD itself. In line with this, low dopamine transporter (DAT) level in the ventral striatum has been found to predispose patients with PD to psychotic symptoms (Jaakkola et al., 2017; Kiferle et al., 2014; Ravina et al., 2012). Taken together with evidence about hallucinations in schizophrenia, de novo hallucinations in PD are thought to arise from a compensatory upregulation of postsynaptic striatal D2 (Jaakkola et al., 2017) inducing D1/D2 pathways imbalance comparable to schizophrenia.

Critically, no studies have directly explored the implication of the DA transmission in reality-monitoring in the general population. In a small sample of 16 patients with schizophrenia, antipsychotic medication has been associated with both reduced reality-monitoring deficit and “target” psychosis symptoms (i.e., symptoms believed to reflect source-monitoring impairment,

including hallucinations and delusions) (Keefe et al., 2003). Moreover, in healthy subjects, transcranial Direct Current Stimulation (tDCS) applied over brain areas involved in reality-monitoring (i.e., prefrontal cortex and temporoparietal junction) has been found to both alter the latter (Mondino et al., 2016) and induce striatal dopamine release (Fonteneau et al., 2018). Taken together, this argues for the involvement of DA system alteration in reality-monitoring impairment.

A long-term perspective of the thesis would be to investigate the involvement of the DA system in reality-monitoring. To do so, we propose to perform an acute pharmacological manipulation of the DA system in healthy individuals either with a DA precursor or a specific antagonist of D2 receptors. We will also examine the effect of DA modulation on reality-monitoring and self-monitoring performances. Each included participant will participate to 3 experimental conditions in a randomized order during 3 distinct visits separated by at least 5 days to allow for total drug washout (see Table 1):

- In the first condition, volunteers will receive a DA precursor (L-dopa, 100mg). L-dopa will be combined with a dose of an Aromatic amino acid decarboxylase inhibitor (Benserazide) 25mg to multiply its bioavailability and with a dose of domperidone 10mg (peripheral antagonist of DA) to minimize the risk of side effects.
- In the second condition, volunteers will receive a D2 antagonist (Sulpiride, 800mg).
- In the third condition, volunteers will receive a placebo (lactose).

	Substance	Dose	T _{max}	½ life
Condition 1	L-dopa	100mg	15-60min (Contin and Martinelli, 2010)	1.5hrs
	AADC inhibitor	25mg		
	Domperidone	10mg		

Condition 2	Sulpiride	800mg	3-6hrs (Kudo and Ishizaki, 1999)	7 heures
Condition 3	Placebo	NA	NA	NA

Table 9. Treatment characteristics. T_{max} : time to reach maximal serum concentration. $\frac{1}{2}$ life: time required for substances to reduce to half of their initial values.

A double-dummy procedure adapted from (Andreou et al., 2014) will be implemented to compensate for the different times to reach maximal serum concentration (T_{max}) between L-dopa (1hr) and Sulpiride (3hrs). Thus, in each condition, a first intake of substance will take place at T1 then a second intake 2 hours later (T2, see Table 2).

	T0	T1	T2 (2hrs after T1)	T3 (3hrs after T1)	T4
First condition : L-dopa	Side effects assessment	Placebo	L-dopa	Reality-monitoring + Self-monitoring testing	Side effects and blinding assessments
Second condition : Sulpiride		Sulpiride	Placebo		
Third condition : Placebo		Placebo	Placebo		

Table 10. Experimental design. During condition 1, volunteers will ingest the placebo at T1 and the active substances (L-dopa / Bensérazide / Domperidone) at T2. During condition 2, volunteers will ingest the active substance (Sulpiride) at T1 and the placebo at T2. During condition 3, volunteers will ingest the placebo at T1 and T2. Reality-monitoring self-monitoring will be measured after pharmacological manipulation, at the time of maximum serum concentration of L-dopa and Sulpiride (at T3). Adverse effects will be assessed at baseline (T0) and at the end of each condition (T4) using specific scales. After taking cognitive tests (T4), blinding will be controlled when participants will be asked to guess which substance they have ingested. Blood pressure, pulse and sublingual temperature will also be measured every 30min during the experiment.

Reality-monitoring will be measured using a behavioral task developed, validated and used in our laboratory (*see section 1.2.1.2*). Participants will also indicate on a scale the degree of confidence they have in their source recognitions. Finally, after each “imagined” or “listened” word, participants will indicate on a scale the degree of vividness of the word. The self-monitoring task will replicate the one used by several authors who evaluated motor speech responses to auditory feedback distortions (Chang et al., 2013; Kort et al., 2014; Ranasinghe et al., 2017; Subramaniam et al., 2018) (*see section 1.2.2.5*). Subjects will wear a microphone and a pair of headphones. They will be instructed to vocalize while listening to real-time auditory feedback. In each trial, the phonation onset will trigger a brief perturbation (either a minimal pitch-induced shift of 1/12th octave or a larger shift of 1/3rd octave) in the pitch of the subject’s feedback.

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We hypothesize that dopamine will modulate reality-monitoring and self-monitoring performances. Specifically, we expect that D2 antagonism will enhance performances whereas DA stimulation will reduce it. We expect that reality-monitoring and self-monitoring performances will correlate.

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7. Appendix

7.1. Cognitive insight in individuals with an at-risk mental state for psychosis: a meta-analysis [Article 5]

*Article 5: Cognitive insight in individuals with an at-risk mental state for psychosis: a meta-analysis. Early Intervention in Psychiatry. 2019. Dondé C., Laprèvote V., **Lavallé L.**, Haesebaert F., Fakra E., Brunelin J.*



Cognitive insight in individuals with an at-risk mental state for psychosis: A meta-analysis

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Abstract

Aim: To compare cognitive insight abilities measured with the Beck Cognitive Insight Scale (BCIS) between individuals with an at-risk mental state (ARMS) and healthy controls.

Method: Review and meta-analysis based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Results: A search for articles investigating cognitive insight in ARMS in the MEDLINE and ScienceDirect databases revealed five studies including 303 ARMS and 376 controls. Regarding BCIS subscales, ARMS individuals displayed significant higher scores for self-certainty than controls with a small-to-moderate effect size ($ES_g = 0.45$ [0.23;0.67], $P < .005$), whereas no significant difference was observed for self-reflectiveness ($ES_g = -0.56$ [-0.18;1.29], $P = .14$). No significant differences were observed between ARMS and controls for overall cognitive insight abilities as indexed by the BCIS composite score ($ES_g = -0.24$ [-0.43;0.91], $P = .45$).

Conclusions: Self-certainty abnormalities seem to predate the expression of full-blown psychotic episode and to be higher in ARMS than in healthy controls. By contrast, ARMS did not display abnormal self-reflectiveness and overall cognitive insight abilities.

KEYWORDS

ARMS, at-risk mental state, BCIS, Beck Cognitive Insight Scale, cognitive insight, meta-analysis

1 | INTRODUCTION

Insight is a complex metacognitive function that is impaired in patients with psychotic disorders such as schizophrenia (Elowe & Conus, 2017). Lack of insight is directly associated with worsened outcome and poorly responds to available treatments (Dondé et al., 2019; Phahladira et al., 2019). Given the evidence that one of the key determinants of psychotic disorders is a lack of appraisal of anomalous experiences, insight deficits could be a critical factor that influences the differentiation of psychosis from other psychiatric condition and from healthy status (Lappin et al., 2007). It has been proposed that 'clinical' insight specifically reflects the awareness of illness and

symptoms, whereas 'cognitive' insight relates to a more general ability to question and reconsider own beliefs and judgements (Beck et al., 2004). The cognitive insight has been suggested to be a prerequisite for clinical insight (Gerretsen et al., 2014). To date, most studies investigating cognitive insight in patients with psychotic disorders have used the Beck Cognitive Insight Scale (BCIS) (Beck et al., 2004). This 15-item self-questionnaire was subjected to a principal components analysis in a large sample of patients with psychotic disorders, yielding two distinct cognitive insight components/subscales: 'self-reflectiveness', which comprises 9 items representing the ability to re-evaluate unusual experiences and correct erroneous inference, and 'self-certainty', which includes 6 items evaluating one's tendency to

be overconfident about one's own judgements (Beck et al., 2004). Each item is rated by the participant on a 4-points Likert scale ranging from 0 ('do not agree at all') to 3 ('agree completely'). Another important score used to rate the BCIS is the overall cognitive insight composite score. This composite score is calculated by subtracting the scores of the self-certainty domain from that of the self-reflectiveness domain. This tool presents the advantage of measuring self-rated insight, which better reflects the subjective experience of insight compared to expert ratings (Tranulis et al., 2008). In samples with full-threshold psychosis (ie, meeting the Diagnostic and Statistical Manual of Mental Disorders criteria for psychotic disorder), lower BCIS scores are correlated with lower neurocognitive performance (Grover et al., 2018), impaired quality of life (Pu et al., 2018) and worsened functional outcome (Sumiyoshi et al., 2016).

The 'at-risk mental state' (ARMS) for psychosis (also referred as 'clinical high-risk' or 'ultra high-risk') is an inclusive clinical construct that captures potentially prodromal psychiatric symptoms in young individuals (McGorry et al., 2018). There are two distinct validated criteria used to identify ARMS individuals: the clinical high-risk (CHR) criteria, assessed using the structured interview for prodromal syndromes criteria (SIPS) (Miller et al., 2003) and the ultra-high-risk (UHR) criteria assessed using the comprehensive assessment of at-risk mental states (CAARMS) (Yung et al., 2005). Although this category was originally introduced with the goal of preventing psychotic disorders, only ~30% of individuals with an ARMS status convert to psychosis, while the remaining will develop non-psychotic disorders or go into full remission (Fusar-Poli et al., 2017). Clinically, individuals with an ARMS status are persons presenting with attenuated psychotic experiences (eg, distorted perceptions, unusual valued ideas) associated to comorbidities, such as depression, anxiety and substance abuse, along with significant functional impairment. ARMS is also associated with poorer academic performance and occupational functioning (Fusar-Poli et al., 2013). Although neurocognitive and social deficits have been repeatedly demonstrated in ARMS (Fusar-Poli et al., 2012), it was originally stated that maintenance of relatively intact insight abilities is a key determinant that differentiates this category from full-blown psychotic disorders, which are, by contrast, characterized by poor levels of insight (Elowe & Conus, 2017). Since then, this assumption has been challenged by several investigations of cognitive insight abilities in ARMS (Clark, 2017; Kimhy et al., 2014; Ohmuro et al., 2018; Rasskazova et al., 2016; Uchida et al., 2014). Surprisingly, some authors have observed higher levels of overall cognitive insight in ARMS individuals compared to unaffected controls (Clark, 2017; Rasskazova et al., 2016), but this result was not replicated by other groups (Kimhy et al., 2014; Ohmuro et al., 2018; Uchida et al., 2014). In addition, specific dimensions of cognitive insight (ie, self-reflectiveness and self-certainty) have been found either decreased (Rasskazova et al., 2016; Uchida et al., 2014) or increased (Clark, 2017; Rasskazova et al., 2016) in ARMS samples. Thus, taking into consideration, the growing interest for the clinical profiling of the ARMS and the clinical importance of insight in the onset and maintenance of full-threshold psychosis, we conducted a meta-analysis of the literature to investigate whether cognitive insight deficits predate expression of

psychosis and are already distinguishable between the at-risk population and healthy controls.

2 | METHOD

2.1 | Literature search strategy

Our meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). The protocol was prospectively registered at the PROSPERO register (CRD42019141154) (Chien et al., 2012).

We searched for articles in the MEDLINE and ScienceDirect databases with no limitation of date. The following headings were used:

MEDLINE: ('ultra-high risk' OR 'clinical high risk' OR 'high clinical risk' OR 'high risk' OR 'at risk' OR 'prodromal psychosis' OR 'basic symptoms' OR 'at-risk mental state' OR 'UHR' OR 'CHR' OR 'ARMS' OR 'CHARMS' OR 'psychosis risk syndrome' OR 'psychosis risk symptoms' OR [prodrom*]) AND ('schizophrenia' OR 'psychosis' OR 'psychotic') AND ('insight' OR 'unawareness' OR 'unaware').

ScienceDirect: ('insight' OR 'unawareness' OR 'unaware') AND ('ultra-high risk' OR 'clinical high risk' OR 'basic symptoms' OR 'at risk mental state' OR 'UHR' OR 'CHR' OR 'ARMS') AND ('schizophrenia' OR 'psychosis').

After excluding duplicate references, two authors (C.D., L.L.) independently screened the title, abstract and keywords of each publication to apply the following inclusion criteria: (a) inclusion of individuals with an ARMS status as determined by the Structured Interview for Prodromal Symptoms (clinical high-risk) or the CAARMS (ultra high-risk), (b) inclusion of a healthy control group, (c) measures of cognitive insight in both groups by a validated version of the BCIS. No restrictions regarding language were applied. Then, the same screening procedure was applied to the full-text of eligible studies. We ensured that different subjects were included in the different studies from the same research groups. The search strategy is described in Figure 1 (PRISMA diagram).

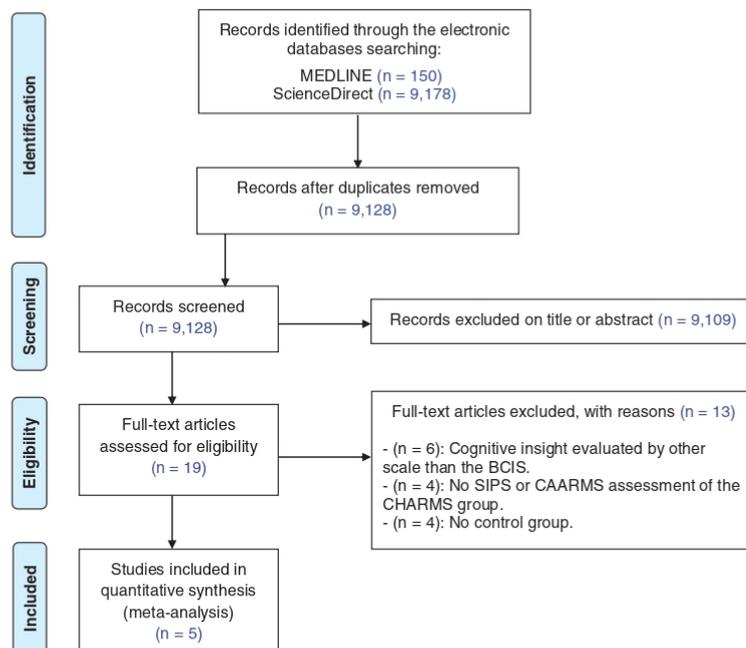
Demographic (age, sex ratio, education level), clinical (global intellectual proficiency, medication, symptoms) and means and SDs for the BCIS, self-reflectiveness sub-score, self-certainty sub-score and overall cognitive insight composite score were extracted from studies included in the meta-analysis. Study outcome was based on BCIS scores in ARMS and control groups.

To measure the overall quality of the included references, a global rating score was calculated for each study using the Standard Quality Assessment (QualSyst tool [(Kmet et al., 2004)]. Total scores obtain for each included study are given in Table 1 and details of the assessment are given in Table S1.

2.2 | Meta-analysis

All statistical analyses were carried out using *compute.es* and *metafor* packages in R Studio software version 1.0.143 (R Core Team R, 2018). The α level for significance was set at $P < .05$.

FIGURE 1 PRISMA Flow diagram for the meta-analysis. ARMS, at-risk mental state; BCIS, Beck Cognitive Insight Scale; CAARMS, comprehensive assessment of at-risk mental state; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SIPS, structured interview for prodromal symptoms



We extracted means + SD for BCIS scores in both ARMS and control groups. These values were transformed into Hedge's g effect sizes (ES g). When studies reported scores on multiple outcomes with no available overall measure (ie, multiple subgroups comparisons), ES g were computed for each measure and aggregated into a single study-ES g , so that each independent sample contributed to a single ES g . Then, a random-effect model was conducted to derive one summary-ES g for each BCIS sub-score (ie, self-reflectiveness, self-certainty and overall cognitive insight) from all study-ES g . The magnitude was interpreted according to Cohen's guidelines (0.2 = small; 0.5 = medium; 0.8 = large effect size [Jacob Cohen, 1988]).

Global heterogeneity of summary-ES g (involving heterogeneity both between and within study ES g) was quantified using Higgins I^2 statistics and its P -value was calculated from the Cochran's Q -test. The I^2 values 25%, 50% and 75% reflected a small, moderate or high degree of heterogeneity, respectively (JPT et al., 2003). Baujat plots were drawn to identify the studies that mostly influenced the summary ES g and contributed to the heterogeneity. A rank correlation test (r^2) was conducted to investigate if the heterogeneity of the summary-ES g was driven by heterogeneity between (r^2 value closer to 1) or within (r^2 closer to 0) study-ES g .

Publication bias was assessed by visual inspection of funnel plots. An Egger's Regression test was performed to determine the significance of potential publication bias (Egger et al., 1997).

3 | RESULTS

Five studies were eligible for our meta-analysis including 303 individuals with an ARMS status and 376 healthy controls (Clark, 2017; Kimhy et al., 2014; Ohmuro et al., 2018; Rasskazova et al., 2016; Uchida et al., 2014) (Table 1). All studies assessed insight abilities with a validated version of the BCIS (English [Clark, 2017; Kimhy et al., 2014], Japanese [Ohmuro et al., 2018; Uchida et al., 2014] and Russian [Rasskazova et al., 2016] languages). All participants were recruited from psychosis high-risk specialized clinics (ARMS) and from the community (controls). In the two studies that reported information about ARMS categorization, the Attenuated Psychotic Symptoms subtype was the most represented (Ohmuro et al., 2018; Uchida et al., 2014) (Table 1). Separate meta-analyses were conducted for each of the three BCIS scores: the *Self-reflectiveness* score, the *Self-certainty* score and the *BCIS composite score* reflecting overall cognitive insight (Figure 2).

- *Self-reflectiveness*: No significant differences were observed between ARMS and healthy controls for the self-reflectiveness domain (ES $g_{\text{self-reflectiveness}} = 0.56 [-0.18; 1.29]$), $P = .14$). Heterogeneity between studies was high and significant ($I^2 = 94.9\%$, Q -test P -value $<.001$), and mostly driven by heterogeneity between studies ($r^2 = .66$).
- *Self-certainty*: Individuals with an ARMS status had significantly higher scores for self-certainty than healthy controls with a small-

TABLE 1 Characteristics of the studies included in the meta-analysis

Study	Group		Controls										
	Diagnosis (tool) and subgroups	Size	Age	Sex ratio	IQ	Education	Medication	Size	Age	Sex ratio	IQ	Education	QualSyst total
Clark (2017) (US)	CHR (SIPS)	55	19.3 (1.7)	36 M/19F	108.7 (12.6)	NR	NR	55	19.3 (2.1)	24M/31F	105.0 (10.3)	NR	18
	Clinical data		SIPS positive: 11.7 (5.8) SIPS negative: 9.7 (6.7) SIPS disorganized: 5.1 (3.9) SIPS general: 6.6 (4.5) GAF: 60.1(16.4)										
Rasskazova et al. (2016) (RU)	CHR (SIPS)	76	20.0 (2.4)	NR	NR	NR	NR	55	20.4 (2.5)	NR	NR	NR	10
Kihmy et al. (2014) (US)	CHR (SIPS)	62	19.7 (3.6)	48M/15F	107.1 (17.3)	7 AP, 12 AD, 43 DF	DF	37	22.3 (4.6)	19M/18F	111.8 (14.0)	NR	19
	Clinical data		SIPS positive: 12.6 (4.5) SIPS negative: 13.1 (6.3) SIPS disorganization: 7.3 (3.5) SIPS general: 9.3 (4.3)										
Uchida et al. (2014) (JA)	UHR (CAARMS) APS 78%, BLIPS 4%, GRD 2%, APS + GRD 14%, APS + BLIPS 2%	60	19.5 (4.2)	22 M/48F	NR	12 AP, 12 AD, 35 DF	DF	200	20.3 (1.9)	81 M/119F	NR	NR	19
	Clinical data		CAARMS thought content: 3.4 (1.3) CAARMS perception: 2.9 (1.4) CAARMS disorganized speech: 1.7 (6.7) GAF: 47.6 (6.7)										
Ohmuro et al. (2018) (JA)	UHR (CAARMS) APS 78.3%, BLIPS 3.3%, GRD 1.7%, APS + GRD 16.7%	50	20.0 (4.1)	NR	101.5 (10.6)	30 AP, 15 AD		29	21.2 (1.0)	NA	111.5 (6.4)	14.4 (0.8)	20
	Clinical data		PANSS positive: 13.0 ± 3.5 PANSS negative: 12.9 ± 5.0 PANSS general: 32.8 ± 7.4 GAF: 48.2 ± 8.3										

Note: Data is presented as mean (SD).

Abbreviations: AD, antidepressant; AP, antipsychotic; APS, attenuated psychotic symptoms; BLIPS, Brief Limited Intermittent Psychotic Symptoms; CAARMS, comprehensive assessment of at-risk mental state; ARMS, at-risk mental state; CHR, clinical high risk; DF, drug-free; GAF, global assessment of functioning; GRD, genetic risk and deterioration syndrome; JA, Japan; NR, no data reported; QualSyst, standard quality assessment tool; PANSS, Positive and Negative Syndrome Scale; RU, Russia; SIPS, structured interview for prodromal symptoms; UHR, ultra high-risk; US, United States.

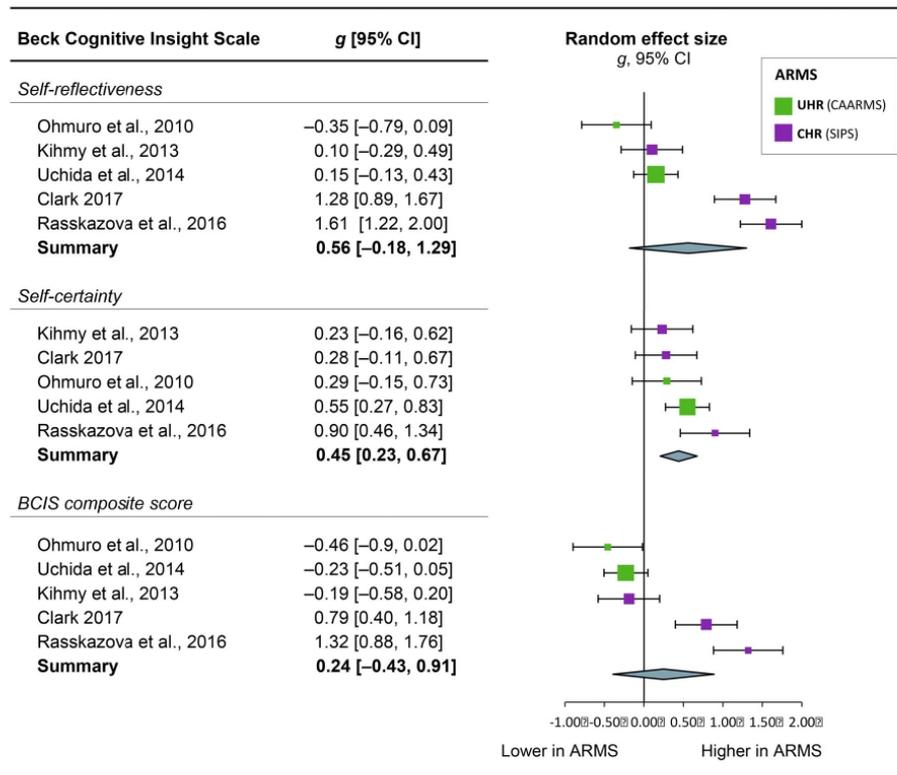


FIGURE 2 Meta-analysis's forest plots of comparisons of cognitive insight domains measured by the BCIS between individuals with an ARMS status and healthy controls. ARMS: at-risk mental state; BCIS: Beck Cognitive Insight Scale; CAARMS, comprehensive assessment of at-risk mental states; CHR, clinical high-risk; SIPS, structured interview for prodromal symptoms; UHR, ultra high-risk

to-moderate magnitude effect size ($ES_{g_{self-certainty}} = 0.45 [0.23; 0.67]$), $P < .001$). Heterogeneity between studies was moderate but did not reach significance ($I^2 = 41.0\%$, Q-test P -value = .14), and was mostly driven by heterogeneity within studies ($\tau^2 = .03$).

- **Overall cognitive insight composite score:** No significant differences were observed between ARMS and healthy controls for overall cognitive insight as indexed by the BCIS composite score ($ES_{g_{overall}} = 0.24 [-0.43; 0.91]$), $P = .45$). Heterogeneity was high and significant ($I^2 = 93.6\%$, Q-test P -value $< .001$), and equally driven by heterogeneity between- and within-studies ($\tau^2 = .54$).

The Baujat plots indicated that the study of Rasskazova et al. (2016) largely influenced all summary-ES $_g$ and contributed to their heterogeneity (Figure S1). In addition, this study demonstrated the highest risk of bias (QualSyst total = 10/22) as compared to the other studies included in the meta-analysis (QualSyst total = 18-to-20/22). After removing this outlier, the three ES $_g$ dropped but their significance was unchanged ($ES_{g_{self-reflectiveness}} = 0.39 [-0.38; 0.97]$, $P = .39$; $ES_{g_{self-certainty}} = 0.38 [0.20; 0.57]$), $P < .001$; $ES_{g_{overall}} = 0.02$

$[-0.56; 0.51]$, $P = .93$). Heterogeneity was still large but mostly driven by heterogeneity within studies regarding self-reflectiveness ($ES_{g_{self-reflectiveness}}$: $I^2 = 92.5\%$, Q-test P -value $< .001$, $\tau^2 = .43$) and BCIS composite score ($ES_{g_{overall}}$: $I^2 = 94.9\%$, Q-test P -value $< .001$, $\tau^2 = .26$). By contrast, heterogeneity was low and non-significant for the self-certainty sub-score ($ES_{g_{self-certainty}}$: $I^2 = 5.73\%$, Q-test P -value $P = .38$, $\tau^2 = .00$).

To identify potential contributors of heterogeneity, we conducted post hoc moderator analyses with variables that were available in all studies included in the meta-analysis (ie, age of ARMS individuals, QualSyst Total score, diagnosis category (CHR (Clark, 2017; Kimhy et al., 2014; Rasskazova et al., 2016)/UHR (Ohmuro et al., 2018; Uchida et al., 2014)). Meta-regressions did not reveal any significant effect of age nor of diagnosis category, but a significant positive effect of the study quality on the three ES $_g$ (Table S2).

Publication bias was not significant according to Egger's Regression tests regarding self-reflectiveness ($z = 0.05$; $P = .96$) and self-certainty ($z = -0.05$; $P = .96$), BCIS composite score ($z = 0.67$; $P = .51$). (Figure S2).

4 | DISCUSSION

This meta-analysis demonstrated no significant difference in overall cognitive insight for individuals with an ARMS status vs healthy control, which corroborates the general conceptualization that insight is intact in ARMS (Fusar-Poli et al., 2012). However, when considering subdomains of cognitive insight, we provided the original finding that ARMS is associated with significant higher rates of self-certainty. It is likely that overconfidence in own judgements reflects the proneness to experience strong and inflexible emerging delusional beliefs in individuals with an ARMS and presenting with positive symptoms (as is the case in the majority of studies included in the meta-analysis). The validity of this idea is supported by observations of higher self-certainty measured by the BCIS in patients with psychosis, a potential outcome of ARMS (Martin et al., 2010; Waman et al., 2007; Kao et al., 2011), as well as significant correlations between self-certainty levels and attenuated psychotic symptoms in ARMS samples (Kimhy et al., 2014; Uchida et al., 2014). However, the lack of clinical data in studies involved in the meta-analysis prevented us to replicate the association between insight scores and psychotic symptoms. Self-certainty may also contribute to the reasoning biases that are observed in individuals with ARMS and full-threshold psychosis, such as jumping to conclusion and belief inflexibility (Rausch et al., 2016; So et al., 2016). Here, our results indicate that higher self-certainty seems to exist not only in people who have franc psychotic disorder but also in people with an ARMS status. By contrast, it is possible that self-reflectiveness and overall cognitive insight are not impaired in this at-risk population. However, ongoing neurodevelopment and social processes in youth with an ARMS status may affect cognitive functions such as insight (Brent et al., 2014). Accordingly, it is likely that the BCIS do not assess the same phenomena in these young individuals as in older patients. This issue should be addressed in future studies comparing cognitive insight in ARMS vs full-threshold psychotic disorders.

Finally, a critical point is the ability of cognitive insight measures to predict transition to psychosis. In the one study that conducted follow-up re-assessments in ARMS, BCIS measurements were not identified as predictors, but the sample did not have sufficient power to detect subtle differences in transition rates (Kimhy et al., 2014). Future ARMS studies should integrate longitudinal evaluations of cognitive insight among assessments to evaluate BCIS measures as potential predictive markers for transition.

Despite the original findings, several limitations to this meta-analysis should be acknowledged. First, we observed large heterogeneity between included studies and, critically, that study quality significantly influenced the effect sizes. It is likely that the aggregation of ARMS subgroups from Raskazova et al. (2016) have mostly contributed to the global heterogeneity. A second limitation is that our samples included unavoidable differences between groups with regard to use of outcome, psychotropic medications and symptoms confounds. Although critical, these variables were not consistently reported across studies and thus, unusable for meta-regressions. The ARMS concept is indeed highly heterogeneous in terms of clinical

characteristics and outcome. For instance, hierarchical clinical staging models of ARMS have been proposed to account for symptom heterogeneity (Ryan et al., 2018; Carrion et al., 2017), and more than 15 different clinical trajectories can be identified in ARMS cohorts (Polari et al., 2018). Moreover, as observed in our meta-analysis, multiple types of psychometric measurements can be used to assess symptoms of ARMS (Fusar-Poli et al., 2008). Consequently, it is likely that these variables have accounted for the global heterogeneity of our results. More investigations are required to identify how delineated clinical features are related to insight in ARMS. Also, given the significant impact of antipsychotic agents on insight levels (Pijnenborg et al., 2015), future studies should entail longitudinal evaluations of both cognitive insight and symptoms in ARMS samples to determine how these co-evolve with medication changes. Third, it is worth mentioning that the BCIS assesses more cognitive mechanisms of insight than the actual conscience of the illness and symptomatology (ie, clinical insight). It would be fruitful to compare BCIS scores with more illness-based assessments to determine how cognitive insight is related to the way illness and symptoms are appraised in the ARMS population (Elowe & Conus, 2017).

In the past few decades, much effort has been put toward characterizing the ARMS clinical features to develop targeted interventions. Our study suggests that assessments of cognitive processes that are relevant for insight should be implemented in the early intervention armamentarium. Specifically, the self-certainty sub-score of the BCIS appears useful to identify cognitive insight impairment in individuals with an ARMS status.

CONFLICT OF INTEREST

None of the authors have a financial interest in any organization or commercial product providing financial support for this research.

AUTHOR CONTRIBUTIONS

Clément Dondé designed the study and wrote the first draft of the manuscript. Jerome Brunelin supervised the study. Layla Lavallé conducted the statistical analyses. Vincent Laprêvotte, Eric Fakra and Frédéric Haesebaert provided critical inputs to the manuscript. All authors reviewed and approved the manuscript in its final form.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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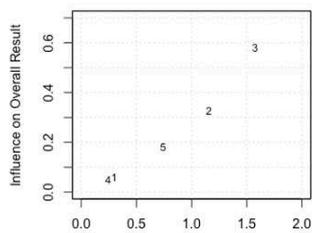
SUPPORTING INFORMATION

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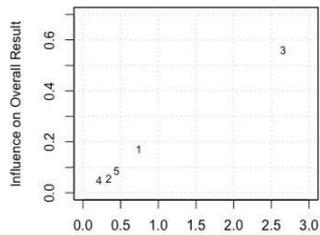
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Studies (yes:2, partial:1; no:0)	1	2	3 Method of subject/ comparison group selection or source of information/ input variables	4	8	9	10	11	12	13	14	Total sum	Summary score
	Question/ objectives	Study design	Description of subject characteristics	Outcome/ Means of assessment	Sample size	Analytic methods	Estimate of variance	Controlled for confounding	Results reported in sufficient detail	Conclusions supported by the results			
Clark 2017	2	2	1	2	1	2	2	2	0	2	2	18	1,64
Rasskazova et al., 2016	1	1	0	0	1	2	2	1	0	1	1	10	0,91
Kihmy et al., 2013	2	2	2	1	2	0	2	2	2	2	2	19	1,73
Uchida et al., 2014	2	2	2	2	2	2	2	2	0	1	2	19	1,73
Ohmuro et al., 2010	2	2	2	1	2	1	2	2	2	2	2	20	1,82

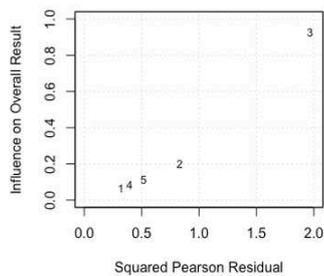
Supplementary Material S1: Rating scores calculated for each study using the Standard Quality Assessment (QualSyst tool¹⁴). Three domains relative to clinical intervention (items 5, 6, 7) were not applicable and thus removed from the table.



BCIS Self-reflectiveness domain



BCIS Self-certainty domain



BCIS composite score
(overall cognitive insight)

Supplementary material S2: Baujat Plots. Studies influence on the summary effect size and their contribution to the heterogeneity.

BCIS: Beck Cognitive Insight Scale.

¹ Kihmy et al., 2013

² Ohmuro et al., 2017

³ Rasskazova et al., 2016

⁴ Uchida et al., 2014

⁵ Clark 2015

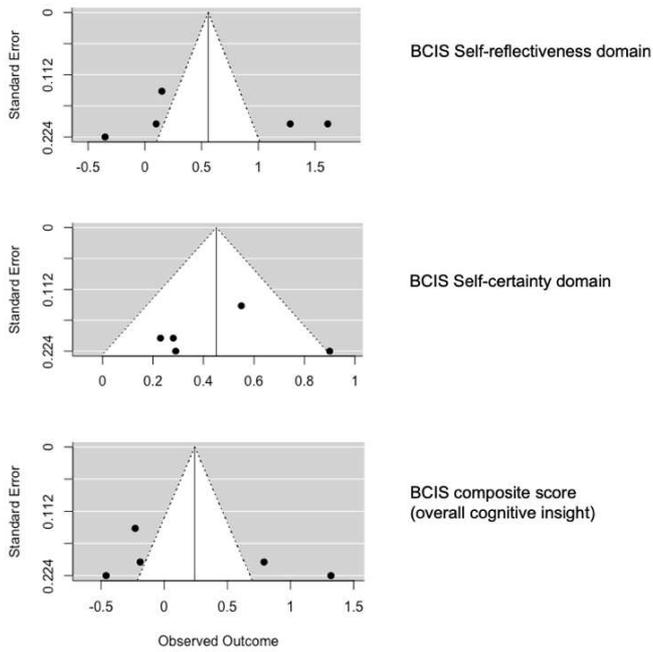
	BCIS composite score			Self-reflectiveness			Self-certainty		
	β	SE	p-value	β	SE	p-value	β	SE	p-value
Age	0.03	1.43	.98	0.42	1.56	.79	-0.32	0.47	.49
UHR	0.34	0.36	.08	0.09	0.39	.08	-0.44	0.18	.96
CHR	-0.63	0.57	.08	-0.10	0.0.62	.08	-0.46	0.28	.96
Quality	0.16	0.06	.003*	0.17	0.07	.02*	0.06	0.03	.04*

Supplementary material S3: Meta-regressions of insight measures for potential confounders in each domain of the Beck Cognitive Insight Scale.

Quality of studies was assessed using the Standard Quality Assessment (QualSyst tool¹⁴)

CHR: Clinical High Risk; UHR: Ultra High Risk; SE: standard error

* $p < 0.05$



Supplementary material S4: Funnel Plots. Publication bias visualisation.

BCIS: Beck Cognitive Insight Scale.

7.2. rTMS for treatment of negative symptoms in schizophrenia: Clinical effect and neural basis [Article 6]

Article 6: rTMS for treatment of negative symptoms in schizophrenia: Clinical effect and neural basis. Encephale. 2019. Lavallé L., Aleman A.



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Opening lecture

rTMS for treatment of negative symptoms in schizophrenia: Clinical effects and neural basis

Traitement des symptômes négatifs de la schizophrénie par rTMS : effets cliniques et fondement neurologique

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Symptoms of schizophrenia, a frequent chronic psychiatric disease, are commonly divided into 2 major categories, positive and negative. Negative symptoms are characterized by marked reductions in goal-directed behavior, which can include reduced initiative, social withdrawal, anhedonia, affective flattening and poverty of speech. No medications have emerged yet to treat effectively negative symptoms [1]. Facing the lack of available efficacious treatment, novel therapeutic solutions are warranted.

Advances in neuroimaging studies have identified that schizophrenia is associated with some impairments in dopamine-dependent frontostriatal interactions implicated in motor, cognitive and motivational control [2]. Indeed, models about apathy involve a lack decision value transmission from ventromedial prefrontal cortex, amygdala and nucleus accubens to the midbrain dopaminergic ascending pathways, resulting in a deficient modulation of goal-directed behavior by the frontostriatal circuits [3]. In a systematic review, Kos et al. [4] revealed similar neural basis of apathy across neurodegenerative disorders, acquired brain injury and psychiatric disorders and confirmed its association with abnormalities in frontal and striatal areas. The ventral tegmental area (VTA) dopaminergic connectivity with prefrontal regions and striatum has been negatively correlated with apathy's level, highlighting its association with deficits in mesocortical dopamine reward pathways [5]. Thus, models about apathy and other negative symptoms showed that frontal-striatal stimulation could normalize neuroplasticity in emotion regulation networks to restore motivated behavior in patients with schizophrenia. One can thus hypothesized that modulating DA subcortical would lead to reduce negative symptoms in schizophrenia. In patients with major depression, it has been reported that repetitive Transcranial Magnetic Stimulation (rTMS) applied over the dorso-lateral prefrontal cortex (DLPFC) inducing dopamine release in the striatum can lead to beneficial

clinical outcomes [6]. TMS is a non-invasive brain stimulation technique in which a changing magnetic field generates a brain electric field, resulting in neural activity or changes in resting potentials. A capacitor charged to a high voltage (up to 8kA) is discharged into the stimulating coil, which in turn produces a magnetic pulse of up to 2 Tesla. Applied over a specific brain region, TMS can modulate the excitability of the stimulated area but also modulated its connectivity within interconnected networks. Altogether, these results suggest that applying rTMS over the DLPFC would reduce apathy and negative symptoms in patients with schizophrenia by modulating subcortical DA release.

Several studies have thus investigated the clinical interest of DLPFC rTMS in patients with negative symptoms of schizophrenia but have produced mixed results. In a meta-analysis including nine randomized sham-controlled trials, Dlabac-de Lange et al. reported a significant superiority of active rTMS over sham to reduce negative symptoms of schizophrenia [7]. In these studies, rTMS was mainly applied over the left DLPFC with high frequencies. In 2015, in a 32-patients double-blind study, a significant improvement of negative symptoms, that remained stable 3 months post-treatment, was observed following 10-Hz rTMS of the bilateral DLPFC during 3 weeks with 2 sessions per day (1 session per side, separated by a 5 hours interval). As observed during pharmacological trials [8], the significant clinical effect was observed when negative symptoms were measured by the Scale for the Assessment of Negative Symptoms (SANS) while no significant effect were reported with the Positive and Negative Syndrome Scale (PANSS) negative symptom subscale. In another study published the same year, 10 Hz rTMS over 3 weeks to the left DLPFC didn't reveal any significant benefits in the treatment of negative symptoms compared to sham stimulation [9]. These latter results could perhaps be explained, in part, by the exclusive use of the PANSS negative symptom subscale as outcome measure and the only left-DLPFC stimulation whereas neuroimaging studies suggest bilateral impairments in negative symptoms. Furthermore, a 3-weeks course of bilateral daily rTMS failed to reveal either substantial improvements in

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neither the negative symptoms measured by SANS and PANSS nor on depressive symptoms measured by the Calgary Depression Scale for Schizophrenia (CDSS) [10]. The alternating stimulation of the left and the right DLPFC within a same session, in which one brain region can inhibit the activation of the contralateral brain area, provides a potential explanation for this result. More recently, a meta-analysis including 18 studies and taking into account recent negative findings showed a significant beneficial effect (effect size of 0.31) of active frontal cortex rTMS to reduce negative symptoms of schizophrenia [11].

It was suggested that a better understanding of rTMS mechanisms of action and of negative symptoms pathophysiology may help optimize stimulation parameters and explain discrepancies observed between previous clinical studies. In line with this, after 3 weeks of 10-Hz treatment of the bilateral DLPFC, an fMRI analysis during the Tower of London (ToL) task showed a significant increase in both the left posterior cingulate cortex (PCC) and the medial PFC (mPFC) activities as well as a significant decrease in the right DLPFC activity. Schizophrenia has been associated with a reduction of the anti-correlation interaction between the default mode network (DMN, including PCC and mPFC) and the DLPFC (which is involved in task-processing) during cognitive tasks. This study highlighted that bilateral DLPFC rTMS reduce the altered interaction between DMN and task-positive network [8] during a planning task. Using ¹H-Magnetic Resonance Spectroscopy (MRS) revealed that bilateral prefrontal TMS induced an increased glutamate and glutamine (Glx) concentration in the left DLPFC, providing a potential explanation for rTMS-induced plasticity by increasing prefrontal cortex metabolism [12]. Immediate effects of one session of non-invasive transcranial stimulation through tDCS or iTBS over the right DLPFC has been studied in a total of 110 healthy participants and measured by MRS in the dorsal striatum (DS), a brain region known to receive glutamatergic efference from the DLPFC [13]. This study suggested that DLPFC stimulation can enhance dopaminergic activity in distal brain regions involved in reward and motivation, including DS, VTA, substantia nigra (SN), and nucleus accumbens (Nacc) [14]. These results are in line with animal models reporting that prefrontal cortex optogenetic stimulation decreased cocaine-seeking behavior by modulating activity in subcortical reward midbrain circuitry [15] and with studies in patients with cocaine use disorder showing that rTMS over the left DLPFC decreased cocaine-seeking behavior [16]. Based on this observed major contribution of the DLPFC on DA release and goal-oriented behavior, Aleman et al developed a new double-blind sham-controlled study to investigate the clinical effect (Apathy Evaluating Scale) and biological effect (MRS and rs-fMRI) of both right DLPFC intermittent Theta Burst Stimulation (iTBS) and prefrontal tDCS (another noninvasive brain stimulation technique). Future studies may also investigate the effect of brain-derived neurotrophic factor (BDNF) gene polymorphism because it has been suggested that it could influence response to rTMS in schizophrenia [17].

In sum, despite meta-analyses highlighted the superiority of active DLPFC rTMS over sham to decrease negative symptoms of schizophrenia, controversies remain regarding the clinical interest of this intervention. Until now, studies have measured negative symptoms using exclusively the SANS and the PANSS negative

symptoms subscale. It would be of interest to conduct studies using other standardized clinical scales to individualize different kind of negative symptoms. In addition, large multicenter trials are needed to better understand the translational neurobiology of rTMS. Future research is needed to investigate and optimize rTMS parameters, especially in evaluating the iTBS use, which seems to be more relevant in medical practice because of its shorter administration duration. Furthermore, future studies should probe the combination of noninvasive neurostimulation (such as rTMS and tDCS) with psychosocial approaches (e.g., behavioral activation). Lastly, combining TMS with brain imaging is an exciting new area of research, promising to help uncover how TMS acts in the brain.

Disclosure of interest

The authors declare that they have no competing interest.

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7.3. Reality-monitoring and visual hallucinations in schizophrenia [article 7]

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Original article

Reality-monitoring deficits and visual hallucinations in schizophrenia



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ABSTRACT

The presence of visual hallucinations in addition to auditory hallucinations (V + AH) is associated with poor prognosis in patients with schizophrenia. However, little consideration has been given to these symptoms and their underlying cognitive bases remain unclear. Based on cognitive models of hallucinations, we hypothesized that V + AH are underpinned by an impairment in reality-monitoring processes. The objective of the present study was to test whether reality-monitoring deficits were associated with V + AH in schizophrenia. This study examined reality-monitoring abilities in two groups of patients with schizophrenia: a group of patients with V + AH (n = 24) and a group of patients with AH only (n = 22). Patients with V + AH were significantly more likely to misremember imagined words as being perceived from an external source, compared to patients with AH only (p = 0.008, d = -0.82). In other words, V + AH patients display a larger externalization bias than patients with AH only. One explanation for these results could be that experiencing hallucinations in two sensory modalities may contribute to increased vividness of mental imagery and, in turn, lead to disruption in reality-monitoring processes. This study helps to refine our understanding of the cognitive processes underlying the presence of both auditory and visual hallucinations in patients with schizophrenia.

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1. Introduction

Hallucinations are classically defined as perception-like experiences that occur without an external stimulus, in an awake state, with the physical properties and the sense of reality of real perceptions, and that are not under voluntary control [1,2]. Hallucinations may involve all sensory modalities but, in patients with schizophrenia, their prevalence differs according to the sensory modality involved. Specifically, their lifetime prevalence is estimated at 64–80% for auditory, 23–31% for visual, 9–19% for tactile, and 6–10% for olfactory hallucinations [3]. Given their predominance, hallucinations in the auditory modality (AH) are considered a hallmark of schizophrenia and have been the focus of most studies in the field. By contrast, relatively little consideration has been given to the co-occurrence of hallucinations in other modalities. Recently, McCarthy-Jones et al. reported that 30–37% of patients with lifetime AH had also experienced visual

hallucinations (VH), and that, in reverse, 83–97% of patients with experience of VH had also experienced AH [3]. This co-occurrence suggests common hallucinatory mechanisms in addition to specific modality-dependent dysfunctions [4]. Critically, the presence of VH in addition to AH (V + AH) is associated with a more severe psychopathological profile and a less favorable prognosis [5]. Due to their impact on functioning, there is a crucial need to increase knowledge about these symptoms and particularly their underlying cognitive mechanisms.

During the last decades, some cognitive models have been proposed to explain positive symptoms such as hallucinations [6]. One of them assumes that hallucinations arise from a failure of reality-monitoring processes, specifically resulting in misattribution of internally generated events, such as thoughts or mental images, as being perceived from an external source [7–9]. This type of misattribution, also called an externalization bias, may result from mental imagery having more perceptual characteristics than expected or from reduced cognitive operations associated with imagined information making the memory unlikely to have been internally-generated [10,11]. Several studies and meta-analyses have supported this model by showing that patients with hallucinations have a greater tendency to misattribute internal

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items to external sources than patients without hallucinations and healthy individuals [12,13]. Even if early reality-monitoring models of hallucinations [7] did not propose that the deficits would concern some specific sensory modalities of hallucinations rather than others, most of the studies focused on AH. For instance, we reported that patients with AH misattributed more words they had imagined as being actually heard compared to patients without AH [13]. To the best of our knowledge, only few studies investigated reality-monitoring deficits in relationship with hallucinations in the visual modality in patients with schizophrenia. They showed that patients with VH misremembered items that had been presented as words as having been presented as pictures [14–16]. These results suggest that a failure in reality-monitoring processes may constitute a good candidate for the mechanism underlying hallucinatory phenomenon. However, little is known about the impact of presenting hallucinations in both visual and auditory modalities on reality-monitoring performance.

In this context, the aim of the present study was to test whether reality-monitoring deficits are associated with V + AH in schizophrenia. To this end, we investigated reality-monitoring performances in two groups of schizophrenia patients with hallucinations: a group with only AH (i.e., patients that never reported VH) and a group with V + AH, as done in studies exploring VH in schizophrenia [17–19]. We hypothesized that patients with V + AH would display more severe reality-monitoring deficits than patients with AH only. More precisely, we proposed that experiencing hallucinations in several sensory modalities would increase the perceptual characteristics associated with imagined events and lead to a more severe externalization bias.

2. Materials and methods

2.1. Participants

Fifty patients with schizophrenia were included in the study. All participants met the DSM-IV-TR criteria for schizophrenia based on a clinical interview with an experienced psychiatrist using the Mini-International Neuropsychiatric Interview (M.I.N.I.) [20]. All participants were native French-speakers and displayed refractory treatment-resistant AH, defined as the persistence of daily AH despite antipsychotic treatment at an adequate dosage for at least 6 weeks. The Positive and Negative Syndrome Scale (PANSS) was used to evaluate the general symptomatology [21] and the Auditory Hallucination Rating Scale (AHRS, range 0–42) was used to provide a specific and extensive measure of AH severity [22]. Participants were carefully divided into two groups based on the presence of VH measured by the item #6 of the Scale for the Assessment of Positive Symptoms (SAPS [23]): a group of patients with AH and no VH (AH group, $n = 24$, SAPS-item #6 = 0) and a group of patients with AH and VH (V + AH group, $n = 22$, SAPS-item #6 ≥ 2 , i.e., VH ranging from “2-mild” to “5-severe” intensity). SAPS-item #6 assess VH by asking if “the patient sees shapes or people that are not actually present”. Participants with questionable VH (SAPS-item #6 = 1) were excluded ($n = 4$). Participants characteristics are detailed in Table 1.

All patients gave their written informed consent. All experiments were approved by a local ethics committee and performed in accordance with relevant guidelines and regulations.

2.2. Reality-monitoring task

Reality-monitoring performances were assessed using a previously described task that measures confusion between imagined words and heard words (‘Hear-Imagine’ task) [13,24]. All participants completed a short practice trial to become acquainted with the task requirements and to ensure the

Table 1
Demographic and clinical characteristics of patients with AH and patients with V + AH.

	AH Group (N = 24)	V + AH Group (N = 22)	P value
Gender (Male/Female)	18 / 6	7 / 15	0.003*
Age (years)	36.2 (9.3)	36.4 (10.2)	0.96
Education (years)	11.3 (2.5)	12.5 (2.6)	0.11
Illness duration (years)	10.6 (8.2)	9.8 (7.0)	0.73
PANSS total score	73.2 (15.5)	73.4 (17.9)	0.96
AHRS score	25.5 (6.4)	27.1 (6.2)	0.42
SAPS- item #6	0 (0)	2.9 (0.9)	–

All values are mean (SD). Groups were compared using two-sample t-tests, except for gender where a Chi-square test was used. * significant difference between groups ($p < 0.05$).

understanding and the good realization of instructions. The task was separated into two phases: an encoding phase and a memory retrieval phase. During the encoding phase, 16 words were presented one by one in a randomized order in the centre of a computer screen for 3 s. Each word was immediately preceded by its respective instruction, either “Imagine yourself hearing the following word” or “Listen to the following word”. Half of the words (8 words) had to be heard and their visual presentation was accompanied by an auditory stimulus (i.e., the experimenter voice speaking the word once). The other half (8 words) had to be imagined by the participant and no auditory stimulus was presented. The memory retrieval phase began immediately after the end of the encoding phase. During this phase, participants were presented with a response grid including the 16 words previously presented during the encoding phase, plus 8 new words which had not previously been presented. For each word, participants were asked to answer whether the word was heard, imagined or if the word was not presented during the encoding phase.

Two main outcomes were measured: 1) the externalization bias, measured as the number of imagined words that were classified as heard (range 0–8), and 2) the internalization bias, measured as the number of heard words that were classified as imagined (range 0–8) [13].

2.3. Statistical analyses

Data were analyzed with JASP (Version 0.9; JASP Team, 2018). Between group comparisons were computed using two-sample t-tests for continuous outcomes and Chi-square tests for categorical data. For misattribution biases comparisons, Cohen’s d effect sizes were also computed. All tests were two-tailed and statistical significance was set at $p < 0.05$. In case of a significant effect, the potential confounding role of gender was assessed using a two-way ANOVA with Group and Gender as between-group factors.

3. Results

3.1. Demographic and clinical characteristics

No significant differences were reported between AH and V + AH groups for age, education, illness duration, AH severity measured by the AHRS and general symptomatology severity assessed by the total PANSS score (all $p > 0.05$, see Table 1). However, the two groups differed significantly on gender ($\chi^2 = 8.626$, $p = 0.003$).

3.2. Reality monitoring performance

Patients with V + AH displayed a significantly higher externalization bias as compared to patients with AH ($t(44) = -2.78$, $p = 0.008$, $d = -0.82$; see Fig. 1). In other words, patients with V + AH

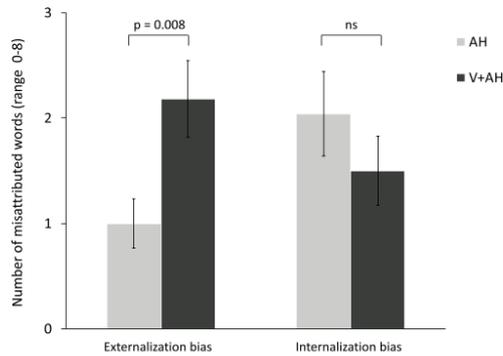


Fig. 1. Comparison of reality-monitoring performance between patients with V + AH (dark grey bars) and patients with AH only (light grey bars). The externalization bias is measured as the number of imagined words that were classified as heard (range 0–8) and the internalization bias is measured as the number of heard words that were classified as imagined (range 0–8). [13] Results are displayed as mean \pm standard error. ns = not significant.

misrecognized more imagined words as being heard ($M = 2.18$, $SD = 1.71$) than patients with AH only ($M = 1.00$, $SD = 1.14$). No difference was found between groups for the internalization bias, i.e. the misrecognition of heard words as being imagined ($t(44) = 1.04$, $p = 0.31$, $d = 0.31$).

In order to rule out the potential confounding role of gender in our analyses, we examined the effect of gender on the externalization bias with a two-way ANOVA with Group and Gender as between-group factors. We found no significant effects of Gender ($F(1, 42) = 0.31$, $p = 0.58$) and Group*Gender interaction ($F(1, 42) = 1.75$, $p = 0.20$). By contrast, the effect of Group remained significant ($F(1, 42) = 4.70$, $p = 0.036$).

4. Discussion

The present study proposed an original investigation of reality-monitoring performance in patients with schizophrenia who present with V + AH. Findings indicated that patients with V + AH displayed a higher externalization bias than patients with AH, which means that patients with V + AH were more likely to remember imagined words as being perceived compared to patients with AH only.

The existence of a misattribution bias in patients with VH has already been described in the literature in schizophrenia [14–16,25]. For instance, Brébion et al. (2008) found that patients with VH were more likely to report that they had seen pictures of items when only the verbal label of these items had been displayed. However, in these studies, reality-monitoring was tested using stimuli in the visual modality only (i.e. words and pictures), making it difficult to decipher whether the externalization bias was modality-specific or not. By contrast, Arguedas et al.'s investigated the modality-specificity of reality-monitoring impairments [26]. Authors found that patients with olfactory hallucinations were less accurate in distinguishing between imagined and smelled odors than patients with AH and healthy controls and, additionally, that patients with AH were less accurate in distinguishing the source of a spoken word. However, the verbal reality-monitoring task used in Arguedas et al.'s design did not involve a distinction between imagined and perceived events, as done in our study, but a distinction between self-produced words and words produced by the experimenter. It is likely that such

distinction is not related to the same cognitive mechanisms as those involved in discriminating imagination from perception.

In our study, we tested reality-monitoring performances in the auditory modality and demonstrated that V + AH patients were more likely to misattribute imagined words as being heard than patients with AH only. Given that the two groups did not differ in AH and other symptoms severity, we propose that the misattributions observed may not be specific of the sensory modality but rather reflect an amodal deficit in discriminating imagination from reality. This interpretation is consistent with Garrison et al.'s study, which reported that even if reality-monitoring accuracy was better for imagined stimuli in the visual than in the auditory modality, the level of externalization bias was independent of the modality of presentation of the stimuli [27]. To confirm that the modality used to measure reality-monitoring did not influence the observed externalization bias, it would be of great interest to include a visual reality-monitoring task, together with the present auditory task, in a further study.

One can hypothesize that patients with V + AH display a more severe misattribution bias because of increased perceptual details associated to the imagined event that may lead to greater confusion when identifying the source of this event. This is consistent with the hypothesis of increased vividness of mental images associated with VH, which has been supported by evidence of a relationship between proneness to VH and vivid imagery in nonclinical people with VH [14]. In addition, the hypothesis of increased perceptual details associated to the imagined event is consistent with the abnormal overactivity of sensory cortex observed during hallucinations such as the hyperactivation of superior temporal regions for AH and visual cortices for VH [28], which might produce more vivid perceptual content than usually associated with imagined events. Alternative explanations for the increased externalization bias independently of the vividness of mental images would be that patients with V + AH associate less cognitive operations information to imagined events [29] or display greater deficits in the ability to compare imagined and real events [30].

Besides, the findings of a misattribution bias in patients with VH is consistent with a previous study showing a greater propensity to report imagined stimuli as percepts in patients with Parkinson disease and VH [31]. Since a similar misattribution bias was reported in nonclinical people with high predisposition to VH, one could hypothesize that the reality-monitoring deficit constitutes a common mechanism that underlies VH regardless of the diagnostic category.

Despite the original findings, several limits should be acknowledged. First, one can hypothesize that the observed difference between groups is supported by the difference in gender proportion between our samples. Since our analyses revealed no effect of gender on the externalization bias, the between-group difference in terms of gender is unlikely to account for the present observation of an increased externalization bias in patients with V + AH. The observed gender imbalance between V + AH and AH patients is in line with some previous studies reporting a higher risk for VH in females than in males [32]. However, a more recent study investigating the prevalence and co-occurrence of hallucinations across the auditory, visual, olfactory, and tactile modalities, in two large samples of people diagnosed with chronic schizophrenia-spectrum disorders found no consistent association between VH (or any modality of hallucination) and gender [3]. Second, we cannot exclude that the more severe reality-monitoring deficits observed in the V + AH group could be due to more severe general cognitive deficits in V + AH. In the current sample, we compared PANSS cognitive dimension scores [33] between groups and observed no differences between V + AH (mean = 11.73, $SD = 3.24$) and AH groups (mean = 11.77, $SD = 3.28$; $p = 0.96$).

However, further studies with standardized cognitive evaluations are required to address this issue. In addition, the greater deficits observed in the V + AH group could be linked to greater visual processing deficits. Indeed, studies in patients with Parkinson disease have reported a relationship between VH and altered visual processing [34,35] and there is also evidence that patients with Parkinson disease and VH showed deficits in both visual perception and source monitoring [31]. To decipher on the contribution of visual abnormalities to the reality-monitoring deficits in patients with schizophrenia, studies investigating visual processing together with reality-monitoring are needed. Third, one potential limitation of the present study is that no healthy individuals were compared to the patient groups. However, regarding repeated evidence of reality-monitoring impairment in schizophrenia (reviewed in [12]), we can reasonably assume that our samples of participants display reality-monitoring deficits. Furthermore, the study was designed to assess the effects that were specific to the sensory modality involved in hallucinations, i.e., AH or V + AH, rather than the effects that were more broadly related to schizophrenia and medication. Fourth, although the task used to measure reality-monitoring processes in our study was similar to the paradigms that have been previously used to assess reality-monitoring, with imagined and heard words presented visually [13,36–38], this task came with some limitations. Indeed, we cannot exclude that participants may not have always followed the instruction to imagine hearing the visually presented words and that it could have affected their performance during the retrieval phase. Finally, the tools used to assess hallucinations in our sample of schizophrenia patients did not allow us to differentiate multimodal hallucinations in different sensory domains at the same time, as well as serial multimodal hallucinations that occurred at separate times. Since simultaneous multimodal hallucinations are associated with a greater sense of reality and distress [39], it would have been relevant to explore whether they were associated to a higher externalization bias.

In summary, we present evidence that patients with schizophrenia who have V + AH display a higher deficit in reality-monitoring abilities than patients with schizophrenia who only have AH. Experiencing hallucinations in two sensory modalities is associated with a greater tendency to misattribute imagined events as being actually perceived from an external source. A better understanding of the cognitive processes underlying the presence of V + AH in patients with schizophrenia could help identify some potential targets for clinical interventions. These findings support the interest of developing psychological interventions that aim to overcome reality-monitoring deficits in patients with V + AH, as done by two previous studies reporting promising results [40,41].

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7.4. Neuroanatomical correlates of reality-monitoring in patients with schizophrenia and auditory hallucinations [Article 8]

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Neuroanatomical correlates of reality monitoring in patients with schizophrenia and auditory hallucinations

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Abstract

Background. Reality-monitoring process enables to discriminate memories of internally generated information from memories of externally derived information. Studies have reported impaired reality-monitoring abilities in schizophrenia patients with auditory hallucinations (AHs), specifically with an exacerbated externalization bias, as well as alterations in neural activity within frontotemporoparietal areas. In healthy subjects, impaired reality-monitoring abilities have been associated with reduction of the paracingulate sulcus (PCS). The current study aimed to identify neuroanatomical correlates of reality monitoring in patients with schizophrenia.

Methods. Thirty-five patients with schizophrenia and AHs underwent a reality-monitoring task and a 3D anatomical MRI scan at 1.5 T. PCS lengths were measured separately for each hemisphere, and whole-brain voxel-based morphometry analyses were performed using the Computational Anatomy Toolbox (version 12.6) to evaluate the gray-matter volume (GMV). Partial correlation analyses were used to investigate the relationship between reality-monitoring and neuroanatomical outcomes (PCS length and GMV), with age and intracranial volume as covariates.

Results. The right PCS length was positively correlated with reality-monitoring accuracy (Spearman's $\rho = 0.431$, $p = 0.012$) and negatively with the externalization bias (Spearman's $\rho = -0.379$, $p = 0.029$). Reality-monitoring accuracy was positively correlated with GMV in the right angular gyrus, whereas externalization bias was negatively correlated with GMV in the left supramarginal gyrus/superior temporal gyrus, in the right lingual gyrus and in the bilateral inferior temporal/fusiform gyri (voxel-level $p < 0.001$ and cluster-level $p < 0.05$, FDR-corrected).

Conclusions. Reduced reality-monitoring abilities were significantly associated with shorter right PCS and reduced GMV in temporal and parietal regions of the reality-monitoring network in schizophrenia patients with AHs.

Introduction

Reality monitoring is a crucial cognitive process in the daily life to differentiate memories of thoughts and imagination from memories of externally derived information [1]. For instance, this process allows us to determine whether an event was generated by our imagination or if it really did occur.

A deficit in the reality-monitoring abilities has been repeatedly observed in patients with schizophrenia compared with healthy individuals (e.g., [2]; for recent review, see [3]). More specifically, several studies have pointed out that patients with schizophrenia and auditory hallucinations (AHs) were more likely to misattribute internally generated stimuli as being perceived from the environment than patients with schizophrenia without AHs and healthy individuals ([4–6]; for review, see [7,8]). This tendency to misattribute imagined events as being perceived is called an externalization bias and is assumed to partly underlie AHs. Indeed, a prominent cognitive model of AHs suggests that they might arise from a misattribution of internal mental events such as inner speech as being externally perceived [9,10].

The neural network underlying reality-monitoring process has been explored in both healthy individuals and patients with schizophrenia in the literature. The prefrontal cortex (PFC), and particularly its medial and anterior part, was found to be a key structure of this network (for review, see [3,11]). Interestingly, a functional neuroimaging study has reported that the externalization bias was correlated with a reduced activation in this specific brain region [12]. In patients with schizophrenia, deficits in the neural activity of the medial PFC have been observed

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during reality-monitoring performances [13,14]. The medial PFC is not the only brain region that may account for the reality-monitoring process. Indeed, the contribution of temporoparietal areas, and particularly their abnormal overactivation, into the experience of externalization bias has been supported by neuroimaging studies [15] as well as noninvasive brain stimulation studies [16].

Although neuroimaging studies have broadly investigated brain activity linked to reality-monitoring performances, less is known about the neuroanatomical correlates of reality monitoring. In recent years, the morphology of a specific structure of the medial PFC, the paracingulate sulcus (PCS), has been investigated. The PCS is a tertiary sulcus that lies in the medial wall of the PFC and runs dorsal and parallel to the cingulate sulcus in a rostro-caudal direction. The PCS presents a great morphological variability within the general population, in that it can be found in none, one, or both hemispheres [17], and its presence affects the morphometry [18,19] and the cytoarchitectonic organization of surrounding cortices [20,21]. The PCS was found to be associated with a wide array of executive and cognitive functions [22], including reality monitoring [23]. Namely, healthy individuals with bilaterally absent PCS showed significantly reduced reality-monitoring performances compared with individuals with present PCS in at least one hemisphere [23]. In schizophrenia patients, some studies showed that reduced PCS length was associated with AHs [24,25]. However, the relationship between the PCS length and reality-monitoring performances remains unclear in patients with schizophrenia and AHs. Particular anatomical features in the medial PFC and specific morphology of the PCS could underpin the relationship between brain activity within these areas and reality-monitoring process.

The present study aimed to identify whether reality-monitoring performances were linked to specific neuro-anatomical features, including PCS length and gray-matter volume (GMV), in hallucinating patients with schizophrenia. Therefore, we conducted a magnetic resonance imaging (MRI) study combining an investigation of reality-monitoring performances, a morphological analysis of the PCS, and a whole-brain voxel-based morphometry (VBM) analysis. We hypothesized that reality-monitoring deficits, and particularly the externalization bias, will be negatively correlated with the PCS length. These hypotheses were based on three lines of work presented above showing that: (a) the absence of PCS is associated with poor reality-monitoring performances [23], (b) shorter PCS length is associated with AHs [24], and (c) AHs are associated with a specific deficit in reality monitoring: the externalization bias [8]. In addition, we hypothesized that poorer reality-monitoring performances, including higher externalization bias, would be associated with lower GMV in the brain regions that were identified as functionally involved in reality monitoring [11] and in the externalization bias [12] (e.g., the medial PFC).

Methods

Participants

Thirty-five patients meeting the DSM-IV-TR criteria for schizophrenia were recruited from our clinical unit for treatment-resistant schizophrenia at Le Vinatier Hospital between 2009 and 2015. All participants were native French speakers and presented daily treatment-resistant AHs, defined as persistent daily AHs despite an antipsychotic treatment at an adequate dosage for more than 6 weeks. Patients' diagnoses were assessed through a formal interview with a trained psychiatrist using the Mini-International Neuropsychiatric Interview [26]. Participants were assessed for the

severity of their symptoms using the Positive and Negative Syndrome Scale (PANSS) [27]. Patients' current antipsychotic medication classes (typical, atypical including clozapine, and combination of classes) were reported in Table 1. Written informed consent was obtained from all participants. All experiments were approved by a local ethic committee (CPP SUD EST VI, Clermont-Ferrand, France) and performed in compliance with relevant guidelines and regulations.

Reality-monitoring task

The task was divided in a presentation phase and a test phase, according to the task used and validated by Brunelin et al. [28]. Briefly, during the presentation phase, 16 words were presented one by one on a computer screen for 3 s, all preceded by an instruction also presented during 3 s. Instructions were "Imagine yourself hearing the following word" or "Listen to the following word." During the test phase, performed immediately after the presentation phase, a 24-word list was presented including the 16 words previously presented (8 imagined and 8 listened) and 8 new words (distractors). Patients had to determine the source for each word (i.e., "Imagined," "Heard," or "New"). Before the task, patients performed a short practice trial to acquaint with requirements of the task and to ensure for their good comprehension.

Three main outcomes were computed according to previous studies [29,30]. (a) Reality-monitoring accuracy was calculated using the following formula:

$$\frac{1}{2} \left(\frac{fii}{fih + fii} + \frac{fhh}{fhh + fhi} \right),$$

where fii is the number of imagined words that were correctly recognized as imagined, fih is the number of imagined words identified as being heard, fhh is the number of heard words correctly identified as heard, and fhi is the number of heard words identified as imagined. This measure of reality monitoring, also known as average conditional source identification measure [31], reflects the proportion of correct source judgments among the item correctly recognized as old. (b) The externalization bias was defined as the number of imagined words recognized as heard among all imagined words incorrectly judged (i.e., as new or heard). (c) Item memory accuracy was calculated as the standardized hit rate (z -score of hit rate, i.e., the proportion of old items identified as old) minus the standardized false alarm rate (z -score of false alarm rate, i.e., the proportion of new items identified as old). Before calculation, hit and false alarm rates were corrected to avoid the values of 0 and 1, as recommended by Snodgrass and Corwin [32]. This measure of item memory, also known as the Signal Detection Theory metrics' d' [33], reflects the sensitivity to discriminate between old and new items.

Magnetic resonance imaging acquisition

MRI acquisitions were performed on a 1.5-T Siemens Magnetom scanner. A 3D anatomic T1-weighted sequence covering the whole brain volume was acquired with the following parameters: 176 transverse slices, TR = 1,970 ms, TE = 3.93 ms, field of view = 256 mm², and voxel size = 1 mm³.

Paracingulate sulcus measurements

The PCS was measured following the measurement protocol described by Garrison et al. [25] (see Figure 1 as an example).

Table 1. Summary of demographic, clinical, and reality-monitoring measures and paracingulate sulcus (PCS) lengths of the 35 patients with schizophrenia and auditory hallucinations.

	N	Mean	SD	Range
Gender (men/women)	21/14			
Handedness (left/right)	4/31			
Age (years)		37.1	8.9	24–52
Education (years)		11.6	2.5	8–16
Duration of illness (years)		10.9	7.5	1–30
Antipsychotic medication				
Typical antipsychotics	14			
Atypical antipsychotics	31			
Including clozapine	12			
Combination of typical and atypical antipsychotics	10			
Positive and Negative Syndrome Scale ^a				
Positive ^a		71.6	14.7	45–110
Negative ^a		19.6	4.2	12–28
General psychopathology ^a		19.1	6.5	9–40
Reality-monitoring task				
Reality-monitoring accuracy		0.73	0.18	0.42–1
Externalization bias		0.41	0.36	0–1
Item memory accuracy d'		2.11	0.74	0.30–3.48
Total intracranial volume (mm ³)		1,496.3	150.1	1,229.0–1,921.9
Left PCS length (mm)		35.2	24.4	0–84.7
Right PCS length (mm)		21.6	20.8	0–78.5

Abbreviation: SD, standard deviation.
^aN = 34 (one missing data).

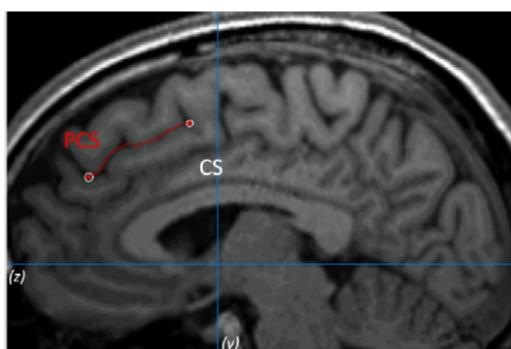


Figure 1. Example of the paracingulate sulcus (PCS) measurement on anatomical magnetic resonance imaging. The PCS is marked in red line and lies dorsal and parallel to the cingulate sulcus. Measurement was performed within the first quadrant (defined by $z < 0$ and $y > 0$) and on the fourth sagittal slice for both hemispheres.

To validate the procedure, inter- and intrarater reliabilities were calculated. See the Supplementary Material for more details.

Voxel-based morphometry analysis

All images were preprocessed and analyzed with the Computational Anatomy Toolbox (CAT, version 12.6; <http://www.neuro>

[uni-jena.de/cat/](http://www.neuro.uni-jena.de/cat/)) implemented in Statistical Parametric Mapping (SPM12) (Wellcome Trust Center for NeuroImaging, London, UK; <http://www.fil.ion.ucl.ac.uk/gate2.inist.fr/spm/software/spm12/>) using MATLAB (R2018a, MathWorks, Inc., Massachusetts, USA). Both processing and analysis were performed following the standard protocol (<http://www.neuro.uni-jena.de/cat12/CAT12-Manual.pdf>) with default settings, unless otherwise indicated. This method has been previously validated and provides a great compromise between good quality and speed of processing [34]. Prior to preprocessing, each image was visually inspected for artifacts. Then, T1 images were corrected for bias field inhomogeneities, segmented into gray matter, white matter, and cerebrospinal fluid, spatially normalized into a standard Montreal Neurological Institute (MNI) space using the DARTEL algorithm, and modulated to allow comparison of the absolute amount of tissue. A second quality control for intersubject homogeneity and overall image quality was achieved using the automated quality check protocol of the CAT12 toolbox. After quality check, the total intracranial volume of each subject was estimated to be used as covariate on the second-level analyses to take into account intersubjects brain size variations. Finally, images were smoothed using an 8-mm Full Width-Half Max (FWHM) kernel.

Statistical analyses

Statistical analyses were conducted using R software (version 3.5.2) [35]. Normality of the data was tested using the Shapiro–Wilk test. Partial Spearman's rank correlations were calculated to assess the

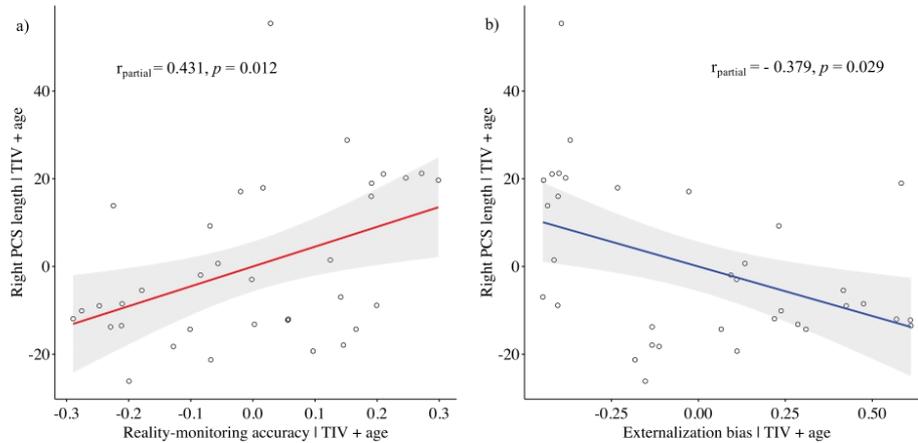


Figure 2. Scatter plots showing the partial correlations between the paracingulate sulcus length in the right hemisphere and (A) reality-monitoring accuracy and (B) the externalization bias, controlling for total intracranial volume and age ($n = 35$).

relationship between PCS lengths (separately for each hemisphere) and outcomes of the reality-monitoring task (reality-monitoring accuracy, externalization bias, and item memory), with total intracranial volume and age as confounding variables. For all analyses, a significance level of $p < 0.05$ was employed. As exploratory analyses, we investigated whether PCS lengths were also related to total positive symptoms, by computing partial Spearman's rank correlations between PCS lengths and total PANSS positive scores, with total intracranial volume and age as confounding variables.

VBM statistical analyses were performed with the CAT12 toolbox (version 12.6). A multiple linear regression model was used to test for voxel-wise correlations between GMV and reality-monitoring outcomes. Total intracranial volume and age were used as confounding covariates in these analyses. A 0.1 absolute masking threshold was applied to avoid artifact on the gray/white matter limit. For all voxel-based analyses, we thresholded statistical maps with an uncorrected $p < 0.001$ at voxel level and with an false discovery rate (FDR)-corrected $p < 0.05$ at the cluster level. Significant clusters were labeled using the Anatomical Automatic Labelling in SPM.

Results

Patients' demographic and clinical characteristics, as well as reality-monitoring outcomes, total intracranial volumes, and PCS lengths for each hemisphere, are presented in Table 1. Details on patients' scores at each individual item of the PANSS positive subscale are provided in the Supplementary Material.

Reality monitoring and PCS length

While controlling for age and total intracranial volume, the PCS length was positively correlated with reality-monitoring accuracy in the right hemisphere (Spearman's partial $\rho = 0.431$, $p = 0.012$; Figure 2A) but not in the left hemisphere (Spearman's partial $\rho = 0.052$, $p = 0.773$). There was a significant negative correlation between the length of the right PCS and the externalization bias (Spearman's partial $\rho = -0.379$, $p = 0.029$; Figure 2B), but no

significant correlation was found for the left PCS length and the externalization bias (Spearman's partial $\rho = 0.171$, $p = 0.340$). No significant correlations were found between PCS lengths and item memory (for the right PCS: Spearman's partial $\rho = 0.137$, $p = 0.448$; for the left PCS: Spearman's partial $\rho = -0.003$, $p = 0.988$).

Exploratory analyses revealed no significant correlations between PCS lengths and total PANSS positive scores (for the right PCS: Spearman's partial $\rho = -0.021$, $p = 0.908$; for the left PCS: Spearman's partial $\rho = -0.108$, $p = 0.555$).

Reality monitoring and GMV

VBM analysis revealed a significant positive correlation between reality-monitoring accuracy and GMV in the right angular gyrus (peak MNI coordinates [23 -59 44], $t = 4.03$, $p < 0.001$; see Table 2 and Figure 3A).

The analysis also revealed a significant negative correlation between the externalization bias and GMV in a cluster encompassing the left supramarginal gyrus and the left superior temporal gyrus ([-60 -42 24], $t = 4.83$, $p < 0.001$), in the right lingual gyrus ([15 -51 -3], $t = 4.71$, $p < 0.001$), and both in the left and the right inferior temporal gyrus and fusiform gyrus (respectively, [-46 -33 -26], $t = 4.60$, $p < 0.001$, and [48 -33 -24], $t = 4.48$, $p < 0.001$; Table 2 and Figure 3B).

Additional VBM analyses revealed a significant negative correlation between item memory and GMV in the right superior frontal gyrus (peak MNI coordinates [26 45 22], $t = 4.57$, $p < 0.001$; Table 2).

Discussion

The present study sought to identify the neuroanatomical correlates of reality monitoring in a sample of schizophrenia patients with AHs. We reported two main findings: (a) the right hemisphere PCS length was positively correlated with reality-monitoring accuracy and negatively correlated with the externalization bias, that is, the misattribution of imagined words to an external source, and (b) the reality-monitoring accuracy was positively correlated with

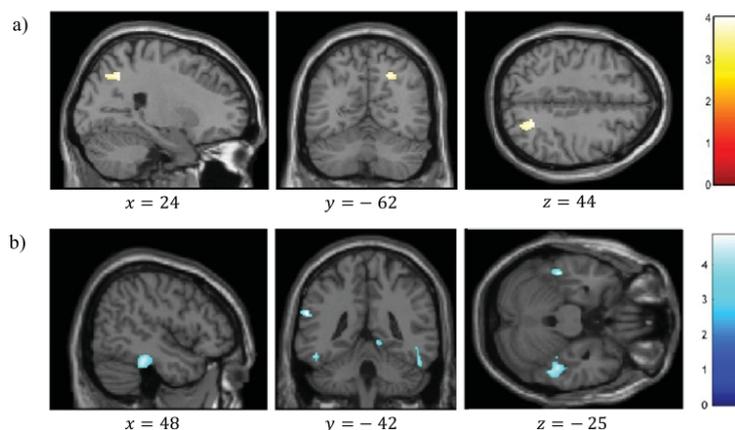


Figure 3. Voxel-based morphometry analysis of correlation between gray-matter volumes and reality-monitoring performances, corrected for total intracranial volume and age ($n=35$). Results are reported using z -values presented in the SPM canonical single subject template with MNI coordinates of the section. Regions that survived a statistical threshold of $p < 0.001$ at the peak-level (FDR-corrected $p < 0.05$ at the cluster level) are shown in (A) for positive correlation with reality-monitoring accuracy and (B) for negative correlation with externalization bias.

Table 2. Clusters showing significant correlations between gray-matter volume and reality-monitoring measures ($n = 35$).

Reality-monitoring scores	Correlation	Anatomical regions	Cluster size	Coordinates (mm)			
				x	y	z	t-value
Reality-monitoring accuracy	Positive	Right angular gyrus	175	23	-59	44	4.03
Externalization bias	Negative	Left supramarginal gyrus/superior temporal gyrus	88	-60	-42	24	4.83
		Right lingual gyrus	236	15	-51	-3	4.71
		Left inferior temporal gyrus/fusiform gyrus	189	-46	-33	-26	4.60
		Right inferior temporal gyrus/fusiform gyrus	540	48	-33	-24	4.48
Item memory	Negative	Right superior frontal gyrus	185	26	45	22	4.57

Note: Statistical threshold of $p < 0.001$ at the peak-level and FDR-corrected $p < 0.05$ at the cluster level.

the GMV in the right angular gyrus, whereas the externalization bias was negatively correlated with the GMV in a set of temporal and parietal areas.

We demonstrated a significant correlation between the reality-monitoring abilities of hallucinating patients with schizophrenia and the length of the PCS in the right hemisphere: the shorter the PCS, the poorer the reality-monitoring accuracy and the greater the externalization bias. On the one hand, these results are highly coherent with those found in healthy subjects associating the absence of PCS with worse overall reality-monitoring accuracy [23]. On the other hand, the region containing the PCS has been associated with both AHs and reality-monitoring abilities [23–25]. Moreover, a recent study has demonstrated that this region causally supports reality monitoring. In healthy subjects, active real-time fMRI neurofeedback training of the paracingulate cortex has been reported to improve the reality-monitoring accuracy for imagined items as well as the functional activity of the paracingulate cortex [36]. If the relationship between the PCS morphology and the functional role of the paracingulate cortex remains unclear, taken together these findings suggest that the PCS morphology may be the structural basis for the causal role of the paracingulate cortex in

reality-monitoring abilities and hallucinations. Indeed, the PCS morphology is known to influence the topography of the medial PFC [21] and to generate a great interindividual variability on the location of the neural activity evoked in the medial PFC during a given cognitive task in healthy subjects [37]. Future fMRI studies should consider this morphological variability when reporting differences in brain activity in the medial PFC during reality-monitoring paradigms. The differences in medial PFC activity observed at the group level during a reality-monitoring task could reflect a different location of the neural activity due to intersubject differences in the PCS morphology. Taking into account this neuroanatomical feature when studying functional patterns of reality monitoring would provide more reliable evidence of a deficit in populations experiencing AHs.

It is noteworthy that the PCS is one of the latest sulci to develop in utero, appearing at the 36th week of ontogeny and maturing to the perinatal period for human [22,38]. This sulcus is thus exposed to environmental factors able to interfere with its development. The reality-monitoring impairment found to be correlated with the PCS length may thus result from defective neurodevelopmental mechanisms. In this line, abnormal reality-monitoring performances

have also been observed before the onset of frank psychotic episode in individuals at risk for schizophrenia within the continuum of psychosis [39]. A deeper investigation of the sulcal ontogeny, and even more of the developmental factors that may influence the PCS morphometry could improve the understanding of its relationship with reality-monitoring deficits.

Consistent with the right lateralization of our findings, a recent study found a reduction of the PCS length only in the right hemisphere of both psychotic and nonclinical voice hearers [40], suggesting the right PCS length reduction to be a specific marker of AHs whatever the clinical condition. By contrast, some studies identified bilateral PCS reductions in schizophrenia patients with AHs as compared with schizophrenia patients without AHs, non-clinical subjects with AHs, and healthy controls [24,25], and some others found specific left PCS reduction in schizophrenia patients with AHs as compared with those without AHs, and healthy controls [41]. Further studies are thus needed to clarify if the length of the right PCS may be considered as a specific neuroanatomical marker of AHs or if the bilateral PCS is only reduced in schizophrenia patients with AHs.

Surprisingly, reality-monitoring performances did not correlate with GMV in medial frontal areas. Yet, the functional capacity of the medial PFC has been largely involved in the reality-monitoring process in both patients with schizophrenia and healthy individuals [13,42], and reduced GMV has been observed in these brain areas in patients with schizophrenia [43]. In addition, the presence/absence of PCS has been associated with GMV in the surrounding frontal regions, and these volumetric changes were related to reality-monitoring performances [23]. Further studies are now needed to investigate a potential relationship between the PCS variability and the surrounding prefrontal volume and its implication on the prefrontal functional capacity during reality monitoring.

As we hypothesized, most of the regions for which the GMV correlated with reality-monitoring performances correspond to the temporoparietal areas previously identified by functional imaging during reality-monitoring tasks. We found several brain structures whose GMVs negatively correlate with the externalization bias, indicating that schizophrenia patients with AHs with reduced GMV in these structures are more likely to misattribute internally generated information to an external source.

First, we observed a negative correlation between the externalization bias and a cluster encompassing the left supramarginal gyrus and the left superior temporal gyrus, which is considered as a part of Wernicke's area (BA 40) involved in auditory and speech processing. Disruption to this system would induce an inadequate treatment of the verbal items presented in reality-monitoring tasks and participate to patients' misattributions of source. In addition, a recent meta-analysis on motor agency specifically highlighted the left BA 40 as an integral part of the body-ownership network [44]. This cluster can thus be considered as an element of both verbal and nonverbal self-production recognition, suggesting its modality-general implication in reality-monitoring processes. Consistently, the GMV and activity of this temporoparietal region have also been associated with AHs in schizophrenia patients [45–47]. The causal implication of temporoparietal regions in reality monitoring has finally been demonstrated by noninvasive stimulation over this region that modulated the externalization bias in both healthy subjects and schizophrenia patients and alleviated AHs in schizophrenia patients [16, 48–50].

The VBM analysis also revealed negative correlations between the externalization bias and gray matter in several posteroinferior temporal regions. Considered as associative visual areas, these

structures have mainly been associated with visual processing and visual hallucinations [47,51,52]. For now, the implications of the correlation between their GMV and externalization bias in our semantic task are unclear, and future studies should clarify the relationship between reduced GMV in these areas and the incorrect source attributions observed in schizophrenia patients with AHs. However, a substantial body of functional studies has already reported an activation of the right lingual gyrus during Theory-of-Mind tasks, involving among other things to make the distinction between internal and external space [53]. On its side, the left inferior temporal gyrus has been shown to specifically activate in the reality-monitoring contrast “correct attributions” versus “mis-attributions” in healthy participants [54].

We identified a significant positive correlation between the reality-monitoring accuracy and the GMV of the right angular gyrus. This result replicates in a population of schizophrenia patients with AHs the results reported by Buda *et al.* [23] in a sample of healthy subjects. The right angular gyrus is engaged in a wide range of tasks reflecting our ability to discriminate the internal from external environment, such as Theory-of-Mind or agency attribution tasks [55,56]. Moreover, several case reports described its causal involvement in out-of-body experiences, a phenomenon referring to an autoscopic experience during which the subject perceive the world from an out-of-body position [57,58]. In this way, our findings contribute to define the right angular gyrus as a pivotal neural locus for the distinction between the self and the external world. Its increased GMV may underlie its overactivity and in turn sustain decreased reality-monitoring performances in schizophrenia patients with AHs.

In addition to the sample size that could be considered as limited for correlation analyses (estimated post hoc power of 0.75), the main limitation of this study is the lack of comparison groups. Additional groups of healthy participants, healthy voice hearers, and patients with schizophrenia without AHs would have allowed us to determine if the structural correlates of reality monitoring are specific to schizophrenia or if they could be expanded to the global population. However, despite this limitation, our study has the advantage of investigating reality monitoring in a homogeneous sample of patients with severe daily treatment-resistant AHs, as compared with mixed samples of patients with heterogeneous symptoms that are usually enrolled in the literature. The particularity of our patient sample in terms of treatment resistance and severity of AHs might also contribute to the differences in the right PCS length observed between our study and other studies including patients with AHs [24,25,41]. Second, the question of the specificity of findings reported in the current study remains open. VBM findings suggested that reality-monitoring performances and item memory were linked to GMV changes in different brain regions. In addition, the PCS length seems to be specifically linked to reality-monitoring performances, that is, to reality-monitoring accuracy and externalization bias, but not to item memory or total positive symptoms. However, further investigations might assess whether reality monitoring might be related to other sulci. Third, one could question how the PCS, which can be considered as a static brain structure, could be related to a dynamic process such as reality monitoring. Although the PCS is expected to remain stable after its maturation during perinatal period, some PCS length changes over time have been described in a longitudinal study with adolescent onset psychosis [59]. Nevertheless, the observed correlation of reality-monitoring outcomes and PCS lengths does not necessarily imply that the PCS length is the only anatomical substrate for reality-monitoring deficits (and the emergence of AHs). Rather, we could

hypothesize a two-hit process with a reality-monitoring deficit that predates the emergence of AHs, since reality-monitoring deficits are also reported in people with an at-risk mental state for psychosis and unaffected relatives of patients with schizophrenia [39], and which might be linked to the PCS length, and a second phase of aggravation of reality-monitoring deficits, together with other neuro-anatomical features, such as GMV alterations.

In summary, this study demonstrated that reality-monitoring performances correlated with both the PCS morphology and the GMV in crucial brain regions engaged in the reality-monitoring neural network in patients with schizophrenia. If the exact relationship between the structural evidence that we have highlighted and their functional implications remains little known, these correlations propose some anatomical substrates for the observed reality-monitoring errors in schizophrenia patients with AHs. Such associations would lead future studies to clarify the relationship between the PCS and GMV variability and reality-monitoring abilities. Finally, further research work should investigate if similar structural features would be associated with AHs in nonclinical hallucinating individuals or if they specifically characterize AHs in schizophrenia.

Supplementary Materials. To view supplementary material for this article, please visit <http://dx.doi.org/10.1192/j.eurpsy.2021.2234>.

Data Availability Statement. The data that support the findings of this study are available from the corresponding author, M.M., upon reasonable request.

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Conflicts of Interest. The authors declare none.

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Supplementary Material

Methods

Paracingulate Sulcus measurements

The paracingulate sulcus (PCS) was measured using Mango brain visualization software (version 4.0.1; <http://ric.uthscsa.edu/mango>) following the measurement protocol described by Garrison et al. (Garrison et al., 2015). T1 images were individually straightened in an orthonormal landmark and the anterior and posterior commissures (AC and PC) were aligned on the same horizontal plane. In the sagittal plane, the origin of the landmark was reset to the AC location and PCS were measured within the first quadrant delineated by $y > 0$ and $z < 0$ (Figure 1). The first step of sulcus identification was to locate the cingulate sulcus on a sagittal slice. It is the first major sulcus running in an anterior-posterior direction, dorsal to the corpus callosum and visible on 5 sagittal slices at least. PCS is defined as a salient sulcus running parallel, horizontal and dorsal to the cingulate sulcus and present on 3 sagittal slices at least. Using ‘trace line’ function, PCS was measured on a sagittal slice, 4 mm to the left or right of the medial line ($x = \pm 4$), from the point at which the sulcus ran in a posterior direction to its end point which is possibly out of the first quadrant. Segments of discontinuous PCS were measured only if they started within the first quadrant and were separated by less than 20mm in length.

Intra- and inter-rater reliabilities for the PCS measurement

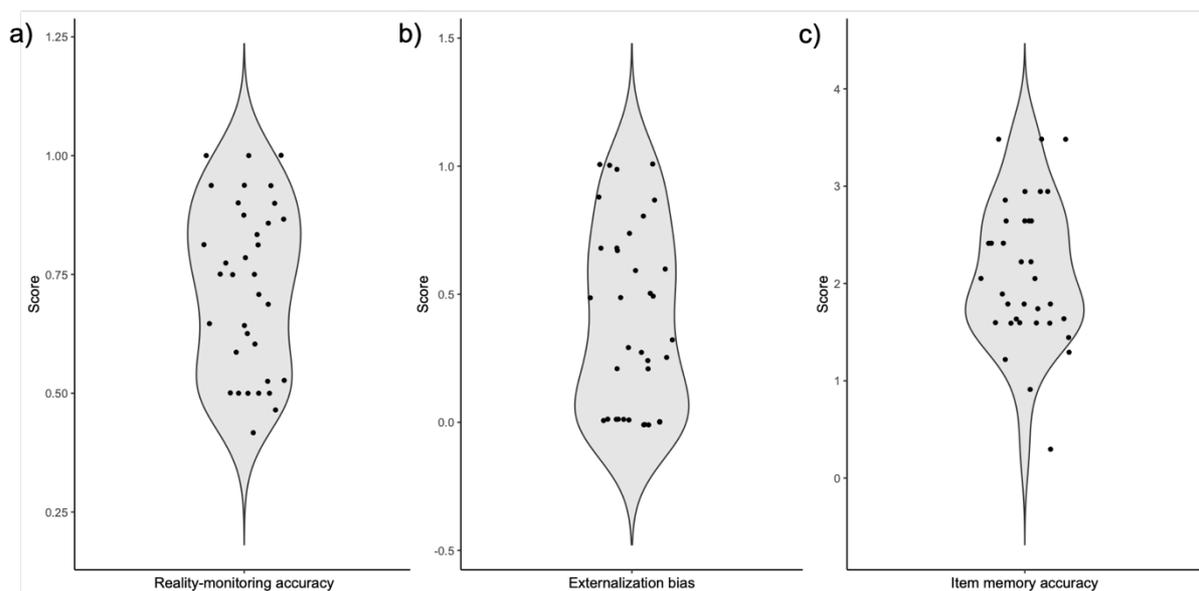
To validate the PCS measurement procedure, the rater who completed all PCS measurements (MP) repeated the PCS measurement for 16 randomly chosen subjects (32 hemispheres). In addition, each PCS of the 35 participants was independently measured by a second rater. Both raters were blind to patients details at all times during measurements. Intra- and inter-rater reliabilities assessed using intraclass correlation coefficients were respectively 0.908 (IC 95% [0.822; 0.954]) and 0.819 (IC 95% [0.724; 0.883]). Intraclass correlation coefficients values between 0.75 and 0.9 indicate a good reliability and values greater than 0.9 indicate an excellent reliability (Koo and Li, 2016).

Supplementary Table 1. Details on patients' scores at each individual item of the PANSS-positive subscale *

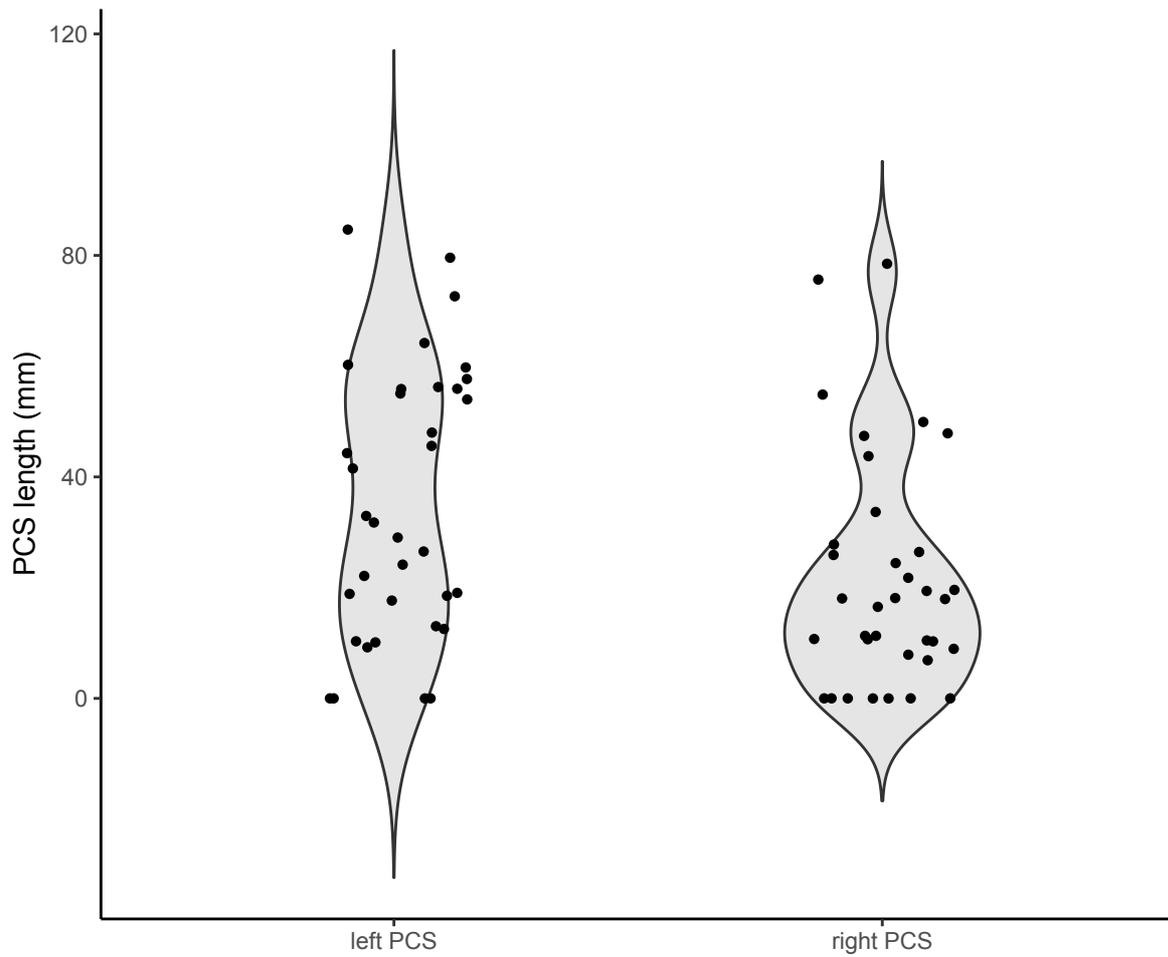
	Mean	SD	Range
PANSS-P1: Delusions	3.97	1.27	1 - 6
PANSS-P2: Conceptual disorganization	2.50	1.46	1 - 6
PANSS-P3: Hallucinatory behavior	5.85	0.86	4 - 7
PANSS-P4: Excitement	1.32	0.88	1 - 5
PANSS-P5: Grandiosity	1.62	1.21	1 - 6
PANSS-P6: Suspiciousness / persecution	3.15	1.11	1 - 5
PANSS-P7: Hostility	1.18	0.63	1 - 4

PANSS = Positive And Negative Syndrome Scale; SD = standard deviation. *PANSS items are rated on a 7-point scale (1=absent, 2=minimal, 3=mild, 4=moderate, 5=moderate severe, 6=severe, and 7=extreme).*

* N = 34 (one missing data)



Supplementary Figure 1. Violin plots of the distribution of outcomes at the reality-monitoring task in the sample of 35 patients with schizophrenia and auditory hallucinations. Outcomes include: a) reality-monitoring accuracy calculated as the proportion of correct source recognition among the items correctly recognized as old, averaged across both sources (imagine and heard); b) externalization bias, defined as the number of imagined items recognized as heard among all imagined items incorrectly judged (*i.e.*, judged as new or heard); and c) item memory accuracy, calculated by subtracting the standardized false alarm rates (*i.e.*, the proportion of new items identified as old) from the standardized hit rates (*i.e.*, the proportion of old items identified as old).



Supplementary Figure 2. Violin plots of the distribution of paracingulate sulcus (PCS) length for each hemisphere in the sample of 35 patients with schizophrenia and auditory hallucinations. PCS lengths are expressed in mm.

7.5. Are psychological debriefing groups after a potential traumatic event suitable to prevent the symptoms of PTSD? [Article 9]

*Article 9: Are psychological debriefing groups after a potential traumatic event suitable to prevent the symptoms of PTSD? Psychiatry Research. 2022. Vignaud P., **Lavallé L.**, Brunelin J., Prieto N.*



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Are psychological debriefing groups after a potential traumatic event suitable to prevent the symptoms of PTSD?

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ABSTRACT

Psychological debriefing is a psychotherapeutic approach developed for early intervention in civilians and professionals who have to cope with a potential traumatic event (PTE). Although initial works claimed that this approach may decrease symptoms of posttraumatic stress disorder (PTSD), some studies have concluded that the clinical benefits of psychological debriefing were limited. Several methodological variations could explain the discrepancies observed among studies. Among these variations, how the approach is administered to participants should have importance, and clinical evidence suggests that debriefing groups instead of individuals could have a beneficial clinical effect. We conducted a systematic search of the literature investigating the clinical effects of psychological debriefing groups on PTSD symptoms after a PTE according to the PRISMA guidelines. Among the 790 articles found, 11 met our inclusion criteria. Most of these articles did not support any beneficial effect of psychological debriefing groups on PTSD symptoms. A large number of methodological variations that may influence the outcomes of these studies were observed. Psychological debriefing groups did not seem efficient in alleviating PTSD symptoms. Further studies of high methodological quality are needed to elucidate the effect of psychological debriefing groups on specific PTSD symptoms and on nonspecific symptoms.

1. Introduction

Posttraumatic stress disorder (PTSD) is among the most debilitating chronic psychiatric diseases. PTSD can last for years and is often comorbid with other psychiatric disorders, especially mood disorders, anxiety disorders and substance use disorders (Kessler, 1995), leading to a general burden and high socioeconomic costs. Depending on socio-demographic features, such as the income of the country of residence, the lifetime prevalence of PTSD varies from 1.3 to 12.2% and from 0.2 to 3.8% within 12 months after a potentially traumatic event (PTE) (Koenen et al., 2017). PTSD classically arises after individuals face a PTE. An event can be qualified as a PTE when a person is exposed to death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence (American Psychiatric Association, 2013). It has been reported that the lifetime prevalence rate of exposure to PTEs in the general population is over 70%, and 30.5% of people will be exposed to at least 4 PTEs in their lives (Benjet et al., 2016).

To decrease the occurrence of PTSD in individuals who have faced a

PTE, several approaches have been developed. Historically, the first structured intervention to be proposed was the Critical Incident Stress Debriefing (CISD). The CISD is a brief group intervention that lasts for less than 2 h and was developed for groups of rescuers in 1983 (Mitchell, 1983). It is classically composed of 7 different phases: (1) introduction, where the debriefers explain the goal and process of the debriefing, (2) facts, where each participant in the debriefing describes his or her position during the event, (3) thoughts, where each participant describes what he or she thought during the event, (4) reaction phase, where emotional reactions and feelings are explored, (5) symptoms phase, which allows each participant to describe his or her physical, emotional, behavioral reactions since the PTE occurred, (6) teaching, in which the debriefers provide information on common reactions after a PTE, and (7) re-entry phase, in which a summary of the process is provided by one debriefer. If administered to children, the intervention may include some adaptations, such as the use of drawings or role playing, to facilitate expression and communication. It focuses on people directly exposed to a PTE. It differs from psychotherapy, as it is a short and early

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intervention, it principally does not target any clinical population but anyone exposed to a PTE, and it seeks help before the potential occurrence of PTSD.

Since its first implementation, psychological debriefing (PD) has been widely used and extensively modified. For instance, individual debriefing, which was thought to facilitate the inclusion of participants in clinical studies, was proposed instead of group debriefing. This approach has also been proposed not only to rescuers but also to victims, to people exposed to repeated PTEs or to a unique event, etc. The clinical usefulness of PD has also been regularly evaluated in clinical trials with various methodologies, outcomes and targeted populations, leading to conflicting findings. Although some studies reported that PD might decrease the occurrence of PTSD, others reported that PD has no preventive effect (Lee et al., 1996) or even that individual PD might increase the occurrence of PTSD (Bisson et al., 1997). In a meta-analysis of studies evaluating the effectiveness of PD after a PTE, Rose and colleagues reported that PD had no beneficial effect on either the specific symptoms of PTSD or other nonspecific psychiatric symptoms that may occur after a PTE, such as depression and anxiety (Rose et al., 2002). Following these works, it was suggested that PD not be systematically offered to victims in clinical settings after a PTE. It was recommended to wait at least 2 weeks after the PTE and to propose therapy only for those who sought help and who presented specific or nonspecific PTSD symptoms (Forbes et al., 2007; Roberts et al., 2009).

However, these recommendations should be considered with caution. Actually, when considering the studies on PD in detail, it should be acknowledged that debriefing has often been practiced in inappropriately. As examples, debriefing was administered to participants even if the event they had to cope with did not fully meet the definition of a PTE (Lee et al., 1996); PD was administered by debriefers who were either not sufficiently trained in the intervention or who were trained but did not have a background in mental health (Carlier et al., 1998; Mayou et al., 2000). More critically, PD was administered at an individual level, although it was designed to be a group intervention (Bisson et al., 1997; Conlon et al., 1999; Lee et al., 1996; Sijbrandij et al., 2006). Administering PD at an individual level instead of at a group level is an important methodological variation that may have influenced clinical outcomes and thus limits the conclusions that can be drawn from the previous meta-analyses. In a nonsystematic review of studies investigating the efficacy of group intervention after a PTE, Prieto and colleagues highlighted that PD could be affect PTSD symptoms and nonspecific symptoms under the condition that PD was administered to a group and not at an individual level (Prieto et al., 2010). They also suggested that applying a PD intervention that is close to the original CISM intervention proposed by Mitchell and colleagues may lead to better outcomes (Prieto et al., 2004).

Following these observations, we proposed to conduct a systematic and critical evaluation of studies where witnesses or victims received psychological debriefing intervention in psychological debriefing groups (PDGs) after a PTE. The aim of this review is therefore to perform a systematic inventory of empirical studies to assess the impact of psychological debriefing groups (PDGs) on PTSD symptoms and to evaluate their methodological quality.

2. Material And methods

A systematic review was conducted following the recommendations of the *preferred reporting items for systematic reviews and meta-analyses* (PRISMA) guidelines (Liberati et al., 2009).

2.1. Eligibility

The inclusion criteria were as follows: i) full-length original articles published in the English language and in peer-reviewed journals; ii) studies that included a control group; iii) participants were directly exposed to a PTE according to the DSM-IV and DSM-5 criteria; iv) PDG

was provided or at least offered to the victims; v) quantitative assessment was performed or the participants fulfilled standardized psychometric scales; and vi) specific symptoms of PTSD were evaluated. There were no age restrictions for inclusion and no time limit between the PTE and PDG.

Studies were excluded from the qualitative synthesis when the following criteria were identified: i) only individual debriefing was provided; and ii) the article was a literature review, letter to the editor or case report.

2.2. Research strategy

We conducted a systematic search in the PubMed, PubPsych and PsycINFO databases until October 2020 using the following MESH words with no limitation of date: ("debriefing" AND "Crisis Intervention"[Mesh]) AND (("Stress Disorders, Traumatic, Acute"[Mesh]) OR ("Stress Disorders, Post-Traumatic"[Mesh])). We also examined the citation lists of the identified publications for additional studies and used the related article function of the PubMed database for other relevant sources of data. Two investigators (PV and LL) independently screened the title, abstract and key words of each reference identified by the search and applied the inclusion and exclusion criteria. For each potentially eligible reference, the same procedure was applied to the full-text article. Discrepancies between the reviewers were resolved via discussion with a third investigator (NP).

2.3. Data extraction

Two investigators (PV and LL) independently extracted the following data (when available): i) the type of traumatic event and the category of victims (civilians or trained staff); ii) demographic data (number of participants, age, sex); iii) characteristics of PDG including the delay between PTE exposure and PDG, the level of expertise of the debriefing practitioner, the group cohesion (i.e., whether participants from the group knew each other before the PTE); and iv) psychometric scales used as study outcomes.

2.4. Quality assessment

The quality of each study was assessed with the QualSyst checklist, which is used to assess the quality of quantitative studies. The QualSyst checklist evaluates the quality of research by encompassing a broad range of methodological criteria and was found to have high reliability (Kmet et al., 2004). This is a 14-item checklist allowing the assessment of research questions, objectives, study design, subject and comparison group, definitions of outcomes, sample size, analytic methods, confounding factors and reports of results. The items were scored depending on the degree to which the specific criteria were met ("yes" = 2, "partial" = 1, "no" = 0). A summary score was calculated for each article by summing the total score obtained across relevant items and dividing it by the total possible score (i.e., 28 - (number of "n/a" X 2)). One reviewer carried out full quality assessments (QualSyst), and a 25% random sample was extracted and evaluated by a second reviewer (NP). In case of discrepancies, these issues were resolved by a third reviewer (JB).

2.5. Data analysis

Due to the large discrepancies between the design and methods of the included studies (type of PTE, type of the participants, delay between the PTE and the PDG, assessed outcomes, type of control group), it was not possible to conduct a reliable meta-analysis. By combining the 5 studies that provided the necessary material to run a meta-analysis (i.e., Pre/post means and SD values in the group debriefing and in the control group): Thabet et al., 2005; Adler et al., 2008; Wu et al., 2011; Tuckey et al., 2014; Tarquinio et al., 2016, we observed a very high between studies heterogeneity ($I^2=99.76\%$, Q p-value < 0.0001). We therefore

choose to conduct a qualitative synthesis of the literature and to not report results from the meta-analysis.

3. Results

3.1. Search results and eligibility

As shown in Fig. 1, 790 articles were identified in the databases, and 66 full-text articles were read after the exclusion of duplicates. Among the 66 full-text articles read, 55 articles were excluded. Thus, 11 articles fulfilled all the inclusion criteria and were eligible for quality assessment and qualitative review.

3.2. Quality assessment

The overall methodological quality of the 11 retrieved articles was estimated to be between 0.5 and 0.96 (possible scores ranged from 0.0 to 1.0). The mean methodological quality score was 0.76. The study by Wu et al., 2012 had the highest methodological quality (0.96), followed by the study by Adler et al., 2009 (0.88). When paying more attention to the QualSyst score, the included studies could be divided into 2 categories: the oldest studies until (Matthews, 1998) had a QualSyst score < 0.7, whereas all the more recent studies had higher scores (Table 1).

3.3. Qualitative synthesis

To report the results of the included studies more clearly, we sorted them into 3 categories: i) studies where the PDG was provided more than one month after PTE exposure in civilians; ii) studies where the PDG was provided within one month following PTE exposure in civilians; and iii) studies where the PDG was provided within one month following PTE exposure in rescue professionals and soldiers.

3.3.1. Studies where the PDG was provided more than a month after PTE exposure in civilians

In a controlled study, Stallard and colleagues included a group of students who witnessed a bus accident. PDG was administered 90 days after the PTE. The clinical impact of PDG on PTSD symptoms was assessed with the Impact of Event Scale (IES-R) in 5 participants. The authors found a significant effect of the PDG on the IES score ($t = 6.73$, $p < 0.01$) (Stallard and Law, 1993). Chemtob and colleagues assessed the clinical efficacy of a PDG administered 6 months after people from Hawaiian Island faced Hurricane Iniki in 1992. In this partly controlled study, PTSD symptoms in two groups of 25 and 18 participants were evaluated using the IES before and after PDG. To provide partial control of the passage of time, the second group was pretested when the first group was retested. After the PDG, participants from the two groups had a lower IES score than at baseline ($F_{(1,40)} = 21.13$; $p < 0.001$), with no significant difference between groups ($F_{(1,40)} = 2.62$; $p > 0.11$) (Chemtob et al., 1997). Chemtob and colleagues developed a second study in a pediatric sample. After a screening step, children identified as having developed PTSD symptoms 2 years after a PTE were allocated to therapeutic intervention groups. In a randomized controlled design, they received either a group intervention ($n = 176$) or an individual treatment ($n = 73$). Participants reported a significant reduction in self-reported trauma symptoms, as assessed with the Kuai Recovery Inventory (KRI) ($F_{(1,200)} = 51.34$; $p < 0.001$). However, no significant differences were observed between the group and individual interventions ($F_{(1,200)} = 1.97$; $p = ns$). PTSD symptoms were assessed with the Children PTSD Reaction Index (CRI) in a subsample of 21 treated children and 16 controls. A significant decrease in PTSD symptoms was observed in the treatment group compared to controls ($t_{34} = 2.76$; $p = 0.01$) (Chemtob et al., 2002).

3.3.2. Studies where the pdg was provided within one month following the pte in civilians

In a nonrandomized controlled study, Matthews and colleagues evaluated PTSD symptoms in care workers who experienced a PTE in

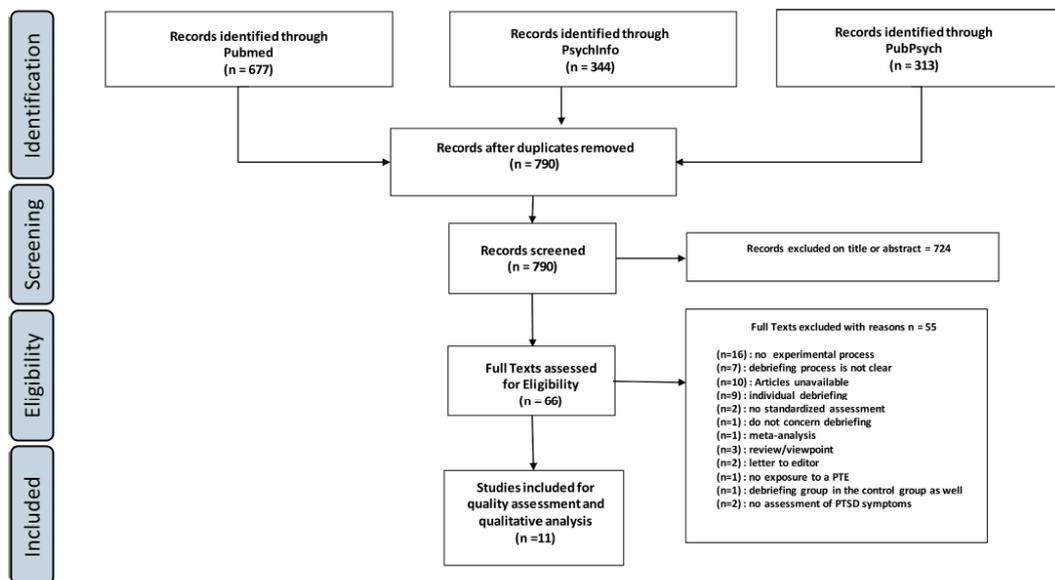


Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

Table 1
Quality assessment of studies with the QualSyst method.

Studies	Tarquinio et al., 2016	Tuckey et al., 2014	Wu et al., 2012	Adler et al., 2009	Adler et al., 2008	Thabet et al., 2005	Chemtob et al., 2002	Deahl et al., 2000	Matthews et al., 1998	Chemtob et al., 1997	Stallard et al., 1993
Criteria yes (2); partial (1); No (0); N/A											
1) Question / objective sufficiently described?	2	2	2	2	2	2	2	2	2	1	1
2) Study design evident and appropriate?	2	2	2	2	2	2	1	2	0	1	1
3) Method of subject/ comparison group selection or source of information/input variables described and appropriate?	1	2	2	2	2	1	2	2	1	1	2
4) Subject (and comparison group, if applicable) characteristics sufficiently described?	2	1	1	1	1	2	1	2	1	1	2
5) If interventional and random allocation was possible, was it described?	2	2	2	2	1	NA	2	2	NA	0	0
6) If interventional and blinding of investigators was possible, was it reported?	0	0	2	0	0	0	NA	2	NA	NA	0
7) If interventional and blinding of subjects was possible, was it reported?	NA	NA		NA	NA	NA	NA	NA	NA	NA	N/A
8) Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? Means of assessment reported?	1	2	2	2	2	2	2	2	2	2	2
9) Sample size appropriate?	1	1	2	2	2	1	2	1	1	1	1
10) Analytic methods described/ justified and appropriate?	2	2	2	2	2	2	2	2	1	2	0
11) Some estimate of variance is reported for the main results?	2	2	2	2	2	2	2	2	2	1	1
12) Controlled for confounding?	2	0	2	2	2	2	1	1	0	0	0
13) Results reported in sufficient detail?	2	2	2	2	2	2	1	0	2	1	1
14) Conclusions supported by the results?	2	2	2	2	2	2	1	2	1	2	2
Total	21	19	25	23	22	20	19	22	13	13	13
QualSyst Score	0.81	0.73	0.96	0.88	0.85	0.83	0.79	0.85	0.59	0.54	0.5

their workplace. The study was divided in 2 areas of inclusion. In the first inclusion area, where a PDG was offered but not mandatory, one group received the proposed debriefing intervention ($n = 14$), while a control group (control group 1, $n = 18$) did not take part in any debriefing. In the second inclusion area, where PDG was not available, a second control group (control group 2, $n = 31$) also completed the survey. The PTSD symptoms assessed with an adapted short version of the Impact of Event Scale (IES) were higher in control group 2 than in the other two groups. In the area where PDG was available, PTSD symptoms were higher in the debriefing group (Mann-Whitney $U = 340$; $p = 0.04$) (Matthews, 1998). In a randomized controlled study, Tarquinio and colleagues (Tarquinio et al., 2016) compared the clinical relevance of PDG ($n = 23$) with 2 groups of eye movement desensitization reprocessing (EMDR, $n = 37$), administered at 2 different time points. The authors found that early recent event protocol - RE-EMDR (provided up to 48 h post PTE, $n = 19$) and delayed RE-EMDR (provided between 48 h and 96 h post PTE, $n = 18$) decreased the PTSD symptoms as assessed with the PCLS at 3 months follow-up, without any difference between both groups (PCLS total: RE-EMDR 31.5 (+/- 4.1) $p < 0.0001$; delayed RE-EMDR 36.6 (+/- 3.6) $p < 0.0001$). In contrast, the PDG group did not show any significant change, regardless of follow-up time (PCLS total: pretest 51.6 (+/- 4.1); 48 h follow-up 52.04 (+/- 2.7); 3 months follow-up 52.7 (+/- 5.1); $p = 0.64$).

In addition to Chemtob and colleagues and Stallard and colleagues

(Chemtob et al., 2002; Stallard and Law, 1993), a third study conducted by Thabet and colleagues evaluated the clinical effects of PDG in children. In this nonrandomized controlled study, a debriefing-like intervention was compared to an educational program and a control group without any intervention. The debriefing-like intervention was an adaptation of Mitchell's debriefing, allowing the children to use drawings to facilitate emotional communication and expression. All the children were refugees living in camps during an ongoing war. No significant difference was identified between the debriefing group and the educational group or between the debriefing group and the control group in terms of the Child Post Traumatic Stress Reaction Index (CPTSD-RI) ($F_{(2; N = 111)} = 0.54$) (Thabet et al., 2005).

3.3.3. Studies where the PDG was provided within one month after a PTE in professionals of rescue and soldiers

Five studies included in this review reported the effect of PDG on professional groups repeatedly exposed to PTEs. These studies all provided the PDG within one month following the PTE. Deahl and colleagues conducted a 2-arm randomized controlled study (RCT) in a group of 106 British soldiers after they returned from a 6-month-long peacekeeping duty. The soldiers were randomly allocated to receive either PDG therapy or no intervention at all. At baseline, the scores obtained on scales assessing PTSD symptoms were very low. No statistically significant difference was found between groups in terms of the

IES total score at either the 3-month ($p = 0.86$), 6-month ($p = 0.05$) or 1-year ($p = 0.19$) follow-up (Deahl et al., 2000). Adler and colleagues conducted an RCT including a large sample of soldiers engaged in peacekeeping deployment. The soldiers had shared exposure to a range of occupational stressors over their 6-month deployment (rather than a specific PTE), and they were assigned to one of three conditions: stress management classes ($n = 359$), PDG ($n = 312$) or no intervention control group ($n = 281$). Baseline measures were taken prior to the deployment and immediately prior to condition allocation; follow-up measures were rated 3–4 months and 8–9 months after the intervention. PDG failed to reduce symptoms of PTSD relative to the other conditions. However, in soldiers most exposed to mission stressors, the PDG was associated with reduced PTSD symptoms compared with stress management (Post Traumatic Check List Scale (PCLS): $p < 0.01$; $d = 0.12$), with no significant difference between the PDG group and the group without intervention. The effect size was small, and it is worth noting that few participants in the study reported exposure to significant stressors during deployment (Adler et al., 2008). To compare different types of post-deployment early intervention, the same group of authors developed a second large RCT including American soldiers returning from a 12-month deployment. Participants received one out of 4 interventions and completed standardized scales up to 4 months after the intervention took place. The intervention was either a PDG program (the so-called Battlemind debriefing) ($n = 271$), a brief stress educational program ($n = 242$) or so-called Battlemind training in its small ($n = 272$) or large version ($n = 274$) depending on the number of attendees per session. The Battlemind training program uses a cognitive and skill-based approach and emphasizes safety, relationships, and common physical, social and psychological reactions to combat. When the whole sample was compared, there was no significant difference between the different interventions in terms of their abilities to reduce PTSD symptoms. When focusing on the subgroup with the highest level of combat stress exposure at a 4-month follow-up, the PDG group (Coef = -3.80 ; SE = 1.91 ; $p < 0.05$) and small (Coef = -6.33 ; SE = 2.18 ; $p < 0.001$) and large (Coef = -5.80 ; SE = 1.99 ; $p < 0.01$) battlemind training groups had reduced PTSD symptoms, as assessed with the PCLS, than the educational stress program group (Adler et al., 2009). Finally, in a 3-arm randomized controlled study, Wu and colleagues compared the effect of the 512 Psychological Intervention Model (512 PIM Model), a slightly modified version of CISD promoting cohesion between participants, with that of CISD and no intervention. The participants were soldiers deployed on a rescue mission after a major earthquake. At the 2- and 4-month follow-ups, PTSD symptoms significantly decreased in the 512 PIM group compared to the CISD and no-intervention groups ($p < 0.01$). There was no difference between the CISD group and the group without any intervention ($p = 0.23$) (Wu et al., 2012).

In another group of qualified staff with repeated exposure to PTEs, Tuckey and colleagues evaluated the effect of PDG on PTSD symptoms in a randomized controlled study. Sixty-seven firefighters were randomly assigned to one of three treatment conditions: (1) PDG, (2) no treatment, or (3) stress management education. Compared to the other two treatments, the PDG was not associated with any significant effect on PTSD symptoms, as measured with the IES-R (Tuckey and Scott, 2014). (See Table 2)

4. Discussion

Here, we aimed to review studies investigating the clinical relevance of PDG on PTSD symptoms. Although PDG was developed almost 40 years ago, only a few studies evaluating its therapeutic effect have been published. The systematic search yielded 11 articles that met our inclusion criteria.

4.1. Effect of PDG on PTSD symptoms

Only two of the eleven included studies reported that the PDG

decreased the typical symptoms of PTSD, such as re-experience, avoidance and hypervigilance (Chemtob et al., 1997; Stallard and Law, 1993). Two additional studies reported significant results only in a subgroup of participants with a high level of traumatic exposure or who received a slightly modified version of the CISD (Adler et al., 2008; Wu et al., 2012). The last seven studies included did not favor PDG over a control approach to improve symptoms of PTSD after a PTE (Adler et al., 2009; Chemtob et al., 2002; Deahl et al., 2000; Matthews, 1998; Tarquinio et al., 2016; Thabet et al., 2005; Tuckey and Scott, 2014).

Since the development of PDG, the group dimension has been considered a central element of the intervention, but this group dimension must meet two main criteria: 1- the ideal group size should be between 5 and 10 participants, and 2- the different participants should know each other before the PTE (e.g., professional group). These fundamental aspects may facilitate the expression of emotions, feelings and thoughts, allow better empathy among participants and, in turn, make storytelling (the basic ingredient of debriefing) more emotionally regulated across participants. However, these 2 crucial criteria were not met in several studies included in this review: in three studies, the debriefed participants did not know each other before the PTE (Chemtob et al., 2002, 1997; Thabet et al., 2005); in one study, the PDG included at most 2 participants (Tarquinio et al., 2016). Interestingly, Wu and colleagues reported a significant effect only after a CISD-based group intervention that particularly promoted group cohesion, suggesting that this is a major parameter that improves the clinical outcome (Wu et al., 2012).

By subcategorizing the included PDG studies, we also observed a severe lack of intrapopulation replication, with only six studies investigating the effects of PDG on civilian PTE victims and five studies investigating the effects of PDG on professional rescuers/military participants. While professionals are a group of interest for research on PTSD, they are repeatedly exposed to PTEs, they are trained to face PTEs, and they probably develop coping mechanisms that could alter their responsiveness to PDG.

Another factor of heterogeneity between studies was the latency between the PTE and PDG, which varied from hours to several years. To put the problem in perspective, the two extreme latencies we included were adopted by Tarquinio and colleagues, who offered PDG in the first 2 days after PTE, and Deahl and colleagues, who offered PDG one to two years after the PTE. The PTE is still ongoing in the study conducted by Thabet and colleagues. Originally, Mitchell proposed that CISD take place between 2 and 10 days after the PTE (Mitchell, 1983). In contrast, the comparison between 2 different PDG administration latencies (less than 10 h after PTE and 48 h after PTE) revealed that immediate PDG had a greater effect on the number and severity of PTSD symptoms than delayed PDG (Campfield and Hills, 2001). Although no clear conclusion should be drawn, the only three significant positive studies included offered PDG between one and three months after the PTE (Chemtob et al., 1997; Stallard and Law, 1993; Wu et al., 2012). Additional studies are needed to confirm this trend.

In the study of Thabet and colleagues, the PTE was still ongoing. Although this contrasts with a basic criterion of first psychological aid, which consists of first protecting the victim from further exposure to threat (Raphael et al., 1996), this is also a good illustration for the configuration where this important type of protection may not be possible in the case of a continuous traumatic situation (CTS) like living in a war zone or being repeatedly exposed to terrorist attacks. A continuous traumatic situation involves several conceptual differences in contrast to a time-limited PTE (and located in the past). First, evaluating whether victims experiencing a CTS have PTSD symptoms is particularly challenging because there may be a high risk to interpret emotional and behavioral reactions as PTSD symptoms although they actually should be considered as adaptive behavior to a continuous threat. Thus re-experiencing, avoidance and hyper vigilance would respectively switch to distress to an imminent threat, adaptive evasion of danger, adaptive alertness (Hoffman et al., 2011). The second aspect is a

Table 2
Main results from included studies investigating debriefing groups after a PTE.

Authors	Study type	Type of traumatic event	N in group debriefing	Type of control intervention (n)	Sex	Mean Age +/- SD	Delay after the PTE (days)	Level of expertise of the debriefing practitioner	Group cohesion	Outcome / Timing of assessment (days post debriefing)	Key findings
Stallard et al., 1993	Non randomized controlled study	Victims of a school bus accident	7 (pediatric)	1st group no intervention (24) 2nd group intervention (126) waiting list (18)	1 M / 6F	Debriefing group: 15.64 +/- 0.5	90	Experienced Clinician 2 x 3h- debriefing sessions	Yes	IES / 90	-Significant reduction at the IES after the PDG and the waiting list -n = 5
Chemtob et al., 1997	Non randomized partly controlled study	Victims of Hurricane	25	1st group no intervention (18) 2nd group intervention (31)	9 M / 34F	Debriefing group: 41.7 +/- 10.8 Waiting list group: 42.1 +/- 10.0	180	Experienced Clinician	No	IES / 90	-Significant reduction at the IES after the PDG and the waiting list -Both avoidance and intrusion sub scores were decreased after PDG
Matthews et al., 1998	Non randomized controlled study	Victims of assault (social workers and nurses)	14	1st group no intervention (18) 2nd group no intervention (31)	14 M / 49F	NA	1-7	Qualified staff	Yes	Non validated scale adapted from IES / NA	-In the area where PDG was available, PTSD symptoms were higher in the debriefed group -Post traumatic symptoms were significantly higher in the group where no PDG was available.
Deahl et al., 2000	Randomized controlled study	Peacekeepers (long time deployment)	54	no intervention (52)	106 M / 0F	24.0 (range 18 - 38)	1-2	Experienced clinician One X 2 h debriefing session	Yes	IES PTSS-10 / 90; 180; 365	-Low scores on IES and PTSS in both groups at baseline. -No statistical difference between groups regardless of timing of follow-up
Chemtob et al., 2002	Randomized single blind controlled study	Victims of Hurricane	176	individual debriefing (73)	97 M / 152F	8.85	2 years	3 school counsellors 1 social worker	No	KRI CRI / 365	-no difference between group in the KRI -lower CRI score in the treated group compared to the untreated group
Thabet et al., 2005	Non randomized controlled study	War refugees	47 (pediatric)	teacher education (22) no intervention (42)	59 M / 52F	Debriefing group: 12.9 Teacher education: 12.3 No intervention: 11.7	PTE still ongoing	Experienced clinicians in the debriefing group Teachers in the teacher education group	No	CPTSD-RI / 90	-No significant clinical change in any intervention
Adler et al., 2008	Randomized controlled study	Peacekeepers (6 months deployment)	312	No intervention (281) Stress management (359)	924 M / 28F	NA	Just after coming back from deployment	Military personnel trained to deliver debriefing	yes	FEK PCLS / 90; 240	-No significant difference between PDG and the control intervention, for the whole sample -In patients with the highest level of traumatic exposure, PDG was associated with less PTSD symptoms compared to stress management but not to no intervention
Adler et al., 2009	Randomized controlled study	Soldiers (12 months combat deployment)	271	Stress education (243) Small Battlemind Training (272) Large	1006 M / 51F	NA	Just after coming back from deployment	Experienced clinicians (Military personnel trained to deliver debriefing as group co-leaders)	yes	PCLS / 120	-No significant difference for PTSD symptoms between interventions at the whole sample level -If high level of combat exposure, patients from the PDG and battlemind training groups

(continued on next page)

Table 2 (continued)

Authors	Study type	Type of traumatic event	N in group debriefing	Type of control intervention (n)	Sex	Mean Age +/- SD	Delay after the PTE (days)	Level of expertise of the debriefing practitioner	Group cohesion	Outcome / Timing of assessment (days post debriefing)	Key findings
				Battlemind Training (274)							reported fewer PTSD symptoms than those from the educational stress group
Wu et al., 2011	Randomized controlled study	Military rescuers (earthquake)	372	No intervention (389)	NA	Debriefing group : 20.1 +/- 3.9 512 PBM : 19.8 +/- 3.6 No intervention : 20.2 +/- 3.5	30	Experienced clinicians	Yes	SI-PTSD / 30; 60; 120	-PTSD symptoms decreased in the group of participants receiving a slightly modified version of CISD promoting cohesion -No significant difference between the traditional CISD group and the sample receiving no intervention
Tusley et al., 2014	Randomized controlled study	Firefighters	20	Education group (28) Screening group (19)	98 M / 24F	NA	3	Experienced clinicians	Yes	IES K10 / 30	-No effect of PDG on posttraumatic stress and psychological distress
Tarquinio et al., 2016	Randomized controlled study	Victims of a violent event (employees)	23	RE-EMDR (19) delayed RE-EMDR (18)	14 M / 9F	CISD: 34.7 +/- 5.5 RE-EMDR: 35.3 +/- 6.7 Delayed RE-EMDR: 33.4 +/- 5.6	In the first 2 days	Experienced clinicians	Yes	PCLS SUDS / 90	-No significant improvement in the PDG (group size of 2 patients max by group)

PDG : Psychological debriefing group; IES: Impact of Event Scale; PTSS-10: Post Traumatic Symptoms Scale 10 items; KRI: Kauai Recovery Inventory; CRI: Child PTSD Reaction Inventory; CPTSD-RI: Child Post Traumatic Stress Reaction Index; PEK: Peacekeeping Events Scale; PCLS: Post traumatic Check List; PTE: Potential Traumatic; SI-PTSD: Structured Interview for PTSD; PIM 512: Psychological Intervention Model 512; Event; RE-EMDR: Recent Event - Eye Movement Desensitisation Reprocessing; K10: Kessler-10; SUDS: Subjective Unit of Distress Scale; CISD: Critical Incident Stress Debriefing; NA: not available.

consequence from the first one. From a therapeutic perspective, helping the individuals exposed to a CTS to manage the stress created by this abnormal situation and helping them to distinguish between reality-based reactions and symptomatic reactions to trauma reminders during a CTS appear more relevant than reprocessing a past PTE (Nuttman-Shwartz and Shoval-Zuckerman, 2016). Decreasing trauma symptoms may also threaten these individuals who must continue to live with real threats. So PDG may not be the most relevant therapeutic tool for individuals exposed to a CTS.

Finally, the PDG was carried out by an experienced clinician trained in the technique in only 8 out of the 11 included studies; this was the case in the 2 studies where the PDG alleviated the PTSD symptoms (Chemtob et al., 1997; Stallard and Law, 1993) and in 6 studies that reported nonsignificant results (Adler et al., 2009; Deahl et al., 2000; Tarquinio et al., 2016; Thabet et al., 2005; Tuckey and Scott, 2014; Wu et al., 2012). Interestingly, the PDG was administered by an experienced clinician in studies with the best methodological quality according to the QualSyst tool (Adler et al., 2009, 2008; Tarquinio et al., 2016; Thabet et al., 2005; Tuckey and Scott, 2014; Wu et al., 2012). However, to the best of our knowledge, the influence of the level of expertise of the debriefing practitioner has never been strictly evaluated.

Beyond these factors of heterogeneity in the included designs, the interpretation of their findings is restricted by several methodological flaws. For instance, some studies only presented pre/post comparisons (Chemtob et al., 1997; Stallard and Law, 1993), and some were controlled by inactive groups (Deahl et al., 2000; Matthews, 1998). Thus, the observed changes in clinical measures could arise due to factors that were not directly related to the intervention, drastically increasing the risk of inflated effect size. Similarly, the conclusions of Matthews and colleagues should be interpreted with caution since they exacerbated the problem of selection bias by allowing their participants choose for themselves whether to be a part of the active group (Matthews, 1998). Finally, it is important to note that designs with small sample sizes, such as Stallard's ($n = 7$) and Matthews' ($n = 14$) studies, are more likely to miss an effect that is actually present by inflating the Type II error rate.

4.2. Effect of debriefing groups on nonspecific symptoms

PTSD is often accompanied by less specific symptoms, such as anxiety, depression, sleep disturbances and comorbid diseases, such as alcohol use disorders or anxiety disorders. If the impact of PDG on these nonspecific symptoms is of major interest, the large heterogeneity in the type of nonspecific symptoms assessed prevented us from including these results in this systematic review. However, it is noteworthy that most studies evaluating anxiety seem to report a beneficial effect of PDG (see (Shalev et al., 1998) and (Stallard and Law, 1993) for positive results; (Deahl et al., 2000) for nonsignificant results), while most studies evaluating depression did not find any significant effect (see (Stallard and Law, 1993) for positive results; see (Adler et al., 2009; Thabet et al., 2005; Wu et al., 2012) for nonsignificant results). Similar to specific symptoms, Wu and colleagues reported that anxiety and depression were decreased only in the group administered the version of the PDG that had been adapted to promote group cohesion. Finally, PDG has been associated with reduced alcohol misuse in some studies (Deahl et al., 2000; Tuckey and Scott, 2014) but increased alcohol misuse by Adler and colleagues (Adler et al., 2008).

4.3. Perspectives

In the late 1990s and 2000s, published trials and meta-analyses (Rose et al., 2002) led to the conclusion that psychological debriefing did not have any benefit and should not be offered after exposure to a PTE. This conclusion was repeatedly reaffirmed by several guidelines with high visibility (Bisson et al., 2019; Forbes et al., 2007; NICE Guidance, 2018). In addition, some trauma-focused psychotherapies,

such as cognitive behavioral therapy (CBT) and eye movement desensitization reprocessing (EMDR), have attracted increasing attention in the scientific literature, as they seem effective in preventing PTSD symptoms (Kornør et al., 2008; Lewis et al., 2020; Roberts et al., 2010), even if their high technicality may limit their dissemination. However, in light of the results reported in our review, the previous work concluding on the inefficacy of PDG is nuanced because of the methodological flaws of current available studies. Our review displayed a high level of heterogeneity in the design of the included studies and a lack of replication in the features that may be critical to deliver PDG (type of included participants, timing to deliver PDG...). Moreover, from a statistic perspective, the way the data analysis was conducted in the included studies is not appropriate to firmly conclude to the ineffectiveness of PDG. Bayesian statistics should have to be conducted to rigorously prove the absence of clinical effect in PDG.

Moreover, the reported rare effect of PDG on PTSD symptoms among all included studies could also be explained by the hypothesis that PDG has little impact on psychopathology. Indeed, the PDG may be considered a kind of social sharing of emotion. If social sharing of emotion is a ubiquitous behavior in humans, it remains questionable whether it facilitates emotional recovery (Rimé et al., 1998). Thus, at an individual level, assessing the effect of PDG on some aspects of global functioning, especially at work (days of missed work for medical reasons, perceived efficiency at work, increased recognition, job satisfaction, and quality of life), could be more accurate. At the group level, it could be more relevant to focus on parameters relevant for group functioning (communication at work; effectiveness at work, social support, etc.). Brom and Kleber reported that PDG may affect these functional outcomes more than specific psychiatric symptoms (Brom and Kleber, 1989).

This review was focused on PDG. As short intervention delivered at a group level, PDG's design is particularly suitable for early intervention after a collective PTE, especially for the victims who may have little interest for a more sophisticated and often longer psychological support. But other group interventions for victims of a PTE were also developed. Either the content of the intervention was deeper just like in the Multiple Stressor Debriefing Model (MSDM, (Armstrong et al., 1991)) or the intervention was more intensive (Kleber and Velden, 2009) and/or composed of multiple sessions just like the Brief Prevention Program (BP, (Foa et al., 1995)). Evaluating systematically these interventions would be a valuable add in the topic early intervention after a PTE.

Given the methodological heterogeneity of the reviewed studies, it seems necessary to further investigate the effectiveness of various parameters, such as the group size, group dynamics, time window and debriefer training. To expand the knowledge on PDG, future studies should also focus on i) the subjective traumatic level of the PTE before patients are enrolled in PDG; ii) whether the control group is active; iii) the effect of PDG on nonspecific symptoms such as anxiety, depression, alcohol misuse and quality of life; iv) comparisons of PDG with individual PD; v) sociodemographic characteristics that could influence the response to the PDG; vi) outcomes that are relevant for the global functioning of the individuals exposed to a PTE and at a group level including communication style, effectiveness at work..

5. Conclusion

Existing literature suggests that PDG has no significant effect on specific symptoms of PTSD but could have a beneficial effect on nonspecific PTSD symptoms associated with PTE exposure. However, the methodological quality of the available studies is heterogeneous; some bias still remains and prevents any firm conclusion on the therapeutic potential of PDG. Further studies are required to elucidate its potential beneficial effect on nonspecific symptoms and the optimal guidelines that should be applied.

Author statement

PV and LL carried out the selection of the articles and independently extracted the data. PV and LL wrote the first version of the manuscript.

NP conceived of the presented idea. NP supervised the project and corrected the draft.

JB supervised the project and corrected the draft.

All authors approved the final version of the manuscript.

Conflict of Interest

All the authors declare they have no conflict of interest

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