UNIVERSITAT DE BARCELONA

Characterization of Counterfactual Reasoning Deficits in Schizophrenia Patients and Non-Psychotic First-Degree Relatives in Comparison with Healthy Control Subjects

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Doctoral Thesis

DOCTORATE IN MEDICINE

Clinical and Experimental Neuroscience

Psychiatry and Mental Health

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2017

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Doctoral Thesis by

Àuria Albacete Belzunces

To obtain the degree of Doctor from the University of Barcelona

Supervisors

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DOCTORATE IN MEDICINE

Clinical and Experimental Neuroscience

Psychiatry and Mental Health Research Group

Department of Clinical Sciences

School of Medicine

University of Barcelona

2017

L'Hospitalet de Llobregat, 9th May 2017

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CERTIFY that they have guided and supervised this doctoral thesis entitled **"Characterization of Counterfactual Reasoning Deficits in Schizophrenia Patients and Non-Psychotic First-Degree Relatives in Comparison with Healthy Control Subjects"**, which is presented in order to obtain the title of doctor by the candidate Àuria Albacete Belzunces. They thereby assert that this thesis fulfills all the required criteria to be defended.

"I can see there's a connection between
not following normal thinking and doing creative thinking.
I wouldn't have had good scientific ideas
if I had thought more normally"

John Forbes Nash Jr.

American Mathematician
1994 Nobel Prize in Economic Sciences

Als meus pares Ginés i Maria Teresa,

al meu germà Albert,

a l'Àlex.

Table of Contents

Foreword

This thesis has been developed within the framework of the Doctoral Program of Medicine of the University of Barcelona. All the research results included have been developed in the *Schizophrenia and Other Non-affective Psychotic Disorders Unit* of the Psychiatry Department of the Bellvitge University Hospital. This unit is linked to the Department of Clinical Sciences of the University of Barcelona, and is part of the research group in Psychiatry and Mental Health of the Bellvitge Biomedical Research Institute (IDIBELL, Catalan acronym). This group is a consolidated research group of the Government of Catalonia (2014SGR1672) and the Biomedical Research Networking Centre in Mental Health (CIBERSAM, Spanish acronym) of the Institute of Health Carlos III.

Personal funding for the development of the research presented includes: APIF-UB grant (2012-2016), University of Barcelona and Fundació Montcelimar Mobility research fellow (2016), Health University of Barcelona Campus (HUBc) Mobility research fellow (2016) and Campus Bellvitge-UB Grant for the finalization of the doctoral thesis (2017).

The present thesis includes four accepted peer-reviewed published journal articles. It has been written in accordance with the procedures indicated by the University of Barcelona and it is presented in order to obtain the International Doctorate title, which is granted by this Institution. The supervisors of this thesis are Dr. Fernando Contreras and Dr. José Manuel Menchón.

With regards to the structure of the thesis, after a general introduction on counterfactual reasoning and schizophrenia, and a methodology section particularly focused on presenting the evaluation of counterfactual reasoning, results of these four studies are reported in the following order:

1. *Counterfactual Reasoning Deficits in Schizophrenia Patients*. Contreras F,* **Albacete A**,* Castellví P, Caño A, Benejam B and Menchón JM. [*co-first authors]. PLoS ONE. 2016 Jan 11(2): e0148440.

2. *Symptomatic Remission and Counterfactual Reasoning in Schizophrenia*. **Albacete A***, Contreras F*, Bosque C, Gilabert E, Albiach A and Menchón JM. [*co-first authors]. Frontiers in Psychology. 2017 Jan 7:2048.

3. *Counterfactual Reasoning in Non-Psychotic First-Degree Relatives of People with Schizophrenia.* **Albacete A**, Contreras F, Bosque C, Gilabert E, Albiach A, Menchón JM, Crespo-Facorro B and Ayesa-Arriola R. Frontiers in Psychology. 2016 Apr 7:665.

4. *Patients with Schizophrenia Activate Behavioural Intentions Facilitated by Counterfactual Reasoning.* Contreras F,* **Albacete A**,* Tebé C, Benejam B, Caño A, and Menchón JM. [*co-first authors]. PLoS ONE. 2017 12(6): e0178860.

In the final part of the thesis, a general discussion is developed and a list of references is attached. An abstract in Catalan is also included with a similar structure to that disclosed.

Finally, it should be mentioned that the present thesis' results have been presented in several international congresses as poster and abstract publications: Biennial Schizophrenia International Research Society Conference, April 2017, Florence; European Conference on Schizophrenia Research, September 2015, Berlin; International Conference in Early Psychosis, December 2014, Tokyo. Moreover, portions of them were presented as an oral presentation by the candidate in the 10th International Meeting on the Early Stages of Mental Illness, Santander (Spain), June 2012.

Acknowledgements

Agraïments

Hi ha moltes persones a qui els dec el meu més sincer agraïment ja que sense elles aquesta tesi no hauria estat possible.

Per començar m'agradaria donar les gràcies a tots els pacients i familiars que han participat en aquest treball i que realment m'han ensenyat què significa viure amb esquizofrènia. A tots ells, el meu més profund respecte i reconeixement.

Per descomptat vull donar les gràcies als meus directors de tesi. En primer lloc, al Dr. Fernando Contreras; sincerament puc dir que sense tu no existiria aquest treball que avui presentem. Des del dia que vaig aparèixer per primer cop pel teu despatx ara ja fa cinc anys, no només m'has donat la oportunitat de fer aquesta tesi, sinó que també m'has ensenyat a organitzar-me les idees, a ser perseverant i no donar-me per vençuda, a diferenciar el que realment és important del que no ho és... en definitiva, a créixer com a persona. Gràcies per ajudar-me durant aquest llarg procés, per confiar en mi en moments crítics i per motivar-me a seguir endavant quan tot semblava impossible. Ho hem aconseguit!

També vull estendre la meva gratitud al Dr. José Manuel Menchón per haver-me donat la oportunitat de treballar en el seu equip de recerca que m'ha permès descobrir aquest apassionant món que és la ciència. Gràcies sinceres pel temps dedicat, el coneixement i els savis consells.

M'agradaria donar les gràcies a totes les persones del Servei de Psiquiatria del Hospital Universitari de Bellvitge-IDIBELL que han estat presents al llarg d'aquest viatge. En especial al Nacho, la Marta C., l'Andrés, totes les noies del despatx, Núria, Neus, Aida, Laura, Marta, Amparo, i per descomptat, la Luisa Fernanda. Per tots els moments compartits, suport, i el més important, per oferir-me la vostra amistat! També vull donar les gràcies al Cristian Tebé del Servei d'Assessoria Estadístic de l'IDIBELL per tot el temps i esforç dedicat, així com a la Marta S., Trevor, Oren, Mònica, Maria, Inés, Clara, Via, Carles, Rosa, Xavi, Eva, Cinto i Mar. A tots vosaltres, moltes gràcies!

También quiero dar las gracias al Dr. Crespo-Facorro y la Dra. Ayesa-Arriola del Instituto de Investigación Marqués de Valdecilla-IDIVAL, així com a la Dra. Clara Bosque, la Dra. Ester Gilabert, el Dr. Jordi Roig i totes les persones que treballen al Hospital de Dia de la Unitat Polivalent de Salut Mental Germanes Hospitalàries i la Unitat de Salut Mental de l'Hospitalet de Llobregat. Gràcies per obrir-me les portes de casa vostra!

Of course, part of this thesis is also from the time I spent in Montréal at the Douglas Mental Health University Institute. I want to thank Dr. Martin Lepage and Dr. Ashok Malla for inviting me to stay in their lab, and of course, to all the members at Douglas that I shared time with, especially Danielle, Carolina, Sophie, Genevieve, Rachel, Gloria, Michael and Karyne. Thank you so much!

A tots els meus amics i amigues que han viscut amb mi aquesta experiència. A la Ester i a la Elia ... a la Elia i a la Ester, que més que ser les meves amigues són com les meves germanes! Per descomptat, a totes les meves psicoamigues; vosaltres sou testimonis de com va començar tot el Setembre del 2005 a la UAB: Núria, Meritxell (sí, sí, a tu Xai!) i Anna. Tampoc em vull descuidar al Jordi, la Sara, el Manel V. i tota la gent de la Palma: Manel P., Rubén, Héctor, Mireia, David, Tala, Jenni i Laura. Tots plegats heu format part d'aquest procés en algun moment. Moltes gràcies per compartir-lo amb mi!

A tota la meva família, avis, tiets i cosins, que han estat al meu costat al llarg de tots aquests anys. Al meu germà Albert, pel seu suport incondicional però sobretot, pel seu bon humor. A la memòria dels meus avis, Concepció i Josep; sempre amb mi. I per descomptat, als meus pares Maria Teresa i Ginés; el vostre exemple, amor i dedicació no només són la raó que avui presenti aquesta tesi, sinó que defineixen la persona que sóc i seré. Per vosaltres, el meu més sincer agraïment.

Finalment, vull donar-li les gràcies a l'Àlex. Tal i com una vegada tu em vas dir a mi, sense el teu suport i la teva comprensió no hagués pogut arribar fins aquí. Gràcies per ensenyar-me a confiar en mi mateixa i en tot el que la vida et pot oferir.

"Tu ets el meu petit món; el passat, present i futur"

Living (2008).

List of Abbreviations

BACS	Brief Assessment of Cognition in Schizophrenia
CAPE-42	Community Assessment of Psychotic Experiences - 42
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CFT	Counterfactual Thinking
CGI-S	Clinical Global Impression Scale – Severity Section
CIT	Counterfactual Inference Test
dlPFC	Dorsolateral Prefrontal Cortex
DMN	Default Mode Network
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders – 3rd ed. revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders – 4th ed.
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders – 4th ed. text revised
FAP	First-Generation Antipsychotic
***f*MRI**	Functional Magnetic Resonance Imaging
GAF	Global Assessment of Functioning Scale
HC	Healthy Control
IPSAQ	Internal, Personal and Situational Questionnaire
IQ	Intelligence Quotient
JTC	Jumping to Conclusions
lPFC	Lateral Prefrontal Cortex
MADRS	Montgomery-Åsberg Depression Rating Scale
MATRICS	Measurement and Treatment Research to Improve Cognition in Schizophrenia
MCCB	MATRICS Consensus Cognitive Battery
mOFC	Medial Orbitofrontal Cortex
mPFC	Medial Prefrontal Cortex
MRI	Magnetic Resonance Imaging
MSCEIT	Mayer-Salovey-Caruso Emotional Intelligence Test

NIMH	National Institute of Mental Health
OFC	Orbitofrontal Cortex
PANSS	Positive and Negative Syndrome Scale
PFC	Prefrontal Cortex
PLE	Psychotic-like Experiences
PPI	Prepulse Inhibition
RDoC	Research Domain Criteria
REL	First-Degree Relative
RT	Reaction Time
SAP	Second-Generation Antipsychotic
SCID	Structured Clinical Interview for DSM-IV
SCZ	Schizophrenia Patient
SOFI	Schizophrenia Objective Functioning Instrument
SPQ-B	Schizotypal Personality Questionnaire - Brief
SUMD	Scale to Assess Unawareness of Mental Disorder – Abbreviated version
TAVEC	Test de Aprendizaje Verbal España-Complutense
ToM	Theory of Mind
UPSA	UCSD Performance-Based Skills Assessment
VBM	Voxel-based Morphometry
vmPFC	Ventral Medial Prefrontal Cortex
WAIS	Wechsler Adult Intelligence Scale
WCST	Wisconsin Card Sorting Test
WHO	World Health Organization

List of Tables and Figures

TABLES

FIGURES

1. Introduction

1.1. Schizophrenia

Schizophrenia is one of the most serious and complex psychiatric illnesses which supposes a great negative impact on the life of the individuals who suffer from it and their loved ones. Coined by Eugen Bleuler in 1911, the term schizophrenia stems from the Greek language and includes the words "schizein" (to split) and "phren" (mind). This clinical syndrome has an unknown etiology and is characterized by a disturbance in cognition, emotion, perception, thinking and behaviour. Despite its relevance, and although management and treatment of the disorder has significantly improved over the last century, schizophrenia still remains challenge in terms of research, clinical intervention, and organization and management of the socio-health services. A revision of the main conceptual aspects of the disorder is presented throughout this section, specifically focusing on one of the key concepts of the present thesis, the cognitive impairment in schizophrenia.

1.1.1. Epidemiology and burden of the disorder

Schizophrenia affects approximately 24 million people worldwide according to the last World Health Organization (WHO) estimates (Piccinelli & Gomez Homen, 1997). Epidemiological estimates indicate that schizophrenia affects 0.4% of the world's population with a reported median incidence of 15.2 over 100,000 individuals per year (Saha *et al.*, 2005); although there is reported variation by race/ethnicity, across countries, and by geographic origin (American Psychiatric Association, 2013). In Spain though, there are no recent epidemiological data concerning schizophrenia since the country does not have a national registry that would make it possible to know the exact number of individuals affected. Nevertheless, results from regional studies have estimated the prevalence at 0.6-0.8% for the adult population (17 years of age and older) and the real annual incidence of 1.9 per 10,000 inhabitants per year for people between the ages of 15 and 54 years (Mata *et al.*, 2000; Vázquez-Barquero *et al.*, 1987, 1995).

Furthermore, schizophrenia is a tremendous health, social and economic burden not only for the patients who suffer from it, but also for their families, other caregivers and wider society (Chong *et al.*, 2016). Associated with a great burden of long-term disability, this disorder is ranked among the top 25 leading causes of disability worldwide in 2013 (Global Burden of Disease study of 2013; Vos *et al.*, 2015) and the fifth in the relation of disorders related to a severe disability among the most developed countries (WHO, 2011). At an economical level, schizophrenia absorbs a huge amount of health-care resources. Specifically, the annual socioeconomic cost of schizophrenia in Spain totals €2.098 billion, of which direct medical costs account for 49.8%, direct non-medical costs 44.1%, and indirect costs 6.1% (Oliva-Moreno *et al.*, 2006).

1.1.2. Etiology

Although it appears that our understanding of the causation of schizophrenia has substantially increased over the years, to date it is still a syndrome of unknown etiology. In fact, owing to the heterogeneity of the symptomatic and prognostic presentations of the disorder, not a single factor can be considered as a cause of it (Sadock & Sadock, 2010). However, what can confidently be asserted is that both genetic and environmental factors are important, although specific exposure and how exactly they cause schizophrenia are still unknown (Tandon *et al.*, 2008).

One of the most well established risks for the disorder is genetic predisposition. It is known that schizophrenia aggregates in families and that having an affected family member substantially increases the risk of developing the condition (Tandon *et al.*, 2008). Results from twin studies have allowed us to estimate the heritability of the disorder in about 80% of the liability for schizophrenia due to genetic factors, either contributing by themselves or through interactions with environmental factors (Sullivan *et al.*, 2003). However, despite a genetic basis for the illness seeming to have been established, the precise mechanisms of inheritance still remain obscure (Arnedo *et al.*, 2015; Tandon *et al.*, 2008). Trying to shed light on this issue, the identification of potential intermediate phenotypes has become an important area of investigation in recent years, not only for providing critical information about the pathophysiology of the disorder but also for its potential to direct early interventions and prevention programs among both schizophrenia patients and at-risk individuals. Also referred as "endophenotypes," these markers reflect the presence of a genetic predisposition

to a certain disease phenotype becoming putative targets for molecular genetic studies (Van Os & Kapur, 2009). Gottesman & Gould presented in 2003 a useful framework for the identification of endophenotypic markers in psychiatry which included five criteria: (1) the endophenotype is associated with the illness in the population, (2) it is heritable, (3) it is primarily state-independent –i.e., it manifests in an individual whether or not the illness is active, (4) it is within families, it co-segregates with illness, and (5) it is found in unaffected family members at a higher rate than in the general population. Different heritable traits have been identified as potential endophenotypes of the disorder to date, including structural magnetic resonance imaging (MRI) brain volume measures, neurophysiological information processing traits, sensitivity to stress and neurocognitive functioning (Bramon *et al.*, 2005; Boos *et al.*, 2007; Nenadic *et al.*, 2012; Sitskoorn *et al.*, 2004).

At the same time, environmental factors also seem to be playing an important role in the development of schizophrenia evidenced by a substantial variation in the incidence of the disorder across places and minority groups (Van Os *et al.*, 2010). The main identified environmental risk conditions for psychosis are prenatal stress, paternal age, malnutrition, infections during pregnancy, perinatal hypoxia, childhood trauma, urbanicity, migration, poverty, minority ethnic groups and cannabis use (Tandon *et al.*, 2008). The exposure to one or more of these factors interacting with a determinate genetic background may alter neuronal migration, myelination and neurotransmission, affecting brain maturation and neuroendocrine responses and leading to psychopathology (European Network of National Networks studying Gene-Environment Interactions in Schizophrenia, 2014).

Among the numerous theories that have been developed over the years trying to identify and understand the relationship between such risk factors and the etiology of the illness, the *neurodevelopmental theory* of schizophrenia is the one with a wealth of supporting evidence (Murray & Lewis, 1987; Weinberger, 1987). This model posits that a proportion of schizophrenia is in fact the result of a genetic predisposition with brain "insults" at various stages of development, subsequently affecting its development and leading to abnormalities expressed in the mature brain (McGrath *et al.*, 2003; Rapoport *et al.*, 2012).

1.1.3. Neural bases

Advances in neuroimaging techniques over the past three decades have allowed us to identify a wide number of brain abnormalities conforming our current knowledge on the neuroanatomical bases of schizophrenia. Unfortunately, though, none of these abnormalities can yet be considered as a diagnostic marker of the disorder. A review is presented throughout this section by presenting main research findings on both structural and functional imaging studies in schizophrenia.

Systematic reviews and meta-analyses of structural MRI studies indicate that whole brain and gray matter volume is reduced and ventricular volume is increased in schizophrenia patients (Andreasen *et al.*, 1990). More specifically, volume reductions have been located in temporal lobe structures, the hippocampus, amygdala, thalamus, and frontal cortex including the left medial and in right and left lateral orbitofrontal cortex (OFC) (Venkatasubramanian *et al.*, 2008; Wright *et al.*, 2000). Studies using voxel-based morphometry (VBM) techniques have also evidenced a reduction in the gray matter density in frontal, temporal, insular and thalamic regions (Glahn *et al.*, 2008; Honea *et al.*, 2005). Brain structural changes in schizophrenia also involve reductions in white matter structures including a decrease in the anterior limb of the bilateral internal capsule, the right temporal lobe and corpus callosum (Bora *et al.*, 2011; Woodruff *et al.*, 1995). Lastly, diffusion tensor imaging studies have documented reduced fractional anisotropy in white matter tracts, including the corpus callosum, the cingulum, arcuate and unicinate fasciculi (Kubicki *et al.*, 2007), and the left posterior pillars of the fornix (Rametti *et al.*, 2009).

Regarding brain functioning, overall, results from functional magnetic resonance imaging (*f*MRI) studies have pointed to alterations in prefrontal, and less consistently, temporal lobe function in schizophrenia (Keshavan *et al.*, 2008). More specifically, one of the most oft-reported findings is decreased activation of the dorsolateral prefrontal cortex (dlPFC), or *hypofrontality*, when challenged with cognitive tasks mediated by this brain structure (Hill *et al.*, 2004). Interestingly though, studies have also found evidence for increased prefrontal activation, or *hyperfrontality*, when patients are engaged in an *n-back* task (Tan *et al.*, 2006). Recent meta-analyses on this topic consistently support this finding; regularly increased activation has been observed in anterior cingulate and left frontal pole regions, areas of the left dorsal and ventral premotor cortex, the ventrolateral prefrontal

cortex and parts of the temporal and parietal cortex (Glahn *et al.*, 2005; Minzenberg *et al.*, 2009). Alterations in the activation of the mOFC, the amygdala and insula activation have also been reported among patients engaged in social decision-making tasks (Baas *et al.*, 2008).

Another further recent functional imaging key finding in schizophrenia is the one evidencing a failure among these patients to deactivate in the medial frontal area which corresponds to one of the two major midline components of the *Default Mode Network* (DMN). This network, which activates "by default" when a person is not carrying out a task, is engaged in internal processes not directly attributed to a specific external task, such as recalling the past and imagining of the future, autobiographical memory, and conceiving the perspective of others (Haatveita *et al.*, 2016). Investigators of this field have suggested that DMN dysfunction might account for the cognitive impairment associated with schizophrenia due to a failure to divert physiological resources away from the DMN during cognitively demanding tasks (Libby & Ragland, 2011; Pomarol-Clotet *et al.*, 2008a; Whitfield-Gabrieli *et al.*, 2009).

1.1.4. Clinical features

Schizophrenia is a clinical syndrome characterized by the presence of a variety of signs and symptoms affecting almost all aspects of mental, emotional and behavioural activity of the individual. However, none of these can be considered as pathognomonic of the disorder due to the significant heterogeneous presentation between individuals over the course of the illness (Andreasen, 1995; Lindenmayer & Kahn, 2006).

Several proposals have been developed over the years trying to cluster this collection of signs and symptoms in separate psychopathological syndromal domains. Tandon *et al.*, 2009 reports the six different domains or categories listed below that have been broadly replicated across a large number of patient cohorts at various stages of schizophrenic illness.

I. **Positive symptoms**: the prototypical psychotic symptoms involving an impaired reality testing. This dimension includes the presence of delusions and hallucinations.

II. **Negative symptoms**: involving alterations in drive and volition, these symptoms include abulia, alogia, anhedonia, apathy, avolition and social withdrawal.

III. **Disorganization of thinking and behaviour**: involving both formal thought disorder (derailment, neologisms and poverty of thought content) and disorganized behaviour (e.g., incongruous affect or markedly inappropriate attire).

IV. **Mood symptoms**: involving alterations in both affective experience and expression including emotional arousal or reactivity in conjunction with positive symptoms or depressive symptoms that can be present in every phase of the illness.

V. **Motor symptoms and catatonia**: involving alterations in both the extent and nature of psychomotor activity represented by a slowness or excessiveness of psychomotor activity. Disorder of motor activity can range from simple isolated movements of posturing, mannerisms and stereotypies to more complex patterns of motion as observed in various catatonic states.

VI. **Cognitive impairment**: including difficulties in almost all cognitive domains (Heinrichs & Zakzanis, 1998), the consideration of these abnormalities as a core feature of schizophrenia has become more relevant over the last years in the study of the characterization and etiology of schizophrenia.

1.1.5. Course of the disorder

Although the classic course of schizophrenia varies substantially across individuals after the first psychotic episode and its predictors are still largely unexplained (American Psychiatric Association, 2013; Ciompi, 1980), the natural history of this illness can be characterized as a sequential trajectory involving different phases or stages that are highly variable in duration, course, and severity of the symptoms (**Figure 1.1.**):

1. **Premorbid phase**: this is the period before the emergence of any sign or symptom, although subtle and nonspecific cognitive, motor and/or social dysfunction are present in the majority of individuals (Walker *et al.*, 2004).

2. **Prodromal phase***:* this period is characterized by a decline in cognitive, social and vocational functioning (Perkins *et al.*, 2006), and the appearance of certain signs and symptoms in an attenuated form – i.e., the individual does not fulfill all the criteria of the disorder (McGorry *et al.*, 1996).

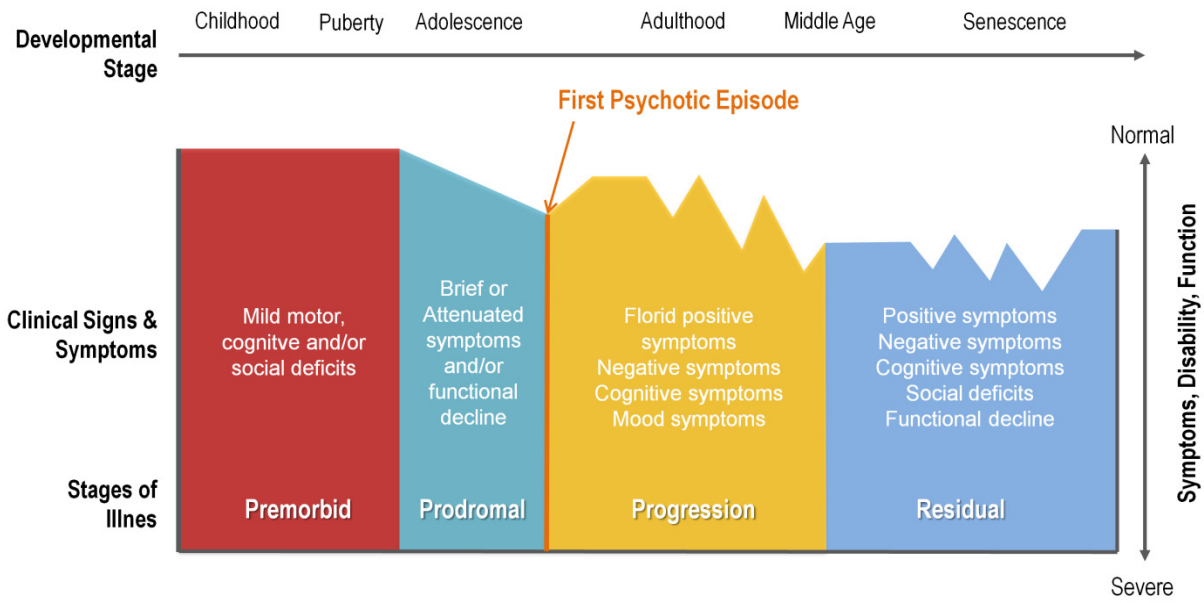

Figure 1.1. Diagram depicting the clinical course of schizophrenia.
Adapted from Lewis and Lieberman (2000).

3. **Onset of illness - first psychotic episode:** this period is characterized with the development of frank psychotic symptoms in the form of a first psychotic episode (American Psychiatric Association, 2013). Typically emerging between the late adolescence and early adulthood, onset can be abrupt or insidious, although 75% to 80% of the individuals present a slow and gradual development of a variety of symptoms before the onset of frank psychosis (American Psychiatric Association, 2013; Perkins *et al.*, 2006).

4. **Progression phase:** this period refers to the clinical progression of schizophrenia, characterized by the presence of repeated exacerbations with partial and variable degrees and duration of inter-episode remission, especially during the initial decade of the illness (Lewis & Lieberman, 2000). A significant functional decline is evident during this phase, which might be in part related to the duration of untreated psychosis (Perkins *et al.*, 2005).

5. **Residual or Stable phase**: during this period, positive symptoms tend to become less severe and negative symptoms more prominent over long-term course. Cognitive symptoms are generally stable over the course of the illness while mood symptoms

vary in severity in partial association with psychotic symptoms (Lewis & Lieberman, 2000; Tandon *et al.*, 2009).

Recovery of varying degrees can occur at any stage of the illness (Harding *et al.*, 1987), with a significant proportion of individuals with schizophrenia exhibiting a substantial improvement (Ciompi, 1980). Notwithstanding the foregoing, the majority of cases resolve in chronic illness (Jääskeläinen *et al.*, 2012; Morgan *et al.,* 2014), with recurrent exacerbations and remissions of active symptoms, presenting a course of progressive deterioration that require formal or informal daily living support (American Psychiatric Association, 2013; Lindenmayer & Kahn, 2006; Perkins *et al.*, 2006). Different symptomatic remission have been developed over the years to facilitate research and to support a positive, longer-term approach to studying outcome in schizophrenia patients, including neurocognitive functioning (Kane, 2007; Leucht *et al.*, 2008; Levine *et al.*, 2011; Levine & Leucht, 2013). One of these criterion receiving noteworthy support from the scientific community (Opler *et al.*, 2007; Van Os *et al.*, 2006) is the remission criteria proposed by Andreasen *et al.* in 2005. Defined as a score of ≤3 (mild) on eight selected items of the Positive and Negative Syndrome Scale (PANSS; Kay *et al.* 1987), this criterion includes two components: a symptom-based (low scores on diagnostically relevant symptoms) and a time criterion (duration of at least 6 months).

1.1.6. Cognitive impairment

Although cognitive impairment has not become accepted as an important feature of schizophrenia until the last recent years, in fact, the recognition of these deficits can be traced back to the turn of the 20th century. Coining the term of "dementia praecox," Emil Kraepelin had already described this disorder as a progressive decline in cognitive abilities such as attention, problem solving and learning, typically occurred in the early adulthood. Interestingly, he also noted that these disturbances had a marked negative impact on these patients' social, vocational and independent functioning (Kraepelin, 1971). However, the analysis of cognitive impairment in schizophrenia was not considered of interest again until the last two decades, when the scientific community resumed the study of the neuropsychological models for this disorder coinciding with the emergence and development of the neurosciences. Thus, the neuropsychological model for the illness understands this cognitive impairment to be the result of a brain dysfunction due to a decreased metabolic

activation of the frontal lobe and the presence of abnormalities in the neural networks connecting frontal, temporal and limbic lobes (Goldman-Rakic & Selemon, 1997). This model has received empirical support of multiple different disciplines within the neurosciences (Andreasen *et al.*, 1997; Frith, 1995).

To date, neurocognitive impairment is held as a core feature of schizophrenia including a disruption in almost all cognitive domains (Green, 1996; Heinrichs & Zakzanis, 1998). These deficiencies are considered as primary deficits of the illness, not secondary to other features such as clinical symptoms or treatment-related factors –i.e., these deficits are manifested similarly among patients who have attained symptomatic remission in comparison to those who have not (Brissos *et al.*, 2011; Buckley *et al.*, 2007), and also seem to be present even before the initiation of treatment with neuroleptic drugs (Saykin *et al.*, 1994). Hence, these findings suggest that, in schizophrenia, psychopathology and cognitive impairment might be caused, at least partially, by distinct pathophysiological processes.

Overall, as collected by Tandon *et al.* (2009), several facts can be currently stated about cognitive impairment in schizophrenia with a fair degree of confidence despite being a relatively recent field of study:

1- Albeit to varying degrees, the prevalence of cognitive impairment seems to be **high** in schizophrenia –i.e., 98% of the patients perform more poorly on cognitive tests than would be predicted by their parents' education level (Keefe *et al.*, 2005).

2- Clearly distinguishing patients from controls, the average cognitive impairment can reach **two standard deviations below the general population** (Heinrichs & Zakzanis, 1998).

3- The schizophrenia cognitive deficit is **largely generalized across performance domains**, although there are certain domains that present additional specific impairments (Dickinson *et al.*, 2008; Heinrichs & Zakzanis, 1998).

4- Cognitive impairment is already observable in the **early stages of the disorder**, including the premorbid phase (Woodberry *et al.*, 2008).

5- Contrary to other prototypical clinical features of the disorder, cognitive deficits seem to **persist through the long-term course** of schizophrenia (Rund, 1998).

6- Current available **antipsychotic treatment** has been shown to present at best a **marginal impact on cognition**, with no substantial differences between first and second generation antipsychotic agents (Heinrichs, 2005).

7- The **course of cognitive function** through schizophrenic illness has **not been definitively outlined** (Bilder *et al.*, 2006).

8- **Non-psychotic relatives** present a **similar pattern** of **cognitive impairment**, although to a lesser degree of severity (Sitskoorn *et al.*, 2004; Snitz *et al.*, 2006).

9- Neurocognitive performance seems to be a **strong correlate** of schizophrenia patients' **real-world functioning** (Fett *et al.*, 2011; Green, 1996).

10- Although cognitive deficits in patients with schizophrenia tend to be more severe and persistent compared to patients with psychotic and non-psychotic affective disorders, they are **not qualitatively different** (Reichenberg *et al.*, 2009).

1.1.6.1. The profile of cognitive impairment in schizophrenia

Although traditionally the existence of deterioration in attentional, mnesic and executive functions has been mainly emphasized in schizophrenia, numerous studies seem to indicate that there is also dysfunction in other domains (Bowie & Harvey, 2006). However, over the years, literature reviews have presented a varied profile of cognitive deficits in schizophrenia which has been explained by the fact that the neurocognitive tests used to explore these deficits do not usually fit neatly into a single domain (Keefe & Harvey, 2012).

Because of this, with the objective of shedding light on this issue and developing a consensus battery to explore cognitive impairment in schizophrenia, a group of experts serving on the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) project (Green *et al.*, 2004; Marder & Fenton, 2004), after an extensive revision, agreed that the most important domains of cognitive deficit in this disorder were: working memory, attention/vigilance, verbal learning and memory, visual learning and memory, reasoning and problem solving, speed of processing, and social cognition (Green *et al.*, 2004). All these seven domains are assessed in the cognitive battery that was developed after, the MATRICS Consensus Cognitive Battery (MCCB; Nuechterlein *et al.*, 2008). Accordingly,

impairment in all these domains was later confirmed in a study developed by Kern *et al.* (2011) by using the MCCB in a group of schizophrenia patients in comparison with a group of healthy controls (**Figure 1.2.**) –i.e., patients obtained lower scores than controls in all functions, with speed of processing and working memory being the most impaired, and reasoning and problem-solving being the functions most preserved.

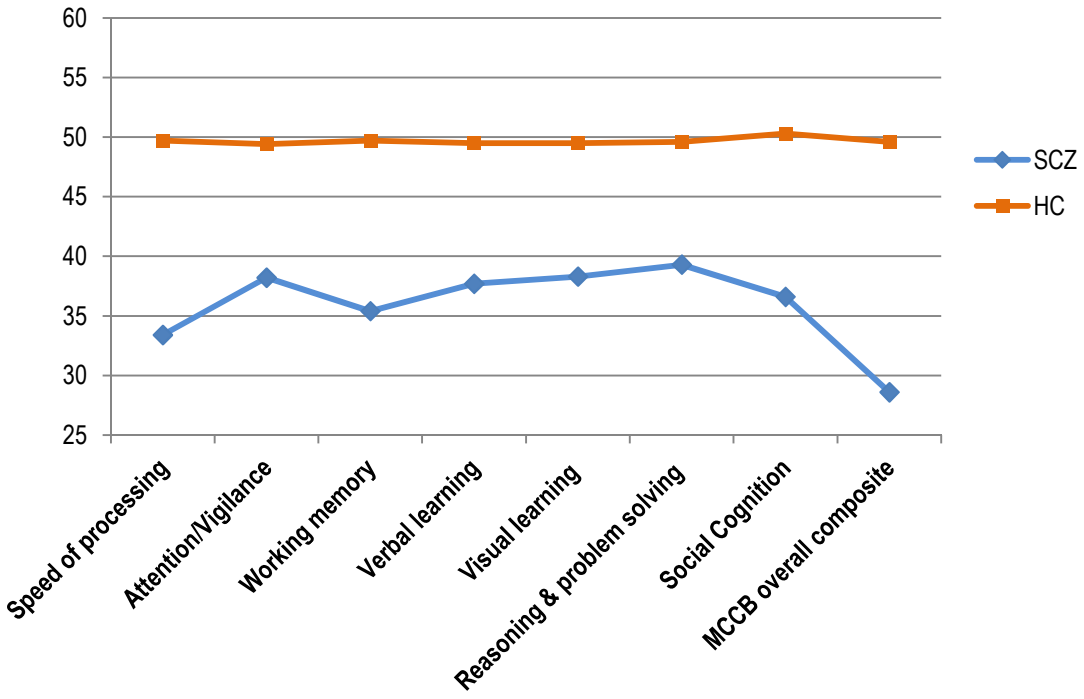

Figure 1.2. Cognitive impairment profile of schizophrenia individuals on the MCCB (age- and gender-corrected T-scores). Adapted from Kern *et al.*, 2011. *HC: healthy controls; SCZ: schizophrenia patients.*

Furthermore, based on the premise that schizophrenia is a profound disorder of basic thought processes (Fusar-Poli *et al.*, 2007; Shad *et al.*, 2006), one area that has been of particular interest over the years is the study of high-order cognitive deficits in this illness. Enabling the understanding and implementation of the necessary steps to solve problems, attack new areas of learning, and think creatively, this myriad of complex abilities encompasses concept formation, problem solving, creativity, decision making, and reasoning (Shuxian, 2009).

Within this context, the study of reasoning impairment in schizophrenia has renewed interest over the last decades because of its potential value to explain the underpinnings of

the disorder (Kruck *et al.*, 2011). The term "reasoning" refers to the ability to draw inferences (conclusions) from some initial information (premises) (Holyoak & Morrison, 2005). Deficits in this area have been widely observed in these patient's by using neuropsychological tests such as the Wisconsin Card Sorting Test (WCST; Heaton *et al.*, 1993). In fact, research has concisely reported poorer performance among schizophrenia patients engaging in this task (Keefe & Harvey, 2012). On this basis, experimental works have tried to explain the disorder in terms of formal reasoning impairment (Garety & Hemsley, 1995; Kemp *et al.*, 1997). For instance, one notable hypothesis in this line stated that schizophrenia might actually be an impairment of commonsense knowing (practical reason) over an enhancement of theoretical rationality. Owen, Cutting and David tested such hypothesis in 2007 evidencing that indeed under conditions where common sense and logic conflict, schizophrenia patients tended to reason more logically than healthy individuals.

Intimately related to this research has been the marked increase over recent years in the study of cognitive biases in schizophrenia influencing the formation of the prototypical psychotic symptoms of the disorder. These cognitive biases are defined as preferences, styles or distortions with which information is processed, and can be conceptualized as "mental shortcuts." Differing from the well-established neuropsychological deficits associated with schizophrenia, these biases are not considered pathological *per se*. However, although these biases occur in healthy individuals as well, they appear to a great extent in people with psychosis and seem to be linked to the formation and maintenance of delusions (Garety & Freeman, 1999; Moritz *et al.*, 2015). Following the seminal work of Garety *et al.* (1991), a significant number of cognitive biases have been identified in schizophrenia: many patients display overconfidence in erroneous judgments (Gawęda *et al.*, 2013; Moritz *et al.*, 2003), have a bias against integrating disconfirmatory evidence (Speechley *et al.*, 2012), tend to over-rely on confirmatory evidence and reasoning heuristics (Balzan *et al.*, 2012), and perhaps most robustly, have been shown to exhibit a jumping to conclusions (JTC) bias (Moritz & Woodward, 2005). JTC reflects a data gathering reasoning bias and has been particularly associated with the intensity of delusional ideation (Garety & Freeman, 1999). In addition, despite the lack of consistent results, there is also mounting evidence for attributional biases (Bentall *et al.*, 1994). In the light of these findings, authors in this filed have started to develop new treatment options specifically focused on addressing these biases in order to reduce delusional symptoms of the disorder. Such interventions include the *Metacognitive Training*

(Woodward *et al.*, 2014), the *Social Cognition and Interaction Training* (Combs *et al.*, 2007) or the *Reasoning Training* (Ross *et al.*, 2011). However, the pattern of results with regards to their efficiency is still not fully consistent across studies (Moritz *et al.*, 2015).

1.1.6.1.1. Social cognition impairment

Social cognition is a multifaceted construct that broadly refers to the mental operations underlying social interactions. Embracing a wide range of skills essential for adequate social functioning and interpersonal success, social cognitive operations typically include perceiving, interpreting and generating responses to the emotions, intentions and dispositions of others (Kern & Horan, 2010). In schizophrenia, social cognition has emerged as a major focus of study over the last years, with data demonstrating impairment in four core domains (Pinkham, 2013):

1. **Emotion Processing:** as one of the most extensively studied social cognition skills in schizophrenia, this domain refers to the ability to perceive and use emotions to facilitate adaptive functioning. Research has evidenced notably inferior performance in schizophrenia patients (Edwards *et al.*, 2002; Kohler *et al.*, 2010).

2. **Social Perception:** referring to the individual's ability to judge social cues from contextual information and communicative gestures (Kern & Horan, 2010), schizophrenia patients present difficulties when having to decode non-verbal cues such as facial expressions (Corrigan *et al.*, 1992; Sergi & Green, 2003).

3. **Theory of Mind (ToM):** as the ability to attribute mental states to oneself or another person (Premack & Woodruff, 1978), also known as *mentalizing*, ToM involves the skill to understand false beliefs, hints, intentions, deception, metaphor, irony, and faux pas (Penn *et al.*, 2006). Research has demonstrated mentalizing impairments in schizophrenia patients (Bora et al., 2009; Sprong *et al.*, 2007).

4. **Attributional Style:** this domain refers to how individuals explain the causes for positive and negative outcomes in their lives. In schizophrenia, the two most common attributional biases described are the *self-serving attributional style* (taking credit for successful outcomes and denying responsibility for negative outcomes) and the

personalizing bias (attributing negative outcomes to others, rather than to situations) (Lee *et al.*, 2004; Penn *et al.*, 2006).

Social cognitive deficits are currently acknowledged as clinically important features of schizophrenia (Penn *et al.*, 2006), emerging in the early stages of the disorder and settling into a stable pattern over time (Addington *et al.*, 2006; Sprong *et al.*, 2007). These deficits have been reported to significantly interfere in these patients' social functioning (Fett *et al.*, 2011).

1.1.6.2. Cognitive impairment in relation with clinical features

The relationship between neuropsychological deficits with clinical features of the disorder has been extensively investigated over the last decades, with its relationship with classic symptomatology being one of the main focuses of study. Traditionally, cognitive deficits have been found to generally be more consistently related with negative symptoms and disorganization than with positive symptoms (Liddle, 1987). Several studies including recent meta-analyses have reported significant associations between severity of both negative and disorganization syndromes and poorer cognitive performance (Dibben *et al.*, 2009; McKenna & Oh, 2005). However, the amount of shared variance with negative symptoms remains relatively small and the pattern of relationship with specific cognitive deficits still remains unclear (Kern & Horan, 2010).

At present though, neurocognitive functioning is considered to be relatively independent of the clinical symptoms of the disorder. This notion is supported by data from studies revealing these deficits (1) to remain stable despite symptom fluctuations and variances (Brissos *et al.*, 2011; Buckley *et al.*, 2007), (2) to predate the onset of the illness (Keefe *et al.*, 2006a), (3) to not be secondary to treatment with antipsychotic medications (Saykin *et al.*, 1994), and (4) to be observed, although to a lesser degree, among those individuals "at-risk" of developing schizophrenia (Kelleher & Cannon, 2011; Snitz *et al.*, 2006).

With regards to its course, research findings show that the development of cognitive dysfunction in schizophrenia appears to follow a predictable pattern (**Figure 1.3.**). Several studies have demonstrated that neurocognitive impairment is present in a mild form during childhood and adolescence before the onset of psychosis. Once psychosis develops, neurocognitive impairment becomes more severe, even before antipsychotic treatment is

initiated. During this early phase of the illness, although some patients may demonstrate a slight improvement with treatment, the majority do not improve at all (Keefe & Eesley, 2006).

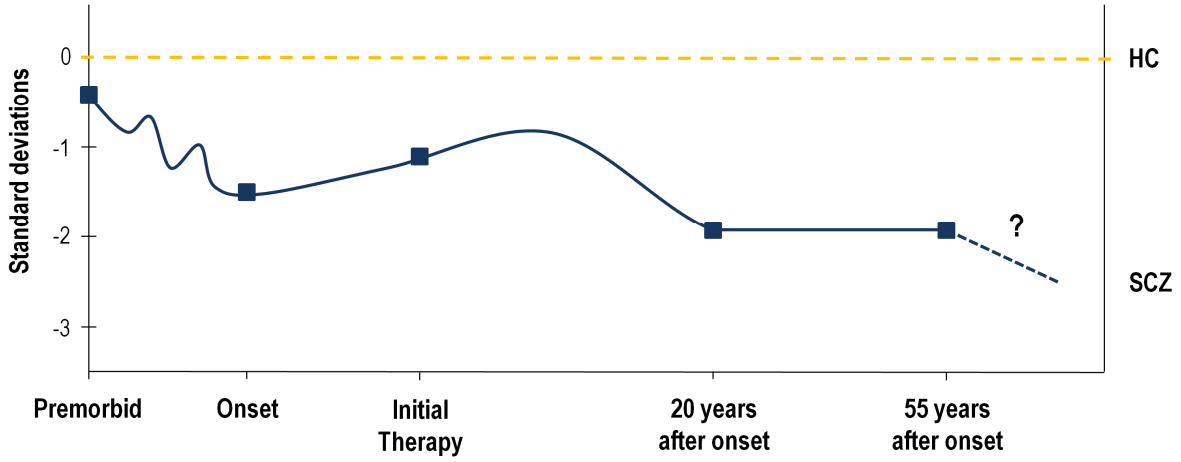

Figure 1.3. Course of cognitive impairment in patients with schizophrenia.
Adapted from Keefe and Eesley (2006). *HC: healthy controls; SCZ: schizophrenia patients.*

Following this early phase, the level of neurocognitive impairment remains relatively stable during adulthood (ages 21-55), and persists into late life, where there may be further decline (Heaton *et al.*, 2001; Keefe & Eesley, 2006). The course of neurocognitive impairment in elderly patients remains uncertain. Notwithstanding, evidence suggests that the neurocognitive deficit of schizophrenia is largely stable, unlike the type of impairment seen in frank progressive degenerative disorders such as Alzheimer's or Huntington's disease (Gold, 2004).

1.1.6.3. Cognitive impairment in relation with functional outcome

Beyond cognitive deficits, schizophrenia is also characterized by the presence of a functioning impairment related to various aspects of outcome, including social deficits, community functioning, and skills acquisition (Keefe & Eesley, 2006). Currently considered as a fundamental therapeutic goal in schizophrenia, functional impairments in living, work, and leisure are essential diagnostic features of schizophrenia, have a high prevalence, and are a significant burden for these patients and their families (American Psychiatric Association, 2013; Bellack *et al.*, 2007). When exploring its causes, evidence indicates that cognitive deficits

are critically related to this functional disability, accounting for 20% to 60% of the variance of functional outcome in these patients (Green, 1996; Green *et al.*, 2000; Velligan *et al.*, 1997). Specifically, research has identified verbal and visual memory, and verbal fluency as the most strongly related cognitive domains (Green *et al.*, 2000; Fett *et al.*, 2011).

Social cognition has also been associated with functioning impairment in schizophrenia. In fact, studies on this topic have found social cognition deficits to be more strongly related with community functioning than general neurocognitive deficits (Pijnenborg *et al.*, 2009). For instance, in a recent meta-analysis by Fett *et al.* (2011), whereas neurocognitive deficits accounted for 15.2% of the variance of functional outcome, social cognition deficit accounted for 23.3%. Other authors have proposed social cognition as a mediating variable between general cognition and functioning. Schmidt *et al.* (2011) found that, while the classic model of neurocognitive deficits accounted for a 14% of the variance of functional outcome, the model including social cognition as a mediator variable accounted for a 21% of the variance. Thus, it is not surprising that, in the light of this evidence, cognitive impairment, and particularly social cognition impairment, has emerged over the last years as an important new target in schizophrenia therapeutics in which research should focus on (Gold, 2004).

1.1.6.4. Cognitive endophenotypes for schizophrenia

Studies of subtle cognitive alterations in non-psychotic relatives of schizophrenia patients have significantly increased over the last decade in an effort to confirm the hypothesis that these deficiencies might be potential endophenotypes for this disorder. Thus, contributing to the etiology of schizophrenia (Byrne *et al.*, 2003; Cannon *et al.*, 2000; Cardno *et al.*, 1999), research has identified a series of putative cognitive deficits that seem to be meeting the fifth criterion for endophenotype validation (Gottesman & Gould, 2003) –i.e., these deficits are found to a lesser degree in the unaffected relatives of people with this disorder. Such deficiencies include alterations in declarative and working memory, sustained attention, verbal fluency, perceptual-motor speed, and certain executive functions (Sitskoorn *et al.*, 2004; Snitz *et al.*, 2006; Szöke *et al.*, 2005). In addition, cognitive biases related to particular symptoms of schizophrenia, such as the data gathering bias known as "jumping to conclusions", have also been described among non-psychotic relatives of patients with schizophrenia (Broome *et al.*, 2007; Van Dael *et al.*, 2006). Regarding social cognition however, data remain inconsistent

(Green *et al.*, 2008). Whereas some studies have found evidence of alterations in these probands compared with normal controls (Albacete *et al.*, 2016; Bediou *et al.*, 2007; Cella *et al.*, 2015; Janssen *et al.*, 2003; Lavoie *et al.*, 2013), other have shown no differences at all (Kelemen *et al.*, 2004; Loughland *et al.*, 2004). Similar deficits have also been observed both in unaffected first-degree relatives high in schizotypy (Chen *et al.*, 1998; Laurent *et al.*, 2000; Vollema & Postma, 2002) and in healthy individuals reporting psychotic-like experiences (Kelleher & Cannon, 2011).

1.1.6.5. Treatment of cognitive impairment

To date, a variety of interventions has been developed in order to address fundamental neurocognitive deficits in schizophrenia. The importance of cognition in relation to functioning has been highlighted over recent years with the formation of projects such as the MATRICS (Green *et al.*, 2004; Marder & Fenton, 2004) aimed at improving outcome by enhancing the cognitive ability of these patients, particularly within a psychopharmacological perspective.

As revised throughout this chapter, the suitability for targeting cognition can be summarized in four essential features demonstrated by previous research about cognitive impairment in schizophrenia (Gold, 2004):

1. Though it is variable in the extent of impairment across cognitive domains, it appears highly prevalent in schizophrenia.
2. It is relatively independent of the clinical symptoms of the illness.
3. It is a relatively stable trait feature of the disorder.
4. It is strongly related to functional outcome of these patients –i.e., suggesting that a change in cognition might result in important changes in illness outcome or the quality of life of patients.

From a pharmacological point of view, although seminal studies on this topic found that second-generation antipsychotic (SAP) treatment provided greater neurocognitive benefit to schizophrenia patients than first-generation or "typical" antipsychotics (FAP) (Keefe *et al.*, 1999), the effect of using antipsychotic medication as treatment for neurocognitive impairment in schizophrenia still remains unclear (Harvey & Keefe, 2001).

Results from recent studies seem to suggest that actually, the impact of atypical antipsychotic medications on neurocognition varies little on average, with minimal benefit from most treatments. Meta-analyses, such as Woodward *et al.* (2005), have reported SAP superiority to FAP at improving cognitive function with effect sizes ranging from 0 to 0.24. Results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study comparing the effects of several SAPs and perphenazine on neurocognitive performance did not evidence significant differences between groups (Keefe *et al.*, 2007). Thus, overall, current data suggests that the impact of antipsychotic medications on neurocognition varies little on average, lacking meaning at a clinical practice level (Swartz *et al.*, 2008) and consequently prompting the development of cognitive rehabilitation approaches designed to help reduce the functional consequences of impairment in elementary neurocognitive function of this disorder (Krabbendam & Aleman, 2003). Among these multiple formats of intervention, one of the programs with most support and promising results over the last years is *Cognitive Remediation Therapy* developed by Wykes *et al.* (2003). Other programs include the *Computer-Assisted Cognitive Strategy* (Vauth *et al.*, 2005), or in a group format, the *Integrated Psychological Therapy* (Roder *et al.,* 2007). Specific cognitive rehabilitation programs targeting social cognition include the *Training of Affect Recognition* (Sachs *et al.,* 2012), and the *Social Cognition and Interaction Training* (Combs *et al.*, 2007). With regards to their efficacy, although there are some studies that do not uphold a significant benefit (Dickinson *et al.*, 2009; Gomar *et al.*, 2015), several studies have reported improvements across a variety of program and patient conditions, not only in cognitive functioning, but in psychosocial functioning and symptoms of the disorder as well (e.g., Grant *et al.*, 2012; McGurk *et al.*, 2007; Wykes *et al.,* 2011).

In sum, evidence to date suggests that the cognitive impairment characteristic of schizophrenia can be improved. Although current pharmacotherapy and cognitive rehabilitation still present a relatively small-to-medium level of efficacy, cognitive rehabilitation interventions seem to overcome SAP therapy –i.e., presenting 1-1.5 versus 0.2-0.5 standard deviations respectively (Wykes & Spaulding, 2011). Thus, even though further research in this field is warranted, cognitive rehabilitation is now recognized as an important tool in the treatment of schizophrenia, with the potential to improve both the cognitive performance and functional outcome of these patients.

1.2. Counterfactual Thinking

> *What if Kennedy had survived his assassin's bullets into second term in the White House? What if the Nazis had triumphed over the Western democracies in the Second World War? What if your parents had never met? There is something at once obsessively compelling and oddly unsettling about confronting the unrealities that might well have been.*
>
> — Neal Roese and Jim Olson (1995, p.xi)

An interesting psychological phenomenon that has recently come to the attention of researchers is how individuals might not be only affected by what did happen, but also by what did not happen. For instance, as Roese and Olson (1995) present, who among us has never wondered how the course of history might have changed if the German army had actually been victorious in WWII? Or from a more personal point of view, what might have been if your parents had never met? Or what if an important choice you made in the past had been different? To think about what might have been, to shift from perceiving the immediate environment to an alternative imagined perspective, is a hallmark of human thought and is known as counterfactual thinking (CFT) (Epstude & Roese, 2008; Van Hoeck *et al.*, 2015). The following sections will give a review of the existing research regarding this phenomenon, the reasoning process that supports it, its role from a functional perspective, and how it is altered by psychiatric disorder and neurological disease.

1.2.1. Definition of concepts

CFT is the process of looking back at events and thinking how things could have turned out differently (Roese, 1997). This kind of thinking is spontaneously activated, usually in the form of a conditional preposition, and generally triggered to a greater extent by negative outcomes (Epstude & Roese, 2008). In this way, most people compare the actual result of the event with "what might have been" by generating different hypothetical outcomes "if only" an alternative event had taken place (Byrne, 2016). In other words, the defining feature of counterfactual thinking is the generation of alternate realities in which a factual outcome is undone by changing one or more antecedent events (Krishnamurthy & Sivaraman, 2002). To

illustrate this concept, consider the example of a student, John, who has failed an important test. Automatically, he could generate a counterfactual thought like, *If only I had studied more, I could have passed the test* (**Figure 1.4.**).

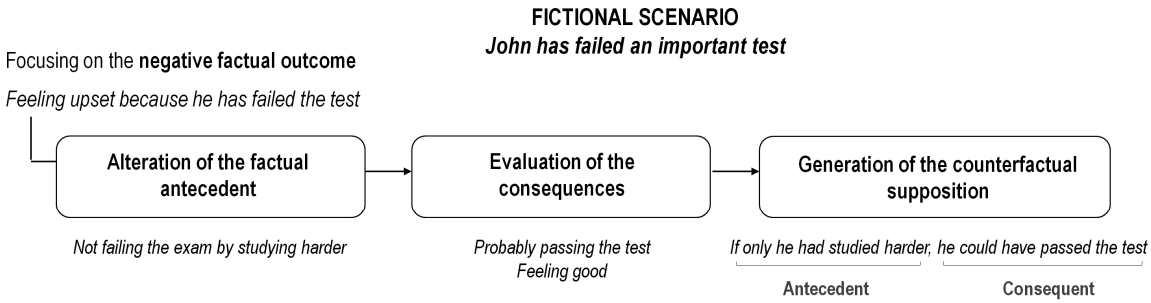

Figure 1.4. Depiction of the counterfactual thought generation process.

CFT is common across nations and cultures (Au, 1983; Gilovich *et al.*, 2003) and appears to be a pervasive, if not an essential, feature of our mental lives (Roese & Olson, 1995). The capacity to entertain counterfactual alternatives to reality emerges early in life, typically by 2 years of age, when children begin to engage in pretend play, temporarily suspending their commitment to reality and adopting the perspective of a pretend situation (e.g., Harris *et al.* 1996). CFT continues to develop throughout childhood; children as young as 3 and 4 obtain the ability to make the correct counterfactual inferences and are able to interpret the cause of an outcome in terms of a contrast between the factual event and the counterfactual alternative in which the outcome did not occur (Harris *et al.*, 1996).

CFT is a constructive process that requires the integration of different cognitive processes; from the engagement of working memory for the storage and manipulation of the elements of the factual situation, to the activation of attentional and executive control functions to evaluate the alternative scenario, the retrieval of memories from past experiences and the involvement of emotional and motivational processing to implement future success-facilitating behaviours (Roese & Olson, 1995; Van Hoeck *et al.*, 2015).

The resultant counterfactual thoughts generated can be classified into specific subtypes based on three dimensions (Roese & Olson, 1995; Roese, 1997):

- **Direction of the counterfactual:** depending on whether the counterfactual posits alternative circumstances that represent a more desirable state of affairs than actuality

(i.e., *upward* counterfactuals), or a worse state than actuality (i.e., *downward* counterfactuals).

- **Structure of the counterfactual:** depending on whether the counterfactual adds a new antecedent not presented in the factual situation (i.e., *additive* counterfactuals), or removes some factual antecedent (i.e., *subtractive* counterfactuals).

- **Focus of the counterfactual:** depending on whether the counterfactual focus is on one's own action (i.e., *internal* counterfactuals), or on the actions of others (i.e., *external* counterfactuals).

These dimensions are not incompatible between them –i.e., a counterfactual thought can be described in terms of these three characteristics. For instance, John's thought of *If only I had studied more, I could have passed the test* is an upward, additive and internal type of counterfactual. Typically, upward counterfactuals are considered to likely have greater preparative consequences than downward counterfactuals –i.e., in order to achieve success, the generation of upward or positive alternatives is more likely to be taken as a schemata for future action (Markam *et al.*, 1993). In accordance, additive and subtractive counterfactuals can also serve a preparative function. Specifically, it appears that additive alternatives might be more efficacious than subtractive alternatives when planning for actions that might lead to success since they are more specific and creative (Roese & Olson, 1995). Interestingly, the dimension of counterfactual direction can also serve an affective function by generating alternatives that make the individual feel better when facing a negative outcome. Accordingly, whereas upward counterfactuals would most probably evoke negative affect (e.g., disappointment or regret), downward counterfactuals tend to elicit positive affect (e.g., relief) (Markam *et al.*, 1993). With regards to the focus of counterfactuals, it is apparent that internal counterfactuals are more useful for self-improvement than the externals since they are more specific in their focus on personal upgrade (Epstude & Roese, 2008).

1.2.1.1. Counterfactual reasoning

As a sub process of CFT, the ability to reason through counterfactual thoughts or counterfactual reasoning refers to the remarkable ability to make inferences through the activation of counterfactual thoughts. In other words, it refers to the ability to infer how an

event might have unfolded differently, without having to directly experience this alternative reality (Roese & Olson, 1995). Both terms are linked and one cannot be understood without the other; in fact, both terms are used indistinctly sometimes by expert authors in this field (Van Hoeck *et al.*, 2015). Thus, considered as an essential property of intelligence itself (Sternberg, & Gastel, 1989a, 1989b), this ability to reach valid conclusions through CFT is achieved by the individual during adolescence (Markovits & Vachon, 1989; Wing & Scholnick, 1986).

Based on the evidence gathered from psychology and neuroscience research, Van Hoeck *et al.* (2015) have proposed a three-stage sequence in which the process of counterfactual reasoning might rely on: *Activation of Mental Simulations, Counterfactual Inference* and *Adaptation* (**Figure 1.5.**).

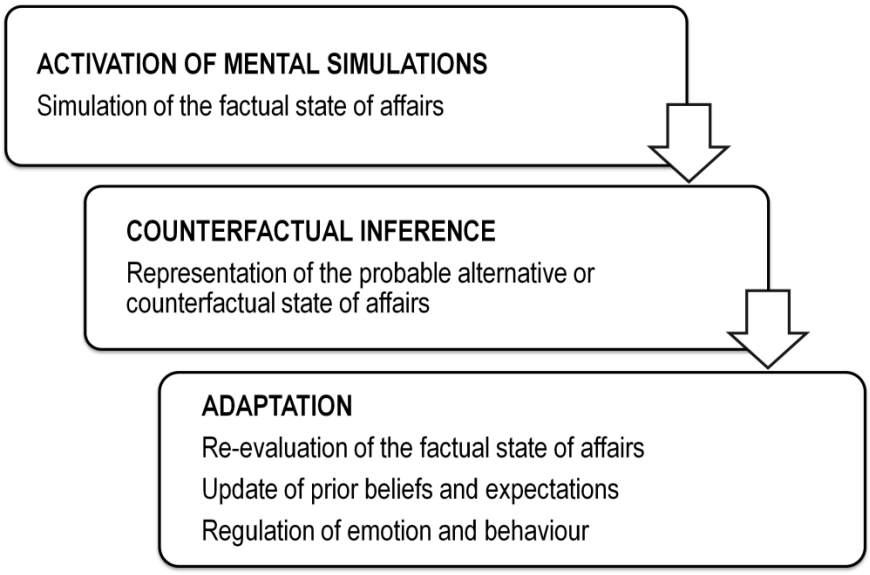

Figure 1.5. A schematic overview of the counterfactual reasoning stages. Adapted from Van Hoeck *et al.*, 2015.

To illustrate these three stages, consider again John's aforementioned fictional scenario. To begin with, reasoning thorough counterfactuals starts on the activation of prior memories that elicit mental simulation of the factual state of affairs (**Stage 1**) –e.g., failing the exam would elicit John to remember the questions on the test, the time that he spent studying for it, etc. This activation subsequently triggers mental simulations of similar situations, providing the basis for constructing mental models of events and imaging

alternative realities "if only" different decisions were made or actions were taken (Markman *et al.*, 2009). The activation of this counterfactual scenario provides the basis to infer how a situation would have played out under different circumstances (**Stage 2**) –e.g., John imagining passing the test if only he had studied harder. Finally, once the counterfactual inference has been generated, this information will allow the individual to re-evaluate the factual state of affairs and update his prior beliefs and expectations (Van Hoeck *et al.*, 2015). By influencing the individual's representation of the factual situation (experience), the counterfactual simulation will promote adaptive behaviour by guiding future planning and problem-solving (**Stage 3**) –e.g., eliciting in John the intention of studying harder the next time that he finds himself in a similar situation.

Thus, preceded by the activation of counterfactual simulated scenarios, this ability to reason through counterfactuals can be described as a complex psychological phenomenon supported by the coordination of multiple mental processes, providing us of new insights into nearby possible worlds in our everyday lives, and enabling learning from the past experience.

1.2.2. Theoretical background

Although philosophers in ancient Greece were already interested in the consideration of "what might have been," it was not until the twentieth century that CFT was widely discussed throughout a variety of disciplines including philosophy, history, political science, and of course, psychology (Roese & Olson, 1995).

With regards to the latter, the first empirical research on the production, storage, and retrieval of counterfactual thoughts can be traced back to the beginnings of the 1970s within the field of cognitive psychology. For instance, Fillenbaum in 1974 described how memory for the counterfactual is more accurate than for semantically similar causal statements, suggesting the proficiency of the individual at cognitive manipulations of counterfactual information.

Importantly though, it was not until Kahneman and Miller's (1986) *norm theory* that research examining CFT significantly increased in psychological research. In fact, this theory has been the guiding theoretical formulation for posterior research on this topic since its

emergence. Briefly, these authors proposed a theory of norms and normality applying it to the phenomena of emotional responses, social judgment, and conversations about causes. Specifically, the term *norms* refers to the concept of precomputed structures constructed ad hoc by recruiting specific representations after and in direct response to specific outcomes. Within this frame, the generation of counterfactual alternatives allows for the construction of norms by retrieving similar experiences stored in memory in order to recapitulate the normal state of affairs. In fact, the more "abnormal" the situation is, the more available counterfactuals will be. *Norm theory* is applied in analyses of the enhanced emotional response to events that have abnormal causes, of the generation of predictions and inferences from observations of behaviour, and of the role of norms in causal questions and answers (Epstude & Roese, 2008; Kahneman & Miller, 1986; Roese & Olson, 1995). Interestingly, situated within the heuristics and biases tradition, *norm theory* examines counterfactual reasoning from the vantage point of biased judgment and decision making (Epstude & Roese, 2008; Kahneman & Tversky, 1982a).

From this seminal work, social psychologists in the 1980s and 1990s focused on the study of counterfactual reasoning in terms of its implications for judgments (e.g., Roese & Olson, 1995) and real-world decision making (e.g., Meyers-Levy & Maheswaran, 1992). Within cognitive psychology, subsequent theoretical approaches were built on *norm theory*'s specification of mental simulation processes, with the mental models perspective or *model theory* by Byrne (2002) being one of the referents. This theory approaches counterfactual thinking in terms of the basic building blocks of reasoning and how particular pieces of information are chained together to form inferences (Byrne, 2002, 2005; Byrne & McEleney, 2000; Feeney & Handley, 2006). Further research on CFT includes the integration of counterfactual judgments with judgments focusing on the present and future (Sanna *et al.*, 2006), or its examination in light of deeper inferential processes, such as conditional, temporal, causal, and social reasoning (Markman & McMullen, 2003).

At present, it is of special relevance the study of CFT from a functional perspective. Typically activated by failed goals, counterfactual reasoning is now considered as a useful, beneficial, and necessary component of behaviour regulation (Epstude & Roese, 2008). A more detailed review of its functional value is provided elsewhere in this chapter in accordance with the main aims of the present thesis.

1.2.3. Neural bases

Traditionally, neurological findings have associated CFT impairment with a prefrontal cortex (PFC) dysfunction. In 1995, Knight and Grabowecky provided evidence from a patient with dlPFC damage who demonstrated an inability to generate counterfactual thoughts. Interestingly, these authors already described how such disruption hindered the ability to avoid making the same mistakes repeatedly.

Results from subsequent *f*MRI studies dovetail with these findings: (1) Gomez-Beldarrain *et al.*, (2005) reported an impoverished ability to generate spontaneous counterfactual thoughts in a group of dlPFC and OFC lesion patients, (2) Ursu & Carter (2005) observed OFC involvement in the counterfactual activation in a group of healthy subjects, and finally (3) Barbey *et al.* (2009) found significant activation of medial PFC (mPFC) in the representation of particular forms of counterfactual inference. Furthermore, although PFC regions seem to be the primary regions activated in people engaging in CFT tasks, *f*MRI studies has evidenced other regions related to episodic memory (De Brigard *et al.*, 2013). Particularly, Van Hoeck *et al.* (2013) observed that structures related to (1) memory processes such as the hippocampus, posterior midline structures, parietal and temporal lobule, and to (2) mentalizing about intentions and goals of oneself and the others including the temporo-parietal junction and mPFC were also engaged in CFT.

Interestingly, by integrating this conjunction of research findings, Van Hoeck *et al.* proposed in 2015 an integrative network of neural systems that the process of counterfactual reasoning might rely on (**Figure 1.6.**):

1. **Mental simulation network:** engaging regions related to the DMN (Pomarol-Clotet *et al.*, 2008a), this network is activated when mentally deconstructing the present state of affairs –i.e., supporting the core processes for observing and interpreting a situation, mentally altering and re-evaluating. Main regions involved include the hippocampus allowing the retrieval of past similar experiences (De Brigard *et al.*, 2013), and mPFC regions facilitating the construction of these self-relevant mental simulations (Van Hoeck *et al.*, 2013). Other structures included in this network are the lateral temporal lobe and inferior parietal lobe (Van Overwalle & Baetens, 2009; Van Hoeck *et al.*, 2013).

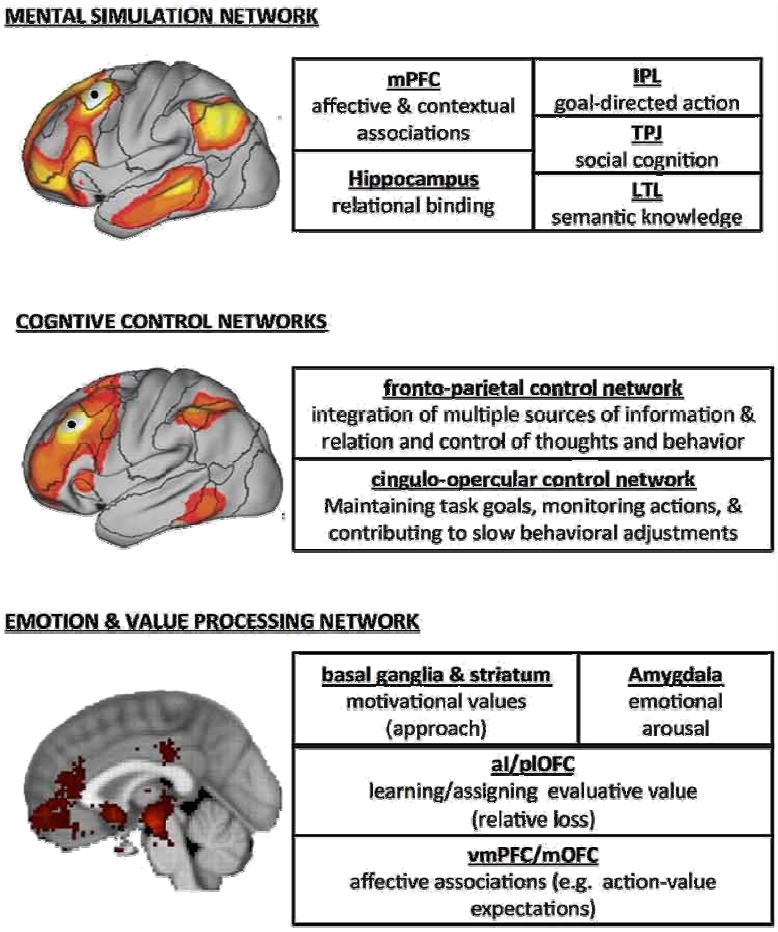

Figure 1.6. Schematic overview of the neural networks supporting counterfactual reasoning. Adapted from Van Hoeck *et al.* 2015. *mPFC: medial prefrontal cortex; IPL: interior parietal lobe; TPJ: temporo-parietal junction; LTL: lateral temporal lobe; al: anterior insula; plOFC: posterior lateral orbitofrontal cortex; vmPFC: ventral mPFC; mOFC: medial OFC.*

2. **Cognitive control networks:** two main control networks have been proposed to enable the mental transformations required for counterfactual inference and reasoning: the fronto-parietal and the cingulo-opercular control networks.

    a. *Fronto-parietal control network:* this network enables the integration of multiple sources of information and supports the regulation and control of thought. The lateral PFC (lPFC), middle cingulated cortex, interior parietal lobe and precuneus are included in its involvement (Nieuwland, 2012; Van Hoeck *et al.*, 2013).

    b. *Cingulo-opercular control network*: involving the dorsal anterior cingulate cortex, the posterior medial frontal cortex, anterior insula/frontal operculum, and the

anterior PFC, this network contributes to behavioural regulation and feeling of regret by updating and maintaining counterfactual action-outcome information (Hampshire *et al.*, 2012; Rudebeck *et al.*, 2013).

3. **Emotion and value processing network**: including the vmPFC, mOFC, amygdala, basal ganglia, lateral OFC and lPFC, this network supports the affect-related aspects of counterfactual reasoning by encoding subjective value and expectations of the present state of affairs, allowing the modulation of the emotional response, and signaling if a corrective behaviour becomes optimal (Coricelli *et al.*, 2007; Nicolle *et al.*, 2011; Roy *et al.*, 2012).

Therefore, it appears that there is no specific neural network for counterfactual reasoning, but this complex psychological phenomenon is actually the result of the interaction of these neural networks, providing the basis for the diverse emotional and evaluative processing required to support reasoning through counterfactuals.

1.2.4. Factors influencing counterfactual thinking

As previously mentioned, CFT is pervasive in everyday life and involves the generation of an infinite number of alternatives for each specific situation. However, people may have neither the time nor the cognitive capacity to consider every possible alternative. Instead, the activation of counterfactual thoughts seems to be constrained by specific aspects or factors of reality that are most readily mutated, for instance, the causal relations between events (McCloy & Byrne, 2000). Thus, several factors have been described over the years as central determinants of counterfactual generation based on Kahneman and Miller's (1986) *norm theory*. These factors are generally organized depending on whether they are based on the mutability of the factual action or event (i.e., antecedent) or the availability of the outcome (i.e., the consequent).

1.2.4.1. Antecedent-based factors

Traditionally, the study of the *antecedent-based* factors has been conceptually centered on the antecedent events leading to counterfactual thought activation. Specifically, on the assessment of how these factors affect the mutability of such antecedent, consequently determining the

semantic content of the resulting counterfactual thought. Interestingly, research has also described how those antecedents perceived to be more mutable, are also those that are typically ascribed greater weight in causal judgements. A list of the most relevant *antecedent-based* factors is presented below:

1. **Actions versus Inactions:** based on Kahneman and Tversky's (1982b) suggestion that actions are actually more mutable than failures to act, research evidences how the generation of counterfactual thoughts is facilitated when having to delete or change a factual action rather than having to imagine a novel action that was not in fact performed.
2. **Controllable versus Uncontrollable antecedents:** this factor is based in the general tendency among individuals to modify those elements that are perceived to be more directly controlled, altered or manipulated (Girotto *et al.*, 1991). In this case, counterfactual generation seems to be enhanced in front of controllable antecedents.
3. **Dynamic versus Static antecedents:** this factor is based on the proposition that dynamic aspects of reality are more mutable than static aspects. Thus, suggesting that counterfactual generation will vary depending on the fluctuation rate of the antecedent element (Kahneman & Miller, 1986).
4. **Unusual versus Routine antecedents:** as one of the central assertions of Kahneman and Miller's (1986) *norm theory*, there is a general tendency to mutate unusual elements into more routine (default) elements. Thus, people tend to generate more likely counterfactual alternatives based on the alteration of an exceptional rather than a usual aspect of the situation/action. Interestingly, this effect reflects the fundamental tendency to create alternatives that instantiate normality or typicality – i.e., seeking to undo unusual outcomes people tend to alter exceptional antecedents to make them more "normal" (Gavanski & Wells, 1989).
5. **Serial position - "Causal Order Effect":** based on the fact that outcomes are usually the result of multiple occurrences comprising a serial chain of events, previous research has focused on whether the serial position of the events influences the judgements of causality. Interestingly, results from these studies reveal a tendency to perceive those events occurring early in a serial chain as the ones exerting greater causal impact (Brickman *et al.*, 1975). In consonance, findings from counterfactual

research evidence a tendency to construct the counterfactual alternative by altering early events rather than later events (Wells *et al.*, 1987; Segura *et al.*, 2002). This primacy effect of antecedent mutability is known as the causal order effect and appears to be restricted to cases involving a causal sequence of events.

In summary, it appears that salient, controllable, dynamic, unusual and early antecedent elements tend to be perceived as more mutable than their counterparts, and consequently, they tend to be seized more readily in the construction of a counterfactual alternative of a factual outcome.

1.2.4.2. Outcome-based factors

On the other hand, counterfactual research has also focused on the *outcome-based* factors that trigger the mental undoing of the factual situation. In fact, the influence that these factors exert is described in terms of their role influencing the availability of the counterfactual thought. Also framed within the *norm theory*, the concept of counterfactual availability refers to the extent to which some characteristic of an evocative outcome would mutate into a more expected one, consequently determining the probability of generating a counterfactual thought (Miller & Gunasegaram, 1990; Roese & Olson, 1995). In other words, the effect of these *outcome-based* factors on counterfactual generation does not specify any mutated antecedent but simply claim the fact that an alternative possibility could have easily been realized (Zhang, 2012). The most relevant of these factors are presented in more detail below:

1. **Expectancy:** the activation of counterfactual thoughts appears to be enhanced by the degree to which the outcome deviates from the individual's expectancies –i.e. the greater the inconsistent expectancy of the outcome, the more probable the generation of expectancy congruent counterfactuals (Roese & Olson, 1995).

2. **Valence of the outcome:** counterfactuals thoughts seem to be more extensively triggered by negative rather than positive outcomes (Kahneman & Miller, 1986). Thus, negative outcomes enhance counterfactual availability based on people's motivation to avoid future negative consequences (Landman, 1987).

3. **Involvement:** evidence suggests that the generation of counterfactual alternatives is more intense when the individual feels more personally involved in the outcome (Macrae & Milne, 1992).

4. **Proximity:** described first by Kahneman and Miller (1986), proximity or closeness of an outcome is one of the more explored variables that influences counterfactual availability, either spatially or temporally. This effect is explained based on the fact that outcomes that approximate (but does not reach) the goal, are more likely to create the feeling that something "almost happened" rather than those that came nowhere near the goal. Accordingly, Kahneman and Varey (1990) further suggested the concept of proximal or *close counterfactuals* which can be defined by three components: these counterfactuals (1) are not phrased as conditional prepositions, (2) are objectively close to having become reality, and (3) derive from the perception of *propensity* toward an unrealized outcome.

In summary, counterfactual generation might be influenced by several factors: expectancy, outcome valence, involvement and proximity. Specifically, the effect of these factors seems to be focused largely on the role they seem to play in the availability of counterfactual thoughts.

1.2.5. Consequences of counterfactual inference

Importantly, the pragmatic relevance of exploring counterfactual reasoning actually relies on the psychological and behavioural consequences that might derive from engaging in this type of reasoning. A review of the most relevant counterfactual reasoning consequences is presented below organized into two different types of effects: affective and judgemental (cognitive) reactions.

1. **Affective reactions:** a certain group of emotions including disappointment, regret and relief, have been reported to specifically predicate on CFT (Kahneman & Miller, 1986). Particularly, because research suggest that these emotions could actually not occur without prior counterfactual inference –e.g., research reporting how the experience of regret is linked to first noticing that a factual situation might have turned out better (Landman, 1993). Thus, evaluations of how a counterfactual

alternative could have been better (contrast effect) and how we might have personally affected such an outcome (causal-inference) are often responsible of eliciting an enhanced emotional reaction (Roese & Olson, 1995; Van Hoeck *et al.*, 2015).

2. **Judgemental reactions:** research in this field evidence how judgemental responses are mediated by both contrast effects and causal inference as well. Specifically, it appears that situations with an unusual antecedent trigger more intense judgements of avoidance (Miller & McFarland, 1986), and situations that seem "almost to have occurred" (either temporal or spatial) provoke an enhanced rumination reaction in the general population (Kahneman & Varey, 1990).

1.2.6. Function of counterfactual thinking

Along with the study of how it is activated and which brain structures are involved in this process, at present, it is of special interest to examine CFT from a functional perspective. Specifically focusing on the study of how when facing a particular deficit or need, the consequences of counterfactual inference are beneficial for the individual. Early studies on this topic described two conceptually distinct functions that counterfactual reasoning might be serving (Roese & Olson, 1995; Roese, 1997):

1. **Preparative Function:** focused on how certain counterfactuals (e.g., *upwards*) facilitate the analysis and understanding of past triumphs or mistakes in order to evoke intentions and behaviours that facilitate future improvement.

2. **Affective Function:** focused on how certain counterfactuals can be used to make individuals feel better –e.g., in front of a negative outcome that elicits discomfort, to generate worse counterfactual alternatives (*downwards*) can help improve the individual's feeling.

Based on these seminal studies, counterfactual reasoning has been widely examined from this perspective, evidencing multiple functions in which it might support adaptive behaviour. Such repertoire include enabling us to learn from past experiences (Byrne, 1997), modulating our emotional state (Roese & Hur, 1997), promoting our creativity (Markman *et al.*, 2007), and supporting future planning and prediction (Roese, 1999). In accordance, being related to the development of ToM (Guajardo *et al.*, 2009; Riggs *et al.*, 1998),

counterfactual reasoning process also seems to be involved in the development of the ability to draw inferences about the intentions, beliefs and feelings of others in social interactions (e.g., in the ability to differentiate lies from sarcasm), which is a central feature for managing and regulating social behaviour (Kern *et al.*, 2009).

Interestingly, counterfactual reasoning also seems to influence day-to-day functioning through the effect that it seems to exert on some specific cognitive biases. One of the most reported is the effect of counterfactuals on the "hindsight bias" which refers to the postoutcome exaggeration of the a priori predictability of the outcome –i.e., when people feel that they "knew it all along" (Roese & Olson, 1996). In this case, counterfactual inference acts by enhancing memory distortions through the retrospectively overestimation of the outcome's likelihood, consequently leading to a suboptimal decision-making process (Roese, 2004; Roese & Olson, 1996).

1.2.6.1. The Functional Theory of Counterfactual Thinking

From a theoretical perspective and organizing previous research findings in this field, Epstude and Roese proposed in 2008 the *Functional Theory of CFT* based on the notion that these thoughts are best explained in terms of their role in behaviour regulation and performance improvement. Recently revisited by these authors (Roese & Epstude, 2017), this theory is constructed on the content-specific pathway concept originally framed in Gollwitzer and Moskowitz's (1996) research on how goals influence actions. Particularly, based on how counterfactuals that are typically activated by failed goals, specify what one might have been done to have achieved such goals (Markman *et al.*, 1993). Within this framework, these authors pose a regulatory loop in which counterfactuals might be promoting behavioural change and learning from past experiences divided into three links or steps. **Figure 1.7.** presents a depiction of this process based on John's aforementioned fictional scenario.

Accordingly, this process begins with the recognition of a problem or negative experience that does not achieve the expected level of success and that activates a counterfactual generation in which typically the antecedent is an action and the consequent is a goal (*Step 1*). From this point, the counterfactual inference is followed by the activation of a behavioural intention (*Step 2*), finalizing with the release of the corresponding corrective

behaviour (*Step 3*). To the extent that such "new behaviour" alleviates the original problem, this mechanism will be effective in consolidating the process of learning from past experiences (Epstude & Roese, 2008). Accordingly, research has documented these three steps in the general population (Roese & Hur, 1997; Smallman & Roese, 2009; Webb & Sheeran, 2006).

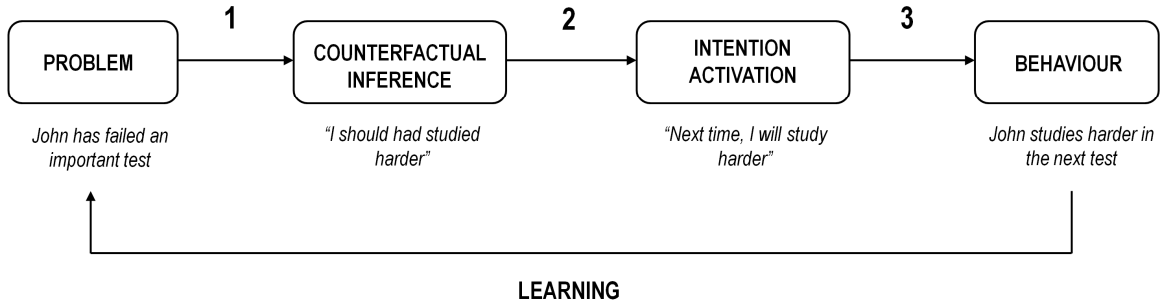

Figure 1.7. Regulatory loop in which counterfactual reasoning influences behaviour and enables learning from past experiences. Adapted from Epstude and Roese (2008).

In summary, these authors' proposal provides a framework for understanding the role of CFT as direct connector to course correction, to goal cognition, and to behaviour regulation. Particularly because, driven by unfulfilled goals, counterfactuals are mental simulations striving for better outcomes and success (Roese & Epstude, 2017).

1.2.7. Counterfactual thinking in relation to psychopathology

Despite being considered as a hallmark of human thought modulating our emotional experiences and future behaviour, little is yet known about how CFT can be altered. In general, research suggests that it can become dysfunctional in two ways: (1) through an excessive generation of counterfactuals that may be associated with excessive problem-focused cognitions (e.g., anxiety or rumination) or an excessive negative affect (e.g., sadness); and (2) through a CFT deficit, that could be associated with an impaired problem-focused cognition (e.g., underachievement or social dysfunction), along with an absence of negative affect (e.g., apathy) (Epstude & Roese, 2008). A review of the literature on the correspondence between counterfactual impairment and specific psychiatric disorders and neurological diseases is presented below by following this schema.

In relation to excessive generation, an altered counterfactual generation pattern has been described in patients with depression, characterized by a tendency to produce counterfactuals that are less feasible than those in the general population –i.e., a tendency to generate alternative scenarios including less plausible actions and/or actions less likely to change the outcome (Markam & Miller, 2006; Quelhas *et al.*, 2008). Other studies have reported an excess of dysfunctional counterfactuals related to the characteristic symptoms of the disorder such as an increased experience of regret (Howlett & Paulus, 2013; Monroe *et al.*, 2005), rumination tendency (Williams *et al.*, 2007) or difficulties in removing negative stimuli from short-term memory (Joormann & Gotlib, 2010). Research has also evidenced how individuals with social anxiety, who are highly concerned about potential past failures and inadequate behaviour, tend to generate greater upward counterfactual thoughts when exposed to fictitious social situations (Kocovski *et al.*, 2005). Accordingly, Roese *et al.* (2009) have also described how the excessive generation of counterfactuals thought is associated with anxiety and rumination. In keeping with this line, results from a single study by Gillan *et al.* (2014) examining counterfactual decision making in a group of patients with obsessive compulsive disorder also evidenced how the ability to compare past (backward) counterfactual scenarios was enhanced among these individuals. These authors proposed that this excess of backward counterfactual inference could be a potential contributor to the obsessive rumination.

When turning to the question of a counterfactual deficit, the focus of research has been the study of patients with a neurological or psychiatric disorder characterized by frontal lobe dysfunction. In the line with previous studies connecting CFT to behaviour in neural circuitry within the PFC (Gomez-Beldarrain *et al.*, 2005; Ursu & Carter, 2005), impairment in this cognitive process has been observed in patients with Parkinson's disease (McNamara *et al.*, 2003), Huntington's disease (Solca *et al.*, 2015) and schizophrenia (Hooker *et al.*, 2000; Roese *et al.*, 2008). In all these clinical conditions, this deficit seems to be related to impairment in the mental simulation and executive function components of counterfactual thought of these patients.

1.2.7.1. Early studies of counterfactual deficit in schizophrenia

Specifically referring to schizophrenia, only two studies have explored to date CFT in this clinical population at two different levels of processing. In the first place, Hooker *et al.* in

2000 developed a study focused on the evaluation of the counterfactual generation and inference in a relatively small sample of 14 patients and 12 controls. By using different methods to quantitatively explore CFT, this study measured the ability to generate spontaneous counterfactual alternatives, as well as the effect of two different determining factors in the counterfactual reasoning process: the proximity and unusualness of the situation. Results indicated that patients generated fewer counterfactual thoughts than controls and showed a different pattern of responses when counterfactually deriving inferences. In addition, this impairment was related to the patients' deterioration in social functioning but not to cognitive functioning.

Secondly, corresponding to the second link of Epstude and Roese's regulatory loop (2008), the effect of counterfactual reasoning on the activation of behavioural intentions was explored by Roese *et al.* in 2008 by using a semantic priming task developed by these authors. With a sample of 15 patients with schizophrenia and 13 healthy subjects, the experiment consisted of 45 trials with a yes/no answer to a declaration of intention (i.e., the intention to do a specific action in the future) in which reaction time (RT) was used as the dependent variable. Each trial presented a negative event that was judged using a within-subject sequential priming paradigm in one of three ways: a counterfactual ("should have"), a neutral control (a word-counting judgement) or a no-judgement baseline. Results showed, that whereas healthy controls responded faster in front of counterfactual judgements relative to control judgements, patients with schizophrenia' RT did not vary among primes –i.e., the counterfactual trial did not facilitate the activation of behavioural intentions compared with the neutral-control trial. Hence, these authors concluded that the link between counterfactual inference and the generation of behavioural intentions was broken in schizophrenia, stating that rehabilitation strategies designed to normalize counterfactual reasoning could not provide any benefit for these patients.

Therefore, in conjunction these findings provided a basis for the study of CFT and counterfactual reasoning as a useful technique for understanding schizophrenia, its symptoms and the day-to-day challenges faced by these patients. However, it should be noted that both these studies presented some methodological limitations that might compromise the results (e.g., with regards to the samples or the experimental designs) that further research could try to address and extend.

1.3. Rationale for the Study

Schizophrenia is one of the most serious and complex psychiatric illnesses supposing a great negative impact on the life of the individuals who suffer from it. Currently, cognitive impairment is described as a core feature of the illness and is characterized by the presence of deficits in almost all neurocognitive and social cognition domains. Considered as a strong correlate of these patients' real-world functioning, such deficiencies are already observable in the early stages of the disorder and seem to be present even before the initiation of treatment with neuroleptic drugs. Interestingly, the study of reasoning deficits and cognitive biases influencing the formation of psychotic symptoms has recently become a relevant field of research in schizophrenia. Importantly, individuals who share unexpressed genetic components of vulnerability to schizophrenia also experience impairments in cognitive function, including the unaffected first-degree relatives of these patients. Currently, it is a high priority to identify the biological underpinnings of cognitive deficits in schizophrenia to develop effective treatments promoting the functional recovery of these patients. One way to do so is through the identification and further characterization of novel cognitive deficits specific for the disorder.

Pervasive in everyday life, CFT involves mental representations of alternatives to past situations that were once factual possibilities but which never occurred. The generation of counterfactual thoughts is mainly activated by negative outcomes in the form of "if only" conditional prepositions. Furthermore, counterfactual reasoning refers to the remarkable ability to make inferences through the generation of counterfactual thoughts. Framed in Kahneman and Miller's (1986) *norm theory*, the ability to infer through counterfactuals seems to be especially constrained by specific factors of reality such as unusualness or proximity of the situation, and the primacy effect in causal sequence of events –i.e., the causal order effect. Overall, although this complex psychological phenomenon seems to be supported by the coordinated interaction between different neural networks, PFC regions seem to be the primary regions that are activated in people engaged in CFT tasks. From a functional perspective, reasoning through counterfactuals seems to serve a behaviour-regulating function, enabling learning from past experiences, modulating emotional state and sustaining future planning and prediction. Interestingly, the study of CFT deficits in candidate clinical populations has been recently considered a relevant object of study since it might help in the

understanding of these patients' symptoms and day-to-day challenges. It is thought that such research could potentially aid in the identification of specific disrupted sub-components and might eventually lead to new diagnostic tools or even new targets for treatment in the future.

Therefore, given that schizophrenia seems to be related, at least in part, to PFC dysfunction and that patients suffering from it show impoverished decision-making and problem-solving skills, as well as a poor ability to generate novel ideas and plan for the future, studies centered on the evaluation of counterfactual reasoning in schizophrenia should be expected; especially for the impact that these deficits might have on these patients' personal and social functioning. Unfortunately, despite preliminary findings seeming to suggest CFT disruption in this disorder, research on this matter is still scarce. Further research is needed in order to properly characterize counterfactual reasoning impairment in schizophrenia since it might lead to the identification of a new primary cognitive deficit of the illness susceptible to becoming a target for treatment in the future.

2. Aims and Hypotheses

2.1. General Aims

The overall aim of the present thesis is to provide new insights into neurocognitive impairment in schizophrenia by further characterizing counterfactual reasoning impairment in this disorder. Using different neuropsychological methodologies, we sought to better describe these deficits and its relationship with cognitive functioning and clinical status by assessing adult schizophrenia patients and non-psychotic first-degree relatives in comparison with healthy control subjects. We hope that our findings might contribute to the enhancement of knowledge on the pathophysiology of the disorder, leading to a better understanding of these patients' day-to-day challenges, and eventually providing new diagnostic tools or even targets for treatment.

2.2. Specific Aims and Hypotheses

In general, the paucity of research on this topic in schizophrenia has given to our investigation an imminent exploratory character with difficulties when having to formulate predictions. Notwithstanding the previously stated, the specific aims and hypotheses for each of the four studies included in this thesis are detailed below.

STUDY 1

"Counterfactual reasoning deficits in schizophrenia patients"

Main Aims

- To study differences in the ability to activate counterfactual thoughts between a group of patients with schizophrenia and a group of healthy control subjects.
- To study the effect of different factors known to influence the counterfactual inference generation in a group of patients with schizophrenia in comparison with a group of

healthy control subjects. The factors that will be explored include (1) the causal order effect, and the (2) "unusualness" and (3) "proximity" of the factual situation.

Secondary Aims

- To study differences in the association between variables related to CFT performance and variables related to neurocognitive functioning in a group of patients with schizophrenia in comparison to a group of healthy control subjects.
- To study associations between CFT performance and specific clinical features of the disorder (e.g., symptom severity or illness duration) in a group of patients with schizophrenia.

Specific Hypotheses

We hypothesize that patients with schizophrenia will activate fewer counterfactual thoughts and will present a different pattern of response when having to derive inferences from counterfactuals with respect to the healthy control subjects. We also expect to find significant associations with severe symptomatology of the disorder and poorer neurocognitive performance in the group of schizophrenia patients.

STUDY 2

"Symptomatic remission and counterfactual reasoning in schizophrenia"

Main Aims

- To study differences in the ability to activate counterfactual thoughts between a group of patients with schizophrenia in a state of symptomatic remission (in the sense of Andreasen *et al.*, 2005) and a group of healthy control subjects.
- To study the effect of different factors known to influence the counterfactual inference generation in a group of patients with schizophrenia in a state of symptomatic remission (in the sense of Andreasen *et al.*, 2005) in comparison with a group of healthy control subjects. The factors that will be explored include (1) the causal order effect, and the (2) unusualness and (3) proximity of the factual situation.

Secondary Aims

- To study associations between variables related to CFT performance and specific clinical features of the disorder (e.g., symptom severity or illness duration) in a group of patients with schizophrenia in a state of symptomatic remission (in the sense of Andreasen *et al.*, 2005).

Specific Hypotheses

We hypothesize that counterfactual disruption, including deficits on the counterfactual thoughts activation and counterfactual-derived inferences, will manifest even though patients are in a situation of symptomatic remission –i.e., suggesting that such deficits might actually be independent of symptomatology. We also expect to find significant associations with other clinical features of the disorder, for instance, longer duration of the illness.

STUDY 3

"Counterfactual reasoning deficits in non-psychotic first-degree relatives of people with schizophrenia"

Main Aims

- To study differences in the ability to activate counterfactual thoughts between a group of non-psychotic first-degree relatives of patients with schizophrenia in comparison with a group of patients with schizophrenia and a group of healthy control subjects.
- To study the effect of different factors known to influence the counterfactual inference generation in a group of non-psychotic first-degree relatives of patients with schizophrenia in comparison with a group of patients with schizophrenia and a group of healthy control subjects. The factors that will be explored include (1) the causal order effect, and the (2) unusualness and (3) proximity of the factual situation.

Secondary Aims

- To study differences in the association between variables related to CFT performance and variables related to neurocognitive functioning in a group of non-psychotic first-

degree relatives of patients with schizophrenia in comparison with a group of patients with schizophrenia and a group of healthy control subjects.

- To study differences in the association between variables related to CFT performance and levels of schizotypy and psychotic-like experiences in a group of non-psychotic first-degree relatives of patients with schizophrenia compared to a group of healthy control subjects.

Specific Hypotheses

We hypothesize that the group of non-psychotic first-degree relatives will perform poorly on all counterfactual measures compared to the healthy controls, but better than the patients with schizophrenia. We also expect to find negative associations between CFT performance and levels of schizotypy and psychotic-like experiences in the group of relatives when compared to the healthy control subjects.

STUDY 4

"Patients with schizophrenia activate behavioural intentions facilitated by counterfactual reasoning"

Main Aims

- To study differences in the activation of behavioural intentions through counterfactual inference between a group of patients with schizophrenia and a group of healthy control subjects. This ability will be explored by using a novel semantic priming paradigm adapted from the original design of Roese *et al.*, 2008.

Secondary Aims

- To study differences in the association between the activation of behavioural intentions through counterfactual inference and variables related to neurocognitive functioning between a group of patients with schizophrenia and a group of healthy control subjects.
- To study differences in the association between the activation of behavioural intentions through counterfactual inference and specific clinical features of the disorder (e.g., symptom severity or illness duration) in a group of patients with schizophrenia.

Specific Hypotheses

By developing a new semantic priming task, we hypothesize that schizophrenia patients will be able to activate behavioural intentions facilitated by counterfactual inference although with more difficulties than healthy controls. We also expect to find significant associations with severe symptomatology of the disorder and poorer neurocognitive performance.

3. Material and Methods

This chapter presents a summary of the material and procedures performed to address the proposed aims. First of all, though, specific characteristics of the method that guide part of the development of this chapter must be taken into account. Particularly, it has to be noted that the four studies included in this thesis were actually part of two different main research projects from Bellvitge University Hospital – IDIBELL as presented below:

- *Study 1* and *Study 4* within **PROJECT 1** (PR077/10).
  2009-2011: "Counterfactual thinking in patients with schizophrenia. Association with neurocognitive and clinical variables."

- *Study 2* and *Study 3* within **PROJECT 2** (PR160/12).
  2012-2016: "Characterization of counterfactual reasoning deficits in schizophrenia patients and first-degree relatives in comparison with healthy control subjects."

Thus, although the counterfactual assessment procedures and the clinical status evaluations did not vary across studies, there were methodological differences between projects that have to be considered: first, the results presented in this thesis were not based on the same sample and second, the neuropsychological evaluation procedure was different between projects. Within this framework, specific differences will be detailed for each study throughout this chapter when appropriate.

3.1. Participants

All the patients with schizophrenia and non-psychotic first-degree relatives included on this thesis were recruited from the outpatient service of the Psychiatry Department at Bellvitge University Hospital and two other associated mental health centers in the same catchment area of the province of Barcelona (Spain): the Polyvalent Mental Health Unit (Germanes Hospitalàries) and the Mental Health Unit of L'Hospitalet de Llobregat (Catalan Institute of Health). Healthy control subjects, without a history of personal (Axis I and Axis II) or family

psychiatric disorders, were recruited from a similar socio-demographic environment as the other probands. The corresponding study procedures were approved by the Clinical Research Ethics Committee of the Ciutat Sanitària de Bellvitge (CEIC Bellvitge), and all probands signed informed consent before entering the corresponding study.

Participants, fluent in Spanish and with 18 or more years of age, were included in each of the corresponding studies after an initial inclusion interview in which mental and personality disorders were assessed using the structured clinical interview for DSM-IV Axis I Disorders (SCID-I; First *et al.*, 1997) and Axis II Personality Disorders (SCID-II; First *et al.*, 1994). **Figure 3.1.** presents a description of the samples used in the current thesis.

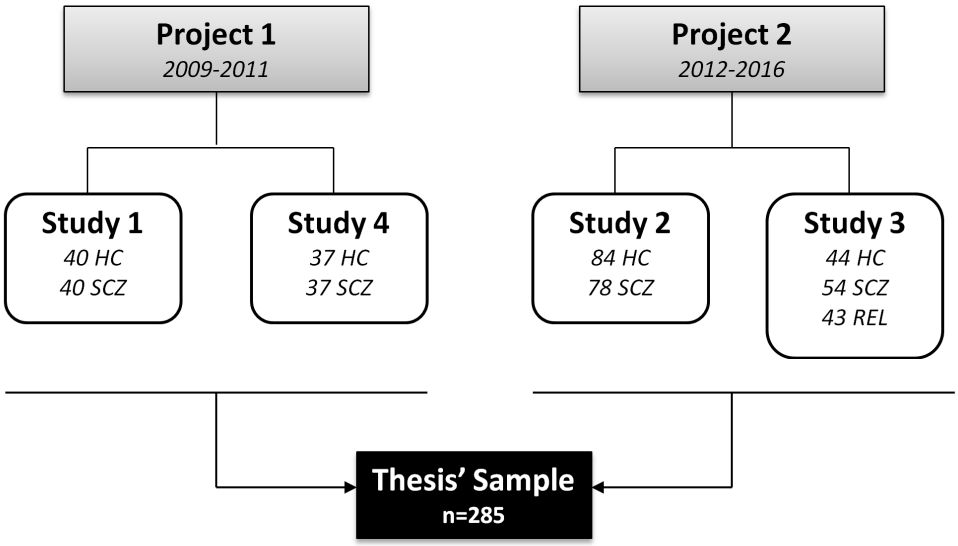

Figure 3.1. Chart of participants included as part of the current thesis procedures.
HC: healthy controls; SCZ: schizophrenia patients; REL: non-psychotic first-degree relatives.

Exclusion criteria for all the three groups of study were: a history of substance use disorder as defined by the DSM-IV-TR (American Psychiatric Association, 2000) with the only exception being nicotine dependence; head trauma involving loss of consciousness; an organic disease with mental repercussions; or an estimated intelligence quotient (IQ) below 70. Additional specific inclusion and exclusion criteria are presented below. All patients with schizophrenia met DMS-IV-TR criteria (American Psychiatric Association, 2000); subjects with diagnoses of bipolar, schizoaffective, delusional or other Axis I disorders were excluded. As well, none of these patients could have undergone electroconvulsive therapy in the six

months prior to study. Additional inclusion criteria for *Study 2* and *Study 3* (as part of *Project 2*) was that all schizophrenia patients had to meet criteria for symptomatic remission as defined by Andreasen *et al.* (2005). Originally proposed to facilitate research and support a positive, longer-term approach to studying outcome in schizophrenia, this criteria is defined as a score of ≤3 (mild) on eight selected items (P1, P2, P3, N1, N4, N6, G5 and G9) of the PANSS (Kay *et al.*, 1987; Peralta & Cuesta, 1994) which has to be maintained for at least 6 months. First-degree relatives of patients with schizophrenia were sampled for *Study 3* including 19 parents, 19 siblings and 5 offspring. These participants were excluded if they had a history of a psychotic disorder (DSM-IV-TR; American Psychiatric Association, 2000).

3.2. Counterfactual Reasoning Evaluation

Following previous reports on the general population, the current thesis has focused on exploring the counterfactual measures presented below:

1. **Activation** of **counterfactual thoughts**.
2. **Generation** of **counterfactual-derived inferences** under the influence of different factors including the examination of:
    a. The causal order effect.
    b. Unusualness of the factual situation.
    c. Proximity (both temporal and spatial) of the factual situation.
3. **Activation of behavioural intentions** through counterfactual inference generation.

The conjunction of methods used to quantitatively explore counterfactual reasoning in this thesis is described in detail below. **Figure 3.2.** presents an overview of the entire evaluation procedure.

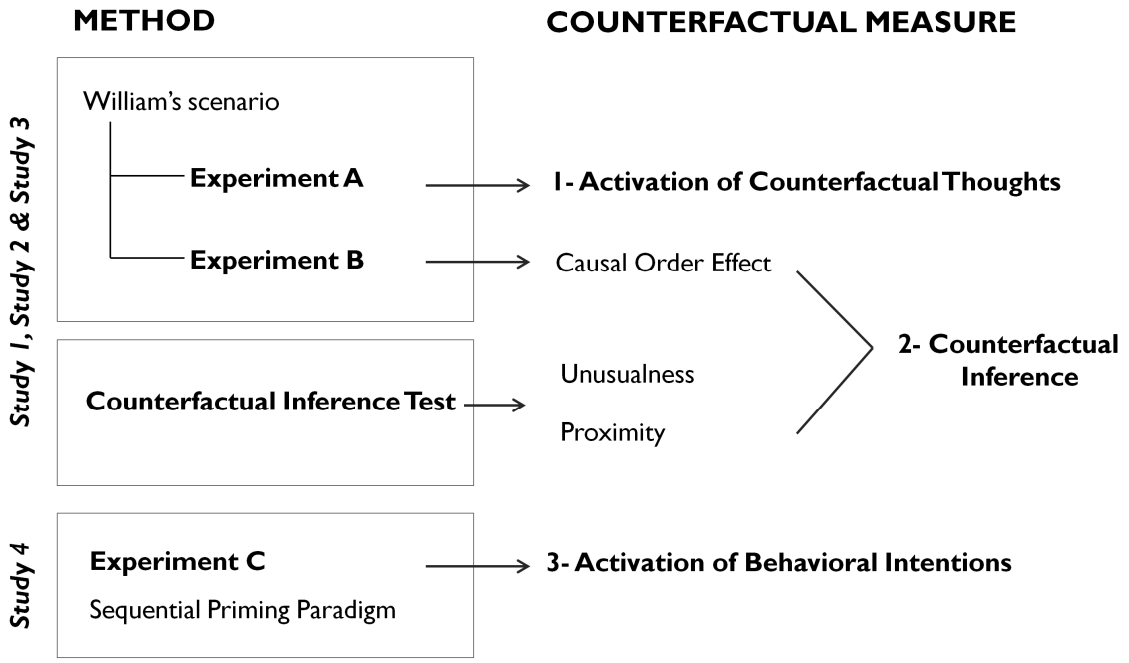

Figure 3.2. Overview of the counterfactual reasoning evaluation procedure.

3.2.1. Experiments A & B: "William's scenario" research paradigm

The research paradigm known as "William's scenario" developed by Wells *et al.* (1987) was the foundation used to carry out the two experiments designed to explore activation of counterfactual thoughts and the causal order effect. This research paradigm is based on the original research by Kahneman and Tversky (1982a), consists of presenting a scenario of four consecutive independent events that result in a negative outcome. In brief, the scenario presents the story of an individual, William, who hears on the radio that a store on the other side of town has a great sale on a limited number of stereo systems. His progress in getting to the store is impeded by four consecutive minor misfortunes: a) a speeding ticket, b) a flat tire, c) a traffic jam, and d) a group of elderly people crossing the street. Because of these mishaps, he arrives late only to find out that the last stereo system has already been sold just a few minutes earlier. For the current thesis, an adaptation from the original experiment by Wells *et al.* (1987) was done – i.e., instead of the fictional character of William, participants on this experiment had to imagine themselves as the main character of the scenario.

In order to avoid first event bias, the researchers randomly change the order of the events using a 4x4 Latin square design – i.e., each event appeared equally often in each of the

four possible positions in the scenario. Thus, after presenting the corresponding version of the scenario to the proband, two experiments were carried out:

3.2.1.1. Experiment A: activation of counterfactual thoughts assessment

The ability to activate counterfactual thoughts was quantitatively examined by asking all the participants to say aloud as many alternatives as possible in order to avoid the final negative outcome in the scenario. These counterfactual thoughts could be original alternatives (e.g., "If only I had called and made a reservation in advance") or alternatives that changed one of the "unfortunate" events (e.g., "If only I hadn't been speeding"). All discrete responses given were recorded by two independent researchers who filtered which answers were real counterfactual thoughts and which ones were illogical or bizarre (e.g., "I continued sleeping"). Participants were given five minutes on average to complete this experiment.

3.2.1.2. Experiment B: the causal order effect assessment

In this experiment, participants were asked to choose which one of the four events was the most probable cause of the negative outcome of the scenario –i.e., the event they would select in order to undo the final result. As previously mentioned, this procedure was based on previous research that has described how the general population usually chooses the first of a chain of events as the main determinant event, even though these events are equal and objectively none is more crucial than the others for the final negative outcome (Segura *et al.*, 2002). Thus, this effect explains how the focus of CFT tends to be influenced by the order in which the information is presented. To complete this experiment, participants had to choose a specific event from the sequence. Those who, even when encouraged, were still unable to choose one of the events, were directly assigned the response type "reasoning blocking." This was done to ensure that these responses were not considered as missing data. The time given to participants to complete this experiment was 60 seconds. Researchers recorded each participant's answer.

It should be noted, though, that the order in which both experiments were administered in the corresponding *Study 1*, *Study 2* and *Study 3* was not the presented above: first the causal order effect was assessed (Experiment B), and second, the activation of counterfactual thoughts (Experiment A). This methodological decision was made based on

well documented attentional and working memory disruption in schizophrenia (Heinrichs & Zakzanis, 1998) that could be compromising their performance on Experiment B particularly.

3.2.2. Counterfactual Inference Test

The Counterfactual Inference Test (CIT) was used to explore the ability of individuals to derive inferences from CFT taking in account different factors described to influence it: the antecedent-based factor of unusualness and the outcome-based factor of proximity (for an overview of the test, see **Table 3.1.**). As mentioned above, this test was designed based on previous research describing how CFT is enhanced when encountering events with outcomes preceded by unusual rather than typical actions (Kahneman & Tversky, 1982a), or events that seem "almost" to have occurred, either spatially or temporally (Kahneman & Varey, 1990). At the same time, the CIT also examines the consequences of the counterfactual inference by enhancing or diminishing the individual's affective and judgemental reactions.

Table 3.1. The Counterfactual Inference Test.

Scenario	Response
1. Janet is attacked by a mugger only 10 meters from her house. Susan is attacked by a mugger 1 kilometer from her house. *Who is more upset by the mugging?*	**a) Janet** b) Susan c) Same/Can't tell
2. Anna gets sick after eating at a restaurant she often visits. Sarah gets sick after eating at a restaurant she has never visited before. *Who regrets their choice of restaurant more?*	a) Anna **b) Sarah** c) Same/Can't tell
3. Jack misses his train by five minutes. Ed misses his train by more than an hour. *Who spends more time thinking about the missed train?*	a) Ed **b) Jack** c) Same/Can't tell
4. John gets into a car accident while driving on his usual way home. Bob gets into a car accident while trying a new way home. *Who thinks more about how his accident could have been avoided?*	**a) Bob** b) John c) Same/Can't tell

Note. The typical pattern of responses (that is, the target counterfactual responses) is indicated in boldface (Hooker *et al.*, 2000).

Originally developed by Hooker *et al.* (2000), the CIT is a multiple-choice, self-reporting instrument consisting of a set of four forced-choice questions; for each, two events with similar outcomes experienced by two subjects are presented. However, the circumstances between them differ such that in one the subjects should think "if only" to a greater extent than in the other. Therefore, Scenario 1 focuses on a general affective reaction ("upset") in the context of a spatial "nearly happened" event; Scenario 2 on a general affective reaction ("regret") in response to an unusual event; Scenario 3 on a judgemental or cognitive reaction ("rumination") brought on by a temporal "nearly happened" event; and Scenario 4 on a judgemental or cognitive reaction ("judgements of avoidance/prevention") in the face of an unusual event (Hooker *et al.*, 2000).

For each situation, three possible answers are presented: a target counterfactual response (the option where CFT is activated to a greater extent), a non-target response (the option where CFT is also activated but less intensely), and a "same/can't tell" answer if the participant considers none of the previous options to be suitable (the option where CFT is not activated at all). **Table 3.2.** summarizes the variables examined in the CIT.

Table 3.2. Summary of the variables examined in the CIT.

Scenario	Aspect of the situation	Reaction
1. Janet & Susan	Spatial "nearly happened" event	*Upset (affective)*
2. Anna & Sarah	Unusual event	*Regret (affective)*
3. Ed & Jack	Temporal "nearly happened" event	*Rumination (judgmental)*
4. Bob & John	Unusual event	*Avoidance (judgmental)*

Each scenario on the test is given a maximum score of 1 if the subject chooses the target counterfactual response; if the subject chooses any of the other answers, the given score is zero. The total score, therefore, may range between 0 and 4, with greater values indicating a counterfactual response closer to a normative pattern. Participants were given five minutes to complete the test.

3.2.3. Experiment C: activation of behavioural intentions assessment

In *Study 4*, an experiment was developed using an adaptation of the sequential priming paradigm originally designed by Roese *et al.* (2008) in order to assess if a preceding counterfactual judgement facilitated the activation of a relevant behavioural intention judgement.

Testing was implemented using desktop computers running DMDX software (Forster & Forster, 2003) and consisted of two blocks of 16 trials preceded by a 2-minute training block. The experiment block had a duration of 10 minutes. In this way, all subjects completed 32 judgement trials that were structured in three stages around a hypothetical negative event (see **Figure 3.3.** for an overview of the procedure): first, a description of a negative everyday event appeared on the screen (stage 1) (e.g., "I have missed the train"); two seconds later, a prime judgement (stage 2) that could be a counterfactual prime (e.g., "I should have") or a neutral-control prime (a factual cue such as "It has five words") appeared.

The main difference from the original proposal by Roese *et al.* (2008) in the current thesis is that the neutral-control prime was modified in order to balance the cognitive load of the procedural work between both type of primes as follows: while in the original experiment participants executed a word-counting judgement, in the *Study 4*, the neutral-control task consisted only of reading a statement as in the counterfactual condition.

Finally, this stage was followed by a subsequent behavioural intention statement that could be semantically related to the action described in the first place or not (stage 3) (e.g., "got out of bed sooner" or "washed the car before"). Participants had to press a key on the computer labelled "yes" or "no" to indicate if the behavioural intention was related to the negative everyday event that preceded it. Trial order was randomized across participants.

Once the experiment was finished, two outcomes were recorded: (1) errors committed during the experiment understood as incorrect associations made by the participants between the first event and the final outcome (e.g., answering "no" when the event and the intention judgement were actually related, or vice versa), and (2) reaction time (RT) to reach a correct association or answer, defined as the time gap from stage 3 and participants' response. RT was recorded as mean and standard deviation of all 32 administered trials (16 counterfactual and 16 neutral-control primes). With regards to latter

measure, it should be noted that in instead of using the raw RT scores, the percentage gain in the reaction time (RT) difference to reach a correct association or answer whether the prime was a counterfactual or a neutral-control cue was calculated. This outcome, the percentage gain, was defined as the difference between RT in the neutral-control prime and RT in the counterfactual prime divided by RT in the neutral-control cue. This decision was based on previous research findings evidencing an arithmetical artefact due to the effect of a general RT slowing in schizophrenia (Pomarol-Clotet *et al.*, 2008b).

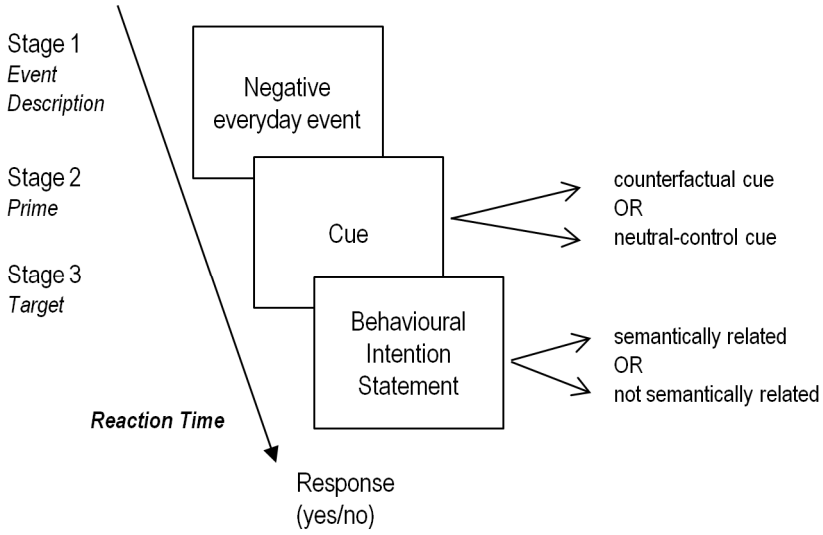

Figure 3.3. Overview of *Study 4*'s sequential priming paradigm.
Adapted from Roese *et al.* (2008).

3.3. Neuropsychological Evaluation

In general, laterality was assessed by means of the Edinburgh Handedness Inventory (Oldfield, 1971) and estimated IQ was calculated from the standardized score [(SS × 5)+50] of the Vocabulary subtest of the Wechsler Adult Intelligence Scale-III (WAIS-III; Wechsler, 1999). However, in *Study 3*, IQ was estimated using a combined score from the Vocabulary and Block Design subtests from the WAIS-III (Wechsler, 1999) based on the proposal by Sattler (2001). Furthermore, two different batteries of standardized neuropsychological tests were administered depending on the research project as follows:

3.3.1. *Project 1* - Brief Assessment of Cognition in Schizophrenia

The Spanish version of this well-validated neuropsychological battery was used to evaluate cognitive performance in *Study 1* and *Study 4* framed in *Project 1* (Segarra *et al.*, 2011). Originally designed by Keefe *et al.* (2004), the Brief Assessment of Cognition in Schizophrenia (BACS) encompasses a broad range of cognitive functions including verbal memory, working memory, motor function, verbal fluency, attention and executive function.

3.3.2. *Project 2's* neuropsychological battery

Cognitive functioning in *Study 3* was assessed using a comprehensive battery of 13 standardized neuropsychological tests designed to encompass all 7 dimensions proposed in the MCCB (Green *et al.*, 2004). **Table 3.3.** summarizes all the neuropsychological tests administered classified by cognitive dimension.

3.4. Clinical Assessments

In accordance with the objectives of the current thesis, a broad range of psychometric instruments was administered depending on each of the studies' objectives to assess psychopathology and level of functioning among schizophrenia patients.

- **The Positive and Negative Syndrome Scale (PANSS)**: This hetero-administered instrument evaluates psychopathology state of patients including both positive and negative symptoms of schizophrenia as well as general psychopathology. Originally developed from the items on the Brief Psychiatric Rating Scale (Overall & Gorham, 1962), the PANSS is a semi-structured interview consisting of 30 items that focuses on the week previous to the assessment and has to be administered by a trained professional. Each item is rated on a 7-point scale using a range of responses from 1 (absence of symptom or does not apply) to 7 (maximum severity of the symptom). Thus, an overall score and a score for each dimension (positive, negative and general symptoms) are obtained from adding the corresponding items of the test. The PANSS was developed by Kay *et al.* (1987), and the Spanish version was adapted by Peralta & Cuesta (1994).

Table 3.3. Neuropsychological battery administered in *Study 3*.

Cognitive domain	**Test**
Attention	Continuous Performance Test-II (Conners *et al.*, 2000)
Processing Speed	Trail Making Test, Form A (Reitan & Wolfson, 1993)
	WAIS-III, Symbol Coding Test (Wechsler, 1999)
	Stroop Test, word-color (Golden, 1978)
Executive function	Trail Making Test, Form B (Reitan & Wolfson, 1993)
	Stroop Test, word-color interference effect (Golden, 1978)
	Controlled Oral Word Association Test, FAS-Test (Loonstra *et al.*, 2001)
	Test Barcelona, Animal Words (Peña-Casanova, 1990)
	Wisconsin Card Sorting Test, WCST-128 (Heaton *et al.*, 1993)
	Tower of London Test (Culbertson & Zillmer, 2001)
Working Memory	WAIS-III, Digit Span Test (Wechsler, 1999)
	WAIS-III, Letter-Number Sequencing Test (Wechsler, 1999)
Verbal Memory	California Verbal Learning Test, Spanish version –TAVEC (Benedet & Alejandre, 1998)
Visual Memory	Wechsler Memory Scale-III, Visual reproduction Tests I and II (Wechsler, 1997)
Social cognition	Mayer-Salovey-Caruso Emotional Intelligence Test – MSCEIT (Extremera & Fernández-Berrocal, 2009)
	Internal, Personal and Situational Attributions Questionnaire – IPSAQ (Kinderman & Bentall, 1996)

WAIS-III: Wechsler Adult Intelligence Scale-III

- **The Clinical Global Impression Scale - Severity Section (CGI-S):** The illness severity section of the CGI was used to assess schizophrenia patient's overall clinical state as a global impression made on the rater. This section is rated on a 7-point scale using a range of responses from 1 (normal) through to 7 (amongst the most severely ill patients). The CGI scale was developed by Guy (1976).

- **The Montgomery-Åsberg Depression Rating Scale (MADRS):** This is a hetero-administered instrument, designed to evaluate ten core symptoms of depressive illness in the adult population, as well as the effects of antidepressant treatment. The MADRS is a brief instrument consisting of 10 items yielding each a score of 0 (absence of symptoms) to 6 (maximum severity of symptoms). Overall score ranges from 0 (normal) to 60 (maximum level of depression). An overall score below 10 indicates absence of depressive illness. The MADRS was originally developed by Montgomery and Åsberg (1979) and the Spanish version was adapted by Lobo *et al.* (2002).

- **The Global Assessment of Functioning Scale (GAF):** This is a hetero-administered scale corresponding to Axis V of the internationally accepted DMS-IV-TR (American Psychiatric Association, 2000). The GAF assigns a clinical judgment in a numerical fashion to the individual's overall functioning level. Impairments in psychological, social and occupational/school functioning are considered, but those related to physical or environmental limitations are not. The scale ranges from 1 (most severely ill) to 100 (superior functioning), and is divided in 10-point intervals with anchor points describing symptoms and functioning that are relevant for scoring.

- **The Scale to Assess Unawareness of Mental Disorder - Abbreviated version (SUMD):** The SUMD is a standardized expert-rating scale used to evaluate awareness or insight across a variety of manifestations of schizophrenia. Based on a direct patient interview, the abbreviated version of this instrument comprises 9 items (current awareness of the following states): (1) having a mental disorder, (2) consequences of a mental disorder, (3) effects of drugs, (4) hallucinatory experiences, (5) delusional ideas, (6) disorganized thoughts, (7) blunted affect, (8) anhedonia, and (9) lack of sociability. Each item is scored on a 6-point scale with higher scores indicating poorer insight. The abbreviated version of the SUMD was developed by Amador *et al.* (1994) and the Spanish version was adapted by Ruiz *et al.* (2008).

Socio-demographic characteristics, medical and psychiatric comorbidities, and clinical variables of schizophrenia, were recorded by means of an in-house standardized evaluation for the entire sample. The daily dose of antipsychotic medication was calculated in chlorpromazine equivalents (Woods *et al.*, 2003; Kane *et al.*, 2003).

3.5. Other Assessments

Levels of schizotypy and psychotic-like experiences (PLE's) were assessed using two different psychometric instruments in non-psychotic first-degree relatives and healthy control subjects:

- **The Schizotypal Personality Questionnaire-Brief (SPQ-B):** Used to measure schizotypal features of personality, the SPQ-B is a self- report instrument consisting of the 22 most reliable items from the original Schizotypal Personality Questionnaire (Raine, 1991). Both instruments were modelled on DSM-III-R criteria for schizotypal personality disorder (American Psychiatric Association, 1987). The SPQ-B yields a total score ranging from 0 to 22 and three subscale scores for each of the three main factors evaluated: Cognitive-perceptual, Interpersonal, and Disorganized. The test was developed by Raine and Benishay (1995), and the Spanish version was adapted by Mata *et al.* (2005).

- **The Community Assessment of Psychotic Experiences-42 (CAPE-42):** Originally developed from the items of the 21-item version of the Peters *et al.*'s (2004) Delusions Inventory. This self-report questionnaire is used to evaluate the presence of clinical psychosis dimensions in the general population. Consisting of 42 items that evaluate the positive (18 items), negative (14 items) and depressive (8 items) dimensions of the psychotic symptoms, this instrument yields a total score and 3 subscales for each dimension with higher scores indicating higher level of psychotic-like experiences reported. The CAPE-42 was designed by Stefanis *et al.* (2002) and the Spanish version was adapted by Fonseca-Pedrero *et al.* (2012).

4. Results

4.1. Study 1

Counterfactual Reasoning Deficits in Schizophrenia Patients

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PLoS ONE. 2016 Jan 11(2): e0148440. [*co-first authors]

Impact Factor (JCR 2015): 3.057 (Quartile1, Multidisciplinary Sciences)

Summary of the results

In general, the results from *Study 1* seemed to support the main hypotheses posited by the research group: counterfactual thought activation and counterfactual inference appeared to be globally altered in the group of schizophrenia patients with respect to healthy control subjects. Specific results are detailed below in order of relevance:

1. Compared to the healthy controls, patients with schizophrenia significantly activated less number of counterfactual thoughts when faced with a negative fictional scenario.

    1a. Schizophrenia patients also tended to be unable to activate any counterfactual thought in order to avert the negative outcome.

2. When exploring the causal order effect, results suggested differences between groups regarding the general pattern of response when attributing causality in front of a negative fictional scenario –i.e., schizophrenia patients tended to deviate from the norm by choosing the first event less frequently than controls.

3. Results from the *Counterfactual Inference Test* (Hooker *et al.*, 2000) revealed that, in comparison with the healthy controls, patients with schizophrenia did not follow the norm when deriving inferences through CFT. Specifically, results suggested that:

    3a. Schizophrenia patients selected a regretful reaction in response to an unusual event (Scenario 2) less frequently than controls.

    3b. Schizophrenia patients selected a reaction of rumination in response to a temporal "nearly happened" event (Scenario 3) less frequently than controls.

4. No significant associations were found between all the counterfactual measures explored and the neuropsychological variables examined.

5. No significant associations were found between all the counterfactual measures explored and the clinical variables examined.

PLOS ONE

RESEARCH ARTICLE

Counterfactual Reasoning Deficits in Schizophrenia Patients

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OPEN ACCESS

Citation: Contreras F, Albacete A, Castellví P, Caño A, Benejam B, Menchón JM (2016) Counterfactual Reasoning Deficits in Schizophrenia Patients. PLoS ONE 11(2): e0148440. doi:10.1371/journal.pone.0148440

Editor: Peter John McKenna, Benito Menni Complejo Asistencial en Salud Mental, SPAIN

Received: June 5, 2015

Accepted: January 18, 2016

Published: February 1, 2016

Data Availability Statement: Data are from the PR077/10 study whose authors may be contacted at fcontreras@bellvitgehospital.cat. Fernando Contreras. Bellvitge University Hospital-IDIBELL, The Clinical Research Ethics Committee of Bellvitge (CEIC). Data from the study is available upon request because of confidentiality restrictions. Interested readers can access data contacting with the Clinical Research Ethics Committee of Bellvitge (CEIC) at presidenciaceic@bellvitgehospital.cat.

Funding: A.A. was supported by a trainee research staff grant awarded by the University of Barcelona (APIF-UB grants). [http://www.ub.edu/web/ub/ca/] P.

Abstract

Background

Counterfactual thinking is a specific type of conditional reasoning that enables the generation of mental simulations of alternatives to past factual events. Although it has been broadly studied in the general population, research on schizophrenia is still scarce. The aim of the current study was to further examine counterfactual reasoning in this illness.

Methods

Forty schizophrenia patients and 40 controls completed a series of tests that assessed the influence of the "causal order effect" on counterfactual thinking, and the ability to generate counterfactual thoughts and counterfactually derive inferences from a hypothetical situation. Socio-demographic and clinical characteristics, as well as neurocognitive variables, were also examined.

Results

Compared to controls, the schizophrenia patients generated fewer counterfactual thoughts when faced with a simulated scenario. The pattern of response when assessing the causality effect of the order was also different between the groups, with the patients being more frequently unable to attribute any ordering of events than the control subjects. Additionally, the schizophrenia patients showed more difficulties when deriving normative counterfactual inferences from hypothetical social situations. None of the counterfactual reasoning measures was associated to any of the cognitive functions or clinical and socio-demographic variables assessed.

C. was supported by a contract awarded by the Agency of University and Research Funding Management of the Catalan Government (AGAUR; 2009SGR1554). [http://www10.gencat.net/agaur_web/AppJava/english/index.jsp] The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

Conclusions

A global impairment in counterfactual thinking characterizes schizophrenia patients. Because of the potential impact of such deficits on psychosocial functioning, targeting counterfactual reasoning for improvement might be considered in future treatment approaches.

Introduction

Counterfactual thinking (CFT) is a specific type of conditional reasoning that takes place when thinking about past events. In this context, most people automatically compare the actual outcome of the event with "what might have been" by generating hypothetical "if only" outcomes supposing an alternative event had taken place [1,2]. For instance, in the fictional situation where John has failed an important test, he might generate a counterfactual thought like, *If I had studied more*, *I could have passed the test*. Theoretically, CFT has been framed in *norm theory* [3] as a biased decision-making process, and in the *mental models perspective* [4] as one of the "building blocks of reasoning." Used in response to real-world experiences, counterfactual reasoning relies on mental models of alternative possibilities that are represented in the form of mental simulations [5]. There is general agreement that CFT is related to other processes such as problem-solving [1], causal judgements [6] and deductive reasoning [7], as well as being important for mood regulation [6] and having a daily life coordination function, influencing behavioural changes and performance improvement [8].

CFT has been studied by examining the ability of individuals to generate counterfactual alternatives, as well as by looking at other effects that have been considered to influence CFT such as order effects. One of the most studied of these latter effects is the "causal order effect," which describes how, when faced with a hypothetical scenario involving a chain of events that has a negative outcome, most subjects tend to choose the first event in the scenario as the main determinant of the outcome [9]. CFT processes have also been studied by examining inferences resulting from CFT in the face of hypothetical social events [3,10].

Regarding CFT's neuroanatomical correlates, the involvement of the prefrontal cortex (PFC) generally and, more specifically, the orbitofrontal cortex (OFC) has been evidenced by studies of patients with PFC lesions [11], traumatic injury to the frontal lobe [12], Parkinson's dementia [13] and Huntington's disease [14]. Patients with these disorders demonstrate difficulties in generating a normal level of counterfactual alternatives as well as in foreseeing the possible negative consequences of their own actions. This may contribute to their tendency to persevere with certain behaviours and strategies that have been proven no longer beneficial. Functional neuroimaging studies have also found that the PFC is activated during CFT tasks [15,16], and more specifically that the OFC is activated in decision-making that has CFT components [17].

Schizophrenia is, among its other clinical features, characterized by delusions and disturbances in the logical structure of thought. Additionally, the disorder is linked to prefrontal dysfunction [18,19], and patients show impoverished decision-making and problem-solving skills, logical reasoning alterations [20], as well as a tendency to perseverate and to have a poor ability to generate novel ideas and plan for the future [21,22]. The presence of cognitive biases involved in the formation and maintenance of positive symptoms has also been increasingly recognized in recent years [23–25]. These biases include an information-gathering cognitive style that is characterized by jumping to conclusions, externalizing attributional biases, and deficits in understanding social situations and the intentions of others—Theory of Mind

(ToM) deficits [26]. It is not clear, though, whether these biases are independent from each other or whether, on the contrary, they represent parts of a yet undetected whole [27]. Taking into account that, in healthy people, CFT is known to play a role in the false belief reasoning development [28], and to enhance memory distortions (e.g., hindsight bias) that contribute to suboptimal decision-making [29], but also to be involved in ToM deficits in schizophrenia patients (i.e., difficulties in the processing of counterfactual information such as sarcasm) [30], it would be interesting to explore this type of conditional thinking within the cognitive biases tradition. Also relevant is the impact these cognitive deficiencies might have on schizophrenia patients' personal and social functioning—on the difficulties they present in their everyday activities, interpersonal relationships, or academic and work performance [31].

However, studies on the relationship between schizophrenia and CFT are scarce, even though this type of investigation involves an interesting and innovative application of a paradigm from experimental cognitive psychology. To our knowledge, there has been only one study to date, which was carried out on a relatively small sample of 14 schizophrenia patients and 12 healthy controls and which used two different CFT measures. First, the generation of spontaneous counterfactual alternatives was explored by asking the participants to recall a negative personal event, after which the total number of thoughts about how this event could have turned out differently was recorded. Second, the ability to make counterfactually derived inferences was assessed using a measure specifically designed for the study, the Counterfactual Inference Test (CIT). The results indicated that the patients generated fewer counterfactual thoughts than the controls and showed a different pattern of responses when counterfactually deriving inferences. Both impairments were related to the patients' deterioration in social functioning but not to cognitive measures including the Vocabulary and Digit Span subtests of the Wechsler Adult Intelligence Scale (WAIS-R) and with the FAS Verbal Fluency test [32].

The aim of the present study was to extend previous research examining CFT in schizophrenia, using a larger sample of patients and control subjects. Moreover, to our knowledge, this is the first time that the causal order effect in CFT has been employed in this patient group. The study further examined whether CFT performance was related to any basic cognitive domains using a detailed neuropsychological battery of tests designed to assess cognitive impairment in schizophrenia—the Brief Assessment of Cognition in Schizophrenia (BACS) [33,34]. Potential associations with socio-demographic and clinical variables were also explored.

Materials and Methods

Study design

This case-control study was conducted in the outpatient services of the Psychiatry Department of Bellvitge University Hospital in Hospitalet de Llobregat, Barcelona, Spain. The Clinical Research Ethics Committee of Bellvitge (CEIC) approved all study procedures, and all subjects gave written informed consent before inclusion.

Participants

Forty schizophrenia patients who met DSM-IV-TR [35] criteria were included in the study. Subjects with diagnoses of bipolar, schizoaffective, delusional or other Axis I disorders were excluded. Four of the schizophrenia patients had been treated with electroconvulsive therapy at least once in their lives, but not within the six months prior to entering the study. Forty healthy control subjects without a history of personal or family psychiatric illness or substance use disorder were recruited from hospital employees. All participants were excluded if they had a history of brain injury, an estimated Intelligence Quotient (IQ) lower than 70 or a mental

disease due to a medical condition. The groups were matched for gender, age and educational level.

Measures and procedures

Mental and personality disorders were assessed in both groups using the structured clinical interview for DSM-IV Axis I Disorders (SCID-I) [36] and Axis II Personality Disorders (SCID-II) [37] prior to enrolment. The examination of the schizophrenia patients was performed on two consecutive days: on the first day, clinical variables were recorded and cognitive function was assessed; on the second day, CFT was evaluated. The assessment of the healthy controls was carried out in a single session. Socio-demographic and clinical variables were recorded by means of an in-house standardized evaluation. Symptoms and severity of illness were assessed using the Spanish version of the Positive and Negative Syndrome Scale (PANSS) [38,39] and the Clinical Global Impression-Schizophrenia Scale (CGI-SCH) [40]. Level of functioning was assessed using the Global Assessment of Functioning (GAF) scale [41]. Pharmacological treatment was recorded, and daily dose equivalents of chlorpromazine were calculated [42].

Neuropsychological testing. A broad range of cognitive domains were evaluated with the Brief Assessment of Cognition in Schizophrenia (BACS), in the Spanish validation of which our group participated [33]. The functions assessed were verbal memory, working memory, motor function, verbal fluency, attention and processing speed, and executive function. Finally, the Spanish version of the vocabulary subtest of the Wechsler Adult Intelligence Scale battery [43] was administered to give an estimate IQ that was relatively resistant to postmorbid decline in the patients.

CFT evaluation. CFT was evaluated with three different tests given in the following order: assessment of the causal order effect, generation of counterfactual thoughts and the ability to make counterfactually derived inferences.

The first two measures were assessed through the research paradigm proposed originally by Wells et al. [9], which consists of a written scenario of four consecutive independent events that result in a negative outcome. In order to avoid first event bias, the researcher randomly changed the order of the events using a 4x4 Latin square design. All participants had to read the scenario, which in brief consisted of an individual who heard on the radio that a store on the other side of town had a great sale on a limited number of stereo systems. His/her progress in getting to the store was impeded by four consecutive minor misfortunes: a) a speeding ticket, b) a flat tire, c) a traffic jam, and d) a group of elderly people crossing the street. Because of these mishaps, he/she arrived late only to find out that the last stereo system had already been sold just a few minutes earlier. This scenario provided the basis for two experiments that were carried out.

First of all, in *Experiment 1*, designed to assess the causal order effect, participants were asked to choose and justify which of the four events was, in their opinion, the most probable cause for the negative outcome and, therefore, the event that they would select in order to undo the scenario. Participants who, even when encouraged, were still unable to choose one of the events, were directly assigned the response type "reasoning blocking." This was done to ensure that these responses were not considered as missing data. The time given to participants to complete this experiment was 60 seconds. Researchers recorded each participant's answer.

Secondly, in *Experiment 2*, the generation of counterfactual thoughts was evaluated by asking the participants to write down possible alternative ways they could have arrived in time to buy the stereo system; these could be either new original alternatives (e.g., "If only I had called and made a reservation in advance") or alternatives that changed one of the "unfortunate"

events (e.g., "If only I hadn't been speeding"). Participants were given five minutes to complete this experiment. The number of different counterfactual thoughts produced was recorded by two independent researchers, who filtered which of the participants' answers were real CFT answers and which ones were illogical or bizarre answers (e.g., "I continued sleeping").

Finally, the Counterfactual Inference Test (CIT), originally developed by Hooker et al. [32], was administered to measure ability to generate counterfactually derived inferences. This test is based on previous research which has shown that CFT influences affective and judgemental (cognitive) reactions regarding social events, and also that CFT is heightened in the face of outcomes preceded by unusual rather than typical actions [3], as well as when individuals are faced with events that seem "almost" (either spatially or temporally) to have occurred [10]. The CIT (for an overview of the test, see Table 1) consists of a set of four forced-choice questions; for each, two events with similar outcomes experienced by two subjects are presented. However, the circumstances between them differ such that in one the subjects should think "if only" to a greater extent than in the other. The target questions vary to reflect different higher order inferences. Therefore, item 1 focuses on a general affective reaction ("upset") in the context of a spatial "nearly happened" event; item 2 on a general affective reaction ("regret") in response to an "unusual" event; item 3 on a judgemental or cognitive reaction ("rumination") brought on by a temporal "nearly happened" event; and item 4 on a judgemental or cognitive reaction ("judgements of avoidance/prevention") in the face of an "unusual" event [32]. Each of the four questions describes a hypothetical social event and participants are given three possible answers: a normative answer (that is, the target counterfactual response), a non-normative response and a "same/can't tell" response if the participant considers none of the previous options to be suitable. The CIT total score is calculated from the typical/normative pattern of responses, based on previous research using a sample of undergraduate control subjects [32]. Each item on the test is given a score of 1 if the subject chooses the normative answer—that is, the option where the subject would most probably think "if only"; if the subject chooses any of the other answers (non-normative or "same/can't tell") they receive a score of zero. Therefore,

Table 1. Counterfactual Inference Test (CIT) [32].

Items	Response
ITEM 1: Reaction of upset (affective) in response to a spatial "nearly happened" event.	**a) Janet**
Janet is attacked by a mugger only 10 feet from her house. Susan is attacked by a mugger a mile from her house. Who is more upset by the mugging?	b) Susan
	c) Same/Can't tell
ITEM 2: Reaction of regret (affective) in response to an "unusual" event.	a) Ann
Ann gets sick after eating at a restaurant she often visits. Sarah gets sick after eating at a restaurant she has never visited before. Who regrets their choice of restaurant more?	**b) Sarah**
	c) Same/Can't tell
ITEM 3: Reaction of rumination (judgemental) in response to a temporal "nearly happened" event.	a) Ed
Jack misses his train by five minutes. Ed misses his train by more than an hour. Who spends more time thinking about the missed train?	**b) Jack**
	c) Same/Can't tell
ITEM 4: Reaction of avoidance (judgemental) in response to an "unusual" event.	**a) Bob**
John gets into a car accident while driving on his usual way home. Bob gets into a car accident while trying a new way home. Who thinks more about how his accident could have been avoided?	b) John
	c) Same/Can't tell

Note. The typical/normative pattern of responses are indicated in boldface [32].

doi:10.1371/journal.pone.0148440.t001

the total score may range between 0 and 4, with greater values indicating a counterfactual response closer to a normative pattern. Participants were given five minutes to complete the test.

Statistical analysis

For the descriptive analyses, absolute and relative frequencies were calculated for categorical variables. Continuous variables were assessed using the mean and standard deviation (SD) for normally distributed variables and the median and interquartile range (Q1-Q3) for non-normally distributed variables. In order to detect differences between groups, Fisher's exact test and χ^2 were used for categorical data, whereas the t-test and the Mann-Whitney-Wilcoxon test were applied to parametric and non-parametric continuous data, respectively. Normality of distributions was checked using the Kolmogorov-Smirnov test. In Experiment 1, in order to test whether the observed proportions departed from the expected p = 0.25 (i.e., equally distributed frequencies per category in each group was considered the null hypothesis), a χ^2 goodness of fit test was performed on each group. In multivariate analyses, linear and logistic regression models were used depending on whether the dependent variable was considered continuous or binary respectively. Finally, General Linear Models were used to assess the possible influence of cognitive variables on CFT measures, generating models adjusted for gender, age and educational level. In all analyses, the differences were assessed using a statistical test based on two-tailed significance at p = 0.05. To account for the multiple comparison issue, the False Discovery Rate (FDR) suggested by Benjamini and Hochberg was applied [44]. The data were managed and analyzed using the statistical software package SPSS (Version 18.0 for Windows SPSS, Inc., Chicago, Ill).

Results

Socio-demographic and clinical characteristics, and neuropsychological performance

Socio-demographic characteristics and neurocognitive measures are summarized in Table 2. More schizophrenia patients were unemployed and single at enrolment, and they obtained statistically significantly lower scores in all cognitive domains than the healthy control subjects. Clinical characteristics for the patients group are shown in Table 3.

CFT evaluation

Experiment 1: The causal order effect. Although the pattern of ordering the events to undo scenarios was found to be different between the schizophrenia patients and the healthy controls (p = 0.033; Table 4), both groups chose the first event to undo the scenario more often than the second, third or fourth event ($p<0.05$ in both groups). The proportion of schizophrenia patients choosing the first event was lower (45% for patients vs. 60% for control subjects), although the difference was not statistically significant (p = 0.179). The patients were significantly more frequently unable to attribute any ordering of events; in other words, they were more frequently unable to choose any event at all (22.5% vs. 5.0%; p = 0.023).

Experiment 2: Generation of counterfactual thoughts. The total number of answers generated spontaneously (both real and non-real counterfactual thoughts) was not significantly different between the schizophrenia patients and the healthy controls (p = 0.173). However, when only the total number of real counterfactual thoughts was taken into account, the patients generated fewer thoughts than the control group (p = 0.015; Table 5). Moreover, the proportion of subjects unable to generate any thought (that is, zero answers) was significantly higher

Table 2. Socio-demographic characteristics and neurocognitive measures.

	Schizophrenia Patients (n = 40)	Healthy Controls (n = 40)	p-value
Socio-demographic characteristics			
Male gender, *n (%)*	23 (57.5)	25 (62.5)	0.65
Age (years)	39.4 (12.2)	39.8 (12.3)	0.88
Educational level (years)	10.4 (3.6)	11.2 (3.3)	0.27
Employment status, *n (%)*			<0.001
Employed	13 (32.5)	35 (87.5)	
Student	2 (5.0)	0 (0.0)	
Unemployed/Retired	25 (62.5)	5 (12.5)	
Civil status, *n (%)*			0.02
Married	7 (17.5)	17 (42.5)	
Single	32 (80.0)	20 (50.0)	
Divorced	1 (2.5)	3 (7.5)	
Hand Dominance (right /left), %	95.0/5.0	97.5/2.5	0.56
Neurocognitive measures			
Estimated Intelligence Quotient	97.3 (12.2)	111.6 (8.9)	<0.001
Verbal memory	34.0 (12.0)	43.7 (6.5)	<0.001
Working memory	14.6 (4.2)	18.4 (3.3)	<0.001
Motor function	67.5 (16.6)	82.9 (9.2)	<0.001
Verbal fluency	27.8 (10.3)	44.7 (8.6)	<0.001
Processing speed	35.4 (14.6)	53.7 (8.4)	<0.001
Executive function	17.9 (3.0)	19.1 (1.7)	0.039

Note. Values presented as means (standard deviation) unless specified otherwise.

doi:10.1371/journal.pone.0148440.t002

Table 3. Clinical measures in schizophrenia patients.

Clinical measures in schizophrenia patients	
Age of onset of schizophrenia (years), *median (range)*	21.5 (15–34)
Duration of illness (years)	16.7 (10.8)
Readmissions (episodes), *median (range)*	2.0 (0–12)
Suicide attempts (episodes), *median (range)*	0.00 (0–4)
CGI-SCH	14.88 (3.1)
GAF, *median (range)*	60.0 (50–80)
Pharmacological treatment[a]	548 (373)
PANSS Dimensions	
Positive symptoms	13.5 (3.4)
Negative symptoms	22.1 (5.9)
General Psychopathology	37.6 (8.8)
Total score	73.15 (16.14)

Note. Values presented as means (standard deviation) unless specified otherwise. CGI-SCH: Clinical Global Impression Scale-Schizophrenia Scale; GAF: Global Assessment of Functioning; PANSS: Positive and Negative Syndrome Scale.

[a]Milligrams per day in chlorpromazine equivalents.

doi:10.1371/journal.pone.0148440.t003

Table 4. Experiment 1: Descriptive and comparative analysis of the causal order effect.

	Schizophrenia Patients (n = 40)	Healthy Controls (n = 40)	p-value
Experiment 1: The causal order effect			
Order of the events, *n (%)*			0.033
1st	18 (45.0)	24 (60.0)	
2nd	7 (17.5)	4 (10.0)	
3rd	4 (10.0)	2 (5.0)	
4th	2 (5.0)	8 (20.0)	
Reasoning blocking[a]	9 (22.5)	2 (5.0)	0.023
1st vs. 2nd, 3rd, 4th, reasoning blocking	18 (45.0)	24 (60.0)	0.179

[a]Unable to choose any event.

doi:10.1371/journal.pone.0148440.t004

among the schizophrenia patients than the healthy controls (22.5% vs. 5.0%). There were no statistically significant correlations regarding any measure of the study and the daily antipsychotic dose taken.

Generation of counterfactually derived inferences. Significant differences were found for the items related to "regret" (general affective reaction) in response to an "unusual" event and to "rumination" (judgemental/cognitive reaction) in response to a temporal "nearly happened" event (Table 6). Regarding the "regret" item, a significant proportion of patients were unable to choose between the normative and the non-normative response, choosing the "same/can't tell" answer (p = 0.042; item 2). In the case of the "rumination" item, a higher proportion of schizophrenia patients selected the non-normative response (p = 0.037; item 3) rather than choosing the normative response or the "same/can't tell" answer.

However, the difference in CIT total score did not reach statistically significant differences (p = 0.130)—that is, both groups generally tended to choose the target counterfactual response.

CFT and socio-demographic, clinical and neurocognitive measures in the schizophrenia patients. After FDR correction, no statistically significantly associations were found between any of the CFT measures and any of the clinical, socio-demographic (S1 Table) or cognitive variables assessed (data not shown).

Table 5. Experiment 2: Descriptive and comparative analysis of the counterfactual thoughts generation.

	Schizophrenia Patients (n = 40)	Healthy Controls (n = 40)	p-value
Experiment 2: Generation of counterfactual thoughts			
Total number of answers generated,[a] *median (Q1*-Q3**)*	2.0 (2.0–3.0)	3.0 (2.0–3.0)	0.173
Number of counterfactual thoughts, *median (Q1-Q3)*	2.0 (1.0–2.0)	2.0 (1.0–3.0)	0.015
Number of counterfactual thoughts, *n (%)*			
0	9 (22.5)	2 (5.0)	
1	10 (25.0)	9 (22.5)	
2	14 (35.0)	15 (37.5)	
3	7 (17.5)	12 (30.0)	
4	0 (0.0)	2 (5.0)	

[a]Including both real and non-real counterfactual thoughts.

*Q1: percentile 25;

**Q3: percentile 75.

doi:10.1371/journal.pone.0148440.t005

Table 6. CIT: Descriptive and comparative analysis of the counterfactually derived inferences assessment.

	Schizophrenia Patients (n = 40)	Healthy Controls (n = 40)	p-value
Total score, *median (Q1*-Q3**)*	2.0 (1.3–3.0)	3.0 (2.0–3.0)	0.130
Upset (item 1), *n (%)*			0.415
Normative response	14 (35.0)	13 (32.5)	
Non-normative response	10 (25.0)	6 (15.0)	
Same/can't tell	16 (40.0)	21 (52.5)	
Regret (item 2), *n (%)*			0.042
Normative response	21 (52.5)	31 (77.5)	
Non-normative response	11 (27.5)	7 (17.5)	
Same/can't tell	8 (20.0)	2 (5.0)	
Rumination (item 3), *n (%)*			0.037
Normative response	26 (65.0)	35 (87.5)	
Non-normative response	11 (27.5)	3 (7.5)	
Same/can't tell	3 (7.5)	2 (5.0)	
Judgements of avoidance (item 4), *n (%)*			0.372
Normative response	25 (62.5)	23 (57.5)	
Non-normative response	6 (15.0)	11 (27.5)	
Same/can't tell	9 (22.5)	6 (15.0)	

*Q1: percentile 25;

**Q3: percentile 75.

doi:10.1371/journal.pone.0148440.t006

Discussion

The present study focused on the assessment of CFT in patients with schizophrenia. Only one previous study has assessed CFT in this group of patients [32], and it found that they generated fewer counterfactual thoughts and showed an altered different pattern of responding compared to healthy controls. Our study examined the influence of the causal order effect in CFT, and the ability to generate counterfactual thoughts and to counterfactually derive inferences. Our results demonstrate significant alterations in schizophrenia patients on all three measures compared to well-matched controls. No significant associations were found with clinical and socio-demographic status, as well as with neuropsychological functioning.

The analyses revealed the causality attribution pattern to be significantly different between the schizophrenia patients and the healthy controls. This might be due to the fact that the patients tended to get blocked more frequently when asked to determine the event they would select in order to undo the scenario and avoid the negative outcome. In other words, and in contrast to previous research with general population, our results suggest that in schizophrenia there is a tendency to deviate from the normative ordering pattern by choosing the first event less frequently than the controls. Thus, this alteration might influence these patients' daily functioning since they do not attribute causality in the same way. Hence, it would be interesting to study this topic in relation to conceptual disorganization or formal thought disorder in schizophrenia.

Our findings are also in line with those of a previous study that found impoverished CFT generation in schizophrenia patients [32]. In this, the patients generated less CFT alternatives when faced with simulated scenarios, but more importantly, they also tended to be unable to generate any CFT (zero answers) that would avert the negative outcome more often than healthy controls. Interestingly, though, the results also suggested that the patients that could activate CFT (i.e., they could generate at least one alternative) to a degree similar to the healthy

controls. Nevertheless, it seems from both this and our study that schizophrenia is a disorder where patients experience difficulties in activating alternative representations to reality and have difficulties in re-imagining a negative outcome in a positive way using conditional reasoning.

When exploring a higher cognitive level of information processing (i.e., the generation of counterfactually derived inferences) in our "bottom-up" experimental design, we obtained results suggesting that schizophrenia patients do not follow the normative counterfactual reasoning pattern: they less frequently selected a regretful reaction in response to an "unusual" event or a judgement-related reaction in response to a "nearly happened" event. Among emotions related to CFT, the experience of regret may have an adaptive function because it can guide future decisions, based on information gathered from the outcome of previous choices [45,46]. Whereas in the normal population, most people react with greater regret to an unusual event, the reaction of the schizophrenia patients in our study was the same regardless of whether the event was usual or unusual. These findings appear to be in line with those of a previous study which found that both schizophrenia patients with prominent positive symptoms and patients with OFC lesions did not report regret and did not anticipate negative consequences resulting from their choices [47].

Regarding cognitive judgement-related reactions, the present study found that schizophrenia patients showed a lower tendency to react with rumination when faced with a negative temporal "nearly happened" event. Their worse performance here reflected the fact that they tended to disregard the negative outcome of a social event and hence exhibit a maladaptive response. These results could be considered consonant with the fact that the negative symptoms of schizophrenia (e.g., blunted affect, emotional withdrawal and apathetic social withdrawal) lead to an inability to deal with emotions or interpersonal relationships. In addition, our results might also contribute knowledge to the study of cognitive biases in schizophrenia. The different patterns of responses that our patients presented when making causality attributions and when counterfactually deriving inferences might be conceptually linked to the study of jumping to conclusions and externalizing attributional biases (e.g., choosing one event from the sequence in the causal order effect experiment) that have been demonstrated in the disorder [23–25], as well as ToM deficits [26] (e.g., perceiving the beliefs and intentions of the CIT characters).

In contradiction with previous research findings [32], our results suggest that the CFT impairment observed was not related to psychosocial functioning deficits in this sample of schizophrenia patients. However, taking in account that in the general population CFT has been proposed as a cognitive process that contributes to effective psychosocial function [8], future studies using other measures of social dysfunction in larger samples of patients may be warranted.

Furthermore, taking into account that schizophrenia is associated with compromise in almost all cognitive domains [48–50], we explored the potential link between the various cognitive functions assessed and CFT performance. However, although the neuropsychological exploration was more extensive than in previous research, the results were that none of the variables examined was associated with CFT impairment. These results are similar to those of Hooker et al. [32], who also failed to find a relationship between CFT performance and any of the neuropsychological variables they assessed. Accordingly, they proposed that CFT could not be explained either by a generalized cognitive deficit or a specific function like verbal fluency. The relationship between basic cognition and higher cognitive processes is controversial: for example, whether social cognitive and basic cognitive processes are associated is a question not yet adequately answered [51–53]. Authorities in this field like Green et al. [54] have suggested that these two domains must overlap, and the argument is about the degree to which they

overlap. In the same way, debate about whether CFT deficits could be the result of a pervasive cognitive impairment or is dependent on a specific deficit in a certain cognitive domain can still be considered to be open.

The present study has some shortcomings that should be acknowledged. Firstly, it is important to note that while the sample used in this study was larger than the one used in previous research [32], it still included only a relatively small number of participants. This could have resulted in a lack of statistical power and greater chances of making a type II error, increasing the possibility that the study was not able to detect actual differences between groups. Secondly, our sample did not meet criteria for clinical stability, although the median total PANSS score was 73.1 (SD = 16.14) which indicates a relatively low level of current symptoms. Future research might consider recruiting patients in remission as defined by Andreasen et al. [55] to assure that their cognitive functions are not biased by active symptomatology. Thirdly, use of a case-control design prevents drawing conclusions on whether the CFT impairment observed originated after or before the onset of the illness.

In conclusion, findings from the current study evidence a global impairment in counterfactual reasoning of schizophrenia patients compared with healthy controls. Because of the potential ecological impact that counterfactual thinking deficits might have on these patients' functional outcomes, we suggest that these deficiencies could be considered as a future target for treatment in schizophrenia. Finally, it would be interesting to study whether CFT could be considered a new cognitive endophenotype for schizophrenia by conducting research among healthy relatives. Considering the NIMH Research Domain Criteria project's new approach to research, we suggest that the study of CFT might be included as a subconstruct alongside other cognitive processes [56].

Supporting Information

S1 Table. Socio-demographic and clinical measures related to CFT measures in the schizophrenia patients group (n = 40). *Note*. All p-values are adjusted by False Discovery Rate (FDR). [a]Causal order effect assessment - 1st vs. 2nd, 3rd, 4th, reasoning blocking. *Logistic regression; **Linear regression.
(PDF)

Acknowledgments

The authors thank Daniel Cuadras and Cristina Baeza for their role in data management and statistical analyses, Cristian Tebé from the Statistical Assessment Service from Bellvitge Biomedical Research Institute-IDIBELL, Joanna Freedman for providing support in the preparation and editing of this manuscript and all of the study participants as well as the staff from the Psychiatry Department, Bellvitge University Hospital.

Author Contributions

Conceived and designed the experiments: FC. Performed the experiments: AA AC BB. Analyzed the data: AA PC. Contributed reagents/materials/analysis tools: AA JMM. Wrote the paper: FC AA JMM.

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S1 Table. Socio-demographic and clinical measures related to CFT measures in the schizophrenia patients group (n=40).

	Causal order effect (Experiment 1)[a]		**Number of counterfactual thoughts generated (Experiment 2)**		**CIT Total score**	
	OR (95%CI)*	p-value*	β (95%CI)**	p-value**	β (95%CI)**	p-value**
Employment status						
Employed/Student vs. Unemployed/Retired	2.67 (0.72 to 9.95)	0.792	-0.63 (-1.29 to 0.04)	1.000	-1.04 (-1.69 to 0.40)	0.099
Civil status						
Married vs. Single/Divorced	1.11 (0.21 to 5.76)	1.000	0.46 (-0.41 to 1.33)	1.000	-0.70 (-1.61 to 0.21)	0.838
Onset of schizophrenia. years	0.97 (0.86 to 1.09)	0.934	0.02 (-0.05 to 0.08)	0.963	-0.02 (-0.08 to 0.05)	0.971
Readmissions. episodes	0.99 (0.75 to 1.31)	0.995	-0.04 (-0.19 to 0.11)	1.000	-0.02 (-0.18 to 0.14)	0.989
Suicide attempts. episodes	0.90 (0.48 to 1.68)	0.932	-0.01 (-0.34 to 0.32)	0.996	0.15 (-0.19 to 0.50)	1.000
PANSS dimensions						
Positive	0.96 (0.79 to 1.16)	0.953	-0.02 (-0.12 to 0.08)	0.987	0.01 (-0.09 to 0.12)	0.970
Negative	0.91 (0.81 to 1.02)	0.949	-0.05 (-0.10 to 0.01)	1.000	0.02 (-0.04 to 0.08)	1.000
General psychopathology	0.96 (0.89 to 1.04)	1.000	-0.01 (-0.05 to 0.02)	1.000	0.01 (-0.03 to 0.05)	0.981
Total	0.96 (0.94 to 1.02)	0.953	-0.01 (-0.03 to 0.01)	1.000	0.01 (-0.02 to 0.03)	1.000
GAF	0.98 (0.88 to 1.09)	0.949	-0.02 (-0.08 to 0.04)	1.000	0.00 (-0.06 to 0.06)	1.000
CGI-SCH	0.93 (0.76 to 1.14)	1.000	0.00 (-0.11 to 0.11)	0.985	0.04 (-0.07 to 0.16)	1.000

Note. All p-values are adjusted by False Discovery Rate (FDR).
[a]Causal order effect assessment - 1st vs. 2nd, 3rd ,4th, reasoning blocking.
*Logistic regression; **Linear regression.

4.2. Study 2

Symptomatic Remission and Counterfactual Reasoning in Schizophrenia

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Frontiers in Psychology. 2017 Jan 7:2048. [*co-first authors]

Impact Factor (JCR 2015): 2.463 (Decile 1, Psychology - Multidisciplinary Sciences)

Summary of the results

In general, results from *Study 2* seemed to support the main hypotheses posited by the research group: the disruption of counterfactual reasoning was present in patients with schizophrenia even though these patients were in a state of symptomatic remission (in the sense of Andreasen *et al.*, 2005). Thus, the present results not only reinforce previous research findings, but also are suggestive of the independence of these deficits from the severity of the classic symptoms of the disorder. Specific results are detailed below in order of relevance:

1. Patients with schizophrenia with symptomatic remission significantly activated fewer counterfactual thoughts than healthy controls when faced with a negative fictional scenario.

2. When exploring the causal order effect, results suggested no differences between groups regarding the general pattern of response when attributing causality when facing a negative fictional scenario –i.e., both groups tended to choose the first event in the sequence as the most decisive one.

3. Results from the *Counterfactual Inference Test* (Hooker *et al.*, 2000) revealed that, compared to the controls, patients with schizophrenia did not follow the norm when deriving inferences through CFT in general. Specifically, results suggested that:

    3a. Schizophrenia patients selected a reaction of upset in response to a spatial "nearly happened" event more frequently than controls (Scenario 1).

    3b. Schizophrenia patients selected a reaction of rumination in response to a temporal "nearly happened" event less frequently than controls (Scenario 3).

4. Among the group of patients with schizophrenia, significant negative associations were found between poorer activation of counterfactual thoughts and two of the clinical variables examined:

    4a. Symptom severity: among those patients with higher scores on all PANSS dimensions.

    4b. Duration of schizophrenia: among those patients with more than ten years of illness duration.

frontiers in Psychology

ORIGINAL RESEARCH
published: 06 January 2017
doi: 10.3389/fpsyg.2016.02048

Symptomatic Remission and Counterfactual Reasoning in Schizophrenia

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OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Psychopathology, a section of the journal Frontiers in Psychology

Received: *09 October 2016*
Accepted: *19 December 2016*
Published: *06 January 2017*

Citation:
Albacete A, Contreras F, Bosque C, Gilabert E, Albiach Á and Menchón JM (2017) Symptomatic Remission and Counterfactual Reasoning in Schizophrenia. Front. Psychol. 7:2048. doi: 10.3389/fpsyg.2016.02048

Counterfactual thinking (CFT) is a type of conditional reasoning involving mental representations of alternatives to past factual events that previous preliminary research has suggested to be impaired in schizophrenia. However, despite the potential impact of these deficits on the functional outcome of these patients, studies examining the role of CFT in this disorder are still few in number. The present study aimed to extent previous results by evaluating CFT in the largest sample to date of schizophrenia patients in symptomatic remission and healthy controls. The relationship with symptomatology, illness duration, and sociodemographic characteristics was also explored.

Methods: Seventy-eight schizophrenia patients and 84 healthy controls completed a series of tests that examined the generation of counterfactual thoughts, the influence of the "causal order effect," and the ability to counterfactually derive inferences by using de Counterfactual Inference Test.

Results: Compared with controls, patients generated fewer counterfactual thoughts when faced with a simulated scenario. This deficit was negatively related to scores on all dimensions of the Positive and Negative Syndrome Scale-PANNS, as well as to longer illness duration. The results also showed that schizophrenia patients deviated significantly from the normative pattern when generating inferences from CFT.

Conclusions: These findings reveal CFT impairment to be present in schizophrenia even when patients are in symptomatic remission. However, symptomatology and illness duration may have a negative influence on these patients' ability to generate counterfactual thoughts. The results might support the relevance of targeting CFT in future treatment approaches, although further research is needed to better describe the relationship between CFT and both symptomatology and functional outcome.

Keywords: counterfactual thinking, schizophrenia, reasoning, symptomatic remission, illness duration

INTRODUCTION

Counterfactual thinking (CFT) is a specific type of conditional reasoning involving mental representations of alternatives to past situations that were once factual possibilities but which never occurred (Van Hoeck et al., 2015; Byrne, 2016). This process is mainly activated by negative outcomes in the form of "if only" conditional prepositions (Kahneman and Tversky, 1982; Roese, 1997; Byrne and McEleney, 2000). For instance, in the fictional scenario where you have arrived late for work, a counterfactual thought like *If only I had woken up earlier, I would had arrived on time* might be automatically generated.

Being regarded within the *norm theory* (Kahneman and Tversky, 1982) and in the *mental models perspective* (Byrne and McEleney, 2000), CFT appears to play a crucial role supporting adaptive behavior by enabling learning from past experiences (Epstude and Roese, 2008), modulating emotional state (Roese and Olson, 1997), promoting creativity (Markman et al., 2007), and supporting future planning and prediction (Smallman and Roese, 2009). Counterfactual reasoning also serves a behavior-regulating function, influencing behavioral changes and performance improvement (Epstude and Roese, 2008). From the perspective of the cognitive biases tradition, CFT is regarded as enhancing memory distortions that contribute to suboptimal decision-making (Roese and Olson, 1996), as well as being involved in the development of false-belief reasoning (Byrne, 2016). Thus, counterfactual reasoning appears to be a constructive process that requires of the integration of different cognitive functions and psychological processes to construct the internal representations of the target scenario (Van Hoeck et al., 2015). In accordance, although prefrontal cortex (PFC) areas seem to be the primary regions involved (Knight and Grabowecky, 1995; Gomez-Beldarrain et al., 2005), recent studies in healthy control subjects have proposed CFT to depend on an integrative network of systems for affective processing, mental simulation and cognitive control, including both cortical and subcortical structures. This proposal considers that counterfactual reasoning might actually rely on the coordination of multiple information processing systems that together enable adaptive behavior (Barbey et al., 2009; Van Hoeck et al., 2012, 2015).

Regarding its assessment, activation of CFT is generally evaluated by focusing on two aspects: (1) the ability of individuals to spontaneously generate counterfactual alternatives; and (2) the assessment of factors that have been described to influence on the CFT generation, for instance the "causal order effect" (Wells et al., 1987) or the "unusualness" and "proximity" of the situation (Kahneman and Tversky, 1982; Kahneman and Varey, 1990).

Neurocognitive impairment is a core feature of schizophrenia and includes deficits in almost all cognitive domains (Heinrichs and Zakzanis, 1998). This impairment is already observable in the early stages of the disorder (Censits et al., 1997; Keefe et al., 2006b; Crespo-Facorro et al., 2011; Cuesta et al., 2015) and seems to be present even before the initiation of treatment with neuroleptic drugs (Saykin et al., 1994). There is general agreement that neurocognitive performance is a strong correlate of schizophrenia patients' real-world functioning (Green, 1996; Fett et al., 2011) and that psychopathology and cognitive deficits in schizophrenia are probably caused, at least partially, by distinct pathophysiological processes, given that these cognitive deficits are manifested similarly among patients who have attained symptomatic remission and also by those who have not (Green et al., 2004; Buckley et al., 2007; Krishnadas et al., 2007; Brissos et al., 2011). It is still unclear, however, whether this cognitive dysfunction (including non-social, social cognition, and reasoning biases deficits) remains steady, declines, or improves over the course of the illness (Bilder et al., 1992; Censits et al., 1997; Rund, 1998; Harvey et al., 1999; Heaton et al., 2001).

Different symptomatic remission criteria in schizophrenia have been developed over the years to facilitate research and support a positive, longer-term approach to studying outcome in these patients, including neurocognitive functioning (Kane, 2008; Leucht et al., 2008; Levine et al., 2011; Levine and Leucht, 2013). With this objective in mind, Andreasen et al. proposed in 2005 a remission criteria including two components: a symptom-based criterion (low scores on diagnostically relevant symptoms) and a time criterion (duration of 6 months). This criteria, which has been validated and supported by expert authors on this field (van Os et al., 2006; Opler et al., 2007), is defined as a score of $\leq$3 (mild) on eight selected items of the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987).

With the aim of adding to knowledge about both brain function in schizophrenia patients and the etiopathogenesis of the disorder, and given that schizophrenia is related to a PFC dysfunction (Goldman-Rakic, 2011), researchers are increasingly exploring counterfactual reasoning in these individuals. As a result of these studies, a general counterfactual reasoning disruption has been described in schizophrenia, including deficits in these patients' ability to generate counterfactual thoughts, in their causality attributing pattern, and in their ability to make counterfactual-derived inferences (Hooker et al., 2000; Contreras et al., 2016). In addition, and alongside other non-social (Sitskoorn et al., 2004; Snitz et al., 2006) and social (Lavoie et al., 2013; Albacete et al., 2016a) cognitive deficits that are shared by first-degree relatives of psychotic patients, difficulties in the generation of counterfactual thoughts have also been observed among non-psychotic first-degree relatives of people with schizophrenia (Albacete et al., 2016b), suggesting that CFT impairment might be a promising candidate cognitive endophenotype for this disorder.

However, although all these findings suggest that CFT disruptions may be a potential target for new psychosocial or pharmacological treatment approaches (Van Hoeck et al., 2015), research on this topic is still scarce. With this objective in mind, the current study reports the assessment of counterfactual reasoning in the largest sample to date of schizophrenia patients in symptomatic remission and healthy control subjects. In accordance with previous research findings of our group, we hypothesize that schizophrenia patients in symptomatic remission will present a poorer performance on all CFT measures explored suggesting the independence of these deficits with symptom severity of the disorder. Using a naturalistic approach, specific objectives include the assessment and comparison between groups of the ability to generate

spontaneous counterfactual thoughts, the "causal order effect," and the ability to make counterfactual-derived inferences. Further associations with symptomatology, illness duration, and sociodemographic characteristics are also explored.

MATERIALS AND METHODS

Study Design

This case-control study was conducted in the Psychiatry Department of Bellvitge University Hospital, Barcelona, Spain. The Clinical Research Ethics Committee of our hospital approved all study procedures. All subjects gave written informed consent before inclusion.

Participants

Participants were recruited from the outpatient services of this Psychiatry Department and two associated mental health centers in the same catchment area: the Polyvalent Mental Health Unit—Benito Menni CASM and the Mental Health Unit of L'Hospitalet de Llobregat - Catalan Institute of Health.

Seventy-eight patients who met DSM-IV-TR (American Psychiatric Association, 2000) criteria for schizophrenia were included in the study. None of these patients had undergone electroconvulsive therapy or other brain stimulation therapies (rTMS or TDCS) in the last 6 months, and they all met the criteria for remission as defined by Andreasen et al. (2005): a score of $\leq$3 (mild) on eight selected items of the PANSS (Kay et al., 1987) (P1, P2, P3, N1, N4, N6, G5, and G9) which is maintained for at least 6 months. Patients whose diagnosis included bipolar, schizoaffective, delusional, or other Axis I disorders were excluded. Eighty-four healthy control subjects were recruited from among hospital employees. In order to be eligible they had to have no history of personal (Axis I and Axis II) or family psychiatric disorder, substance abuse, or suicide attempt.

For both the patient and control groups, additional exclusion criteria were a history of head trauma involving loss of consciousness, an organic disease with mental repercussions, or an estimated intelligence quotient (IQ) below 70. Groups were matched by gender, age, and educational level (measured in years).

Measures and Procedures

Mental and personality disorders were assessed in all potential participants prior to enrolment using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First et al., 1997) and Axis II Personality Disorders (SCID-II; First et al., 1994). These individual testing sessions lasted 2 h on average. The clinical rating scales and neurocognitive tests were administered by experienced psychiatrists and psychologists from our team, who also collected the sociodemographic data.

Sociodemographic Characteristics and Clinical Assessment

Sociodemographic data was collected for all participants and included age, gender, educational level, and current occupational and civil status. The Vocabulary subtest of the Wechsler Adult Intelligence Scale-III (Wechsler, 1999) was administered to give an estimate IQ that was relatively resistant to postmorbid decline in the patients. The laterality was assessed through the Edinburgh Handedness Inventory (Oldfield, 1971). Psychopathology was assessed using the Spanish adaptation of the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987; Peralta and Cuesta, 1994). Level of functioning was measured with the Global Assessment of Functioning Scale (GAF; American Psychiatric Association, 2000). The daily dose of antipsychotic medication was calculated in chlorpromazine equivalents (Kane et al., 2003).

Assessment of Counterfactual Thinking

Using set of three different measures, CFT was quantitatively assessed by exploring (1) the spontaneous generation of counterfactual thoughts and (2) some of the factors known to influence it, including the "causal order effect" and the specific characteristics of the situation (such as the "unusualness" or "proximity" of the situation) by using the Counterfactual Inference Test (CIT; Hooker et al., 2000).

On the basis of the research paradigm designed originally by Wells et al. (1987), CFT generation and the "causal order effect" were firstly assessed. This paradigm consists of a scenario involving four consecutive independent events that result in a negative outcome. To avoid first-event bias, the order of the events was randomly changed using a 4 × 4 Latin square design. In the present study, the scenario, which was read aloud to each participant, involved an individual who hears on the radio that a store on the other side of town is offering big price reductions on a limited number of stereo systems. His/her progress in getting there is then impeded by four consecutive minor misfortunes: (a) a speeding ticket, (b) a flat tire, (c) a traffic jam, and (d) a group of elderly people crossing the street. Because of these events, he/she arrives late only to find out that the last stereo system has already been sold just a few minutes earlier. Two experiments were then administered in the following order:

Experiment 1: The causal order effect

In this first experiment, participants were asked to choose which one of the four events would they select in order to reverse the scenario. This procedure is based on previous research findings suggesting that CFT tends to be influenced by the order in which the information is presented. Specifically, this effect refers to the tendency among healthy control subjects to choose the first event of a sequence as the most decisive one for the final negative outcome (Wells et al., 1987; Segura et al., 2002). Those participants who were unable to select one event were assigned with the response type "reasoning blocking" to ensure that these answers were not considered as missing data.

Experiment 2: Generation of counterfactual thoughts

In this second experiment, all participants were asked to say aloud all the possible alternatives they could imagine in order to avoid the final negative outcome of the scenario. These alternatives could be new original ones (e.g., "If only I had called and made a reservation in advance") or related to one of the misfortunate events (e.g., "If only I hadn't been speeding"). Two independent researchers filtered which answers were real counterfactual thoughts and which ones were illogical or bizarre answers (e.g., "I continued sleeping").

Finally, the *Counterfactual Inference Test (CIT)*, originally designed by Hooker et al. (2000), was administered to assess the ability to generate counterfactual-derived inferences in front of different hypothetical social situations (for an overview of the test, see **Table 1**). This self-reporting instrument is based on previous research which has shown not only how specific characteristics of the situation might influence the generation of an inference by enhancing CFT—i.e., situations with outcomes preceded by unusual rather than typical actions (Kahneman and Tversky, 1982) and events that seem "almost" (either spatially or temporally) to have occurred (Kahneman and Varey, 1990), but also how CFT, once activated, can influence the individual's affective and judgmental reactions to the situation (Kahneman and Tversky, 1982; Kahneman and Varey, 1990).

The CIT presents a set of four scenarios in which two events with similar outcomes are experienced by two different individuals. The circumstances of each pair of events differ such that one of the individuals should think "if only" to a greater extent than the other does. The target questions vary so as to reflect different higher-order inferences: Scenario 1 focuses on a general affective reaction ("upset") in the context of a spatial "nearly happened" event, Scenario 2 on a general affective reaction ("regret") in response to an "unusual" event, Scenario 3 on a judgmental or cognitive reaction ("rumination") brought on by a temporal "nearly happened" event, and Scenario 4 on a judgmental or cognitive reaction ("judgements of avoidance/prevention") in the face of an "unusual" event. For each scenario, participants are given three possible answers: (1) a target counterfactual response, that is, the option where the subject would most probably think "if only"; (2) a non-target counterfactual response, that is, the option where CFT is also activated but is less likely; and (3) a "same/can't tell" answer, in the event that the participant considers none of the previous options to be suitable. The CIT Total score is calculated from the typical/normative pattern of responses, based on previous research using a sample of undergraduate control subjects (Hooker et al., 2000). Each scenario is given a maximum score of 1 if the subject chooses the normative response, that is, the target counterfactual answer; if the subject chooses any of the other answers the score assigned is zero. Consequently, the total score ranges between 0 and 4, with higher values indicating a response pattern closer to the normative pattern.

Statistical Analysis

Absolute and relative frequencies were calculated for categorical variables, whereas for continuous variables mean (M) and standard deviation (SD) were used for normally distributed variables and the median and interquartile range (IQR) for non-normally distributed variables. Differences between groups where explored by using Fisher's exact test and χ^2 for categorical data, whereas the *t*-test and the Wilcoxon rank sum test were applied for parametric and non-parametric continuous data, respectively. Normality of distributions was checked using the Kolmogorov-Smirnov test. Multivariate linear regression analysis was used to examine differences between groups in Experiment 2 and in CIT Total score adjusted by age, gender, and estimated IQ. In all analyses, differences were assessed using a statistical test based on two-tailed significance at the 5% level ($\alpha = 0.05$). Data were managed and analyzed using R 3.1.3.

RESULTS

Sociodemographic and Clinical Characteristics

Sociodemographic and clinical characteristics are presented in **Table 2**. Compared with control subjects, more schizophrenia patients were single and either unemployed or retired at enrolment, and they also had a lower estimated IQ score.

Experiment 1: The Causal Order Effect

No differences were observed between groups when choosing one event as being the most relevant for reversing the scenario

TABLE 1 | The counterfactual inference test (Hooker et al., 2000).

Scenario	Response
1- Reaction of upset (affective) in response to spatial "nearly happened" event	**a) Janet**
Janet is attacked by a mugger only 10 m from her house. Susan is attacked by a mugger 1 kilometer from her	b) Susan
house. Who is more upset by the mugging?	c) Same/Can't tell
2- Reaction of regret (affective) in response to an "unusual" event	a) Anna
Anna gets sick after eating at a restaurant she often visits. Sarah gets sick after eating at a restaurant she has	**b) Sarah**
never visited before. Who regrets their choice of restaurant more?	c) Same/Can't tell
3- Reaction of rumination (judgemental) in response to a temporal "nearly happened" event	a) Ed
Jack misses his train by five minutes. Ed misses his train by more than an hour. Who spends more time thinking	**b) Jack**
about the missed train?	c) Same/Can't tell
4- Reaction of avoidance (judgemental) in response to an "unusual" event	**a) Bob**
John gets into a car accident while driving on his usual way home. Bob gets into a car accident while trying a new	b) John
way home. Who thinks more about how his accident could have been avoided?	c) Same/Can't tell

Typical pattern of responses—that is, the target counterfactual responses—are indicated in boldface (Hooker et al., 2000).

TABLE 2 | Sociodemographic and clinical characteristics of the sample.

	Schizophrenia patients ($n = 78$)	Healthy controls ($n = 84$)	p-value
SOCIODEMOGRAPHIC CHARACTERISTICS			
Male gender, *n (%)*	50 (64.1)	45 (53.6)	0.230
Age (years)	40.2 (11.0)	41.7 (12.2)	0.759
Educational level (years)	9.8 (2.9)	10.7 (2.9)	0.050
Employment status, *n (%)*			<0.0001
Employed/Student	18 (23.1)	65 (77.4)	
Retired	39 (50.0)	8 (9.5)	
Unemployed	21 (26.9)	11 (13.1)	
Civil status, *n (%)*			<0.0001
Married	13 (16.7)	40 (47.6)	
Single	31 (36.9)	57 (73.1)	
Divorced	8 (10.3)	10 (11.9)	
Hand Dominance (right), *n (%)*	71 (91)	79 (94)	0.760
Estimated IQ	97.1 (10.7)	107 (10.8)	<0.0001
CLINICAL MEASURES			
Age at onset of schizophrenia (years), *median (IQR)*	23.43 (19.0–28.7)		
Duration of the illness (years), *median (IQR)*	15.02 (7.39–24.26)		
Readmissions (episodes), *median (IQR)*	2.00 (1.00–3.00)		
Suicide attempts (none), *n (%)*	60 (76.9)		
GAF	65.2 (7.8)		
Pharmacological treatment[a], *median (IQR)*	550 (350–888.25)		
PANSS dimensions			
Positive symptoms	13.26 (3.06)		
Negative symptoms	20.75 (4.60)		
General psychopathology	34.92 (7.28)		
Total score	68.9 (13.1)		

Values presented as means (standard deviation) unless otherwise specified. IQR, interquartile range; GAF, global assessment of functioning; PANSS, positive and negative syndrome scale.

[a] *Milligrams per day of chlorpromazine equivalents.*

($p = 0.197$); in other words, the general pattern of response was not different between groups. Specifically, results showed that both patients and controls tended to choose the first event as the main determinant. The proportion of participants unable to choose any of the events (i.e., the "reasoning blocking" answer) was not significantly different between the two groups ($p = 0.078$).

Experiment 2: Generation of Counterfactual Thoughts

Schizophrenia patients in symptomatic remission not only generated significantly fewer spontaneous alternatives (including both real and non-real counterfactual thoughts, $p = 0.000$) but also fewer counterfactual thoughts in comparison with healthy controls ($p < 0.0001$). These significant differences were independent of gender, age, and estimated IQ ($p < 0.0001$; **Figure 1**).

CIT: Generation of Counterfactually Derived Inferences

Two significant differences were found between groups on the CIT (**Table 3**): whereas in Scenario 1 (upset in a spatial "nearly happened" event) patients chose the target-counterfactual answer more frequently ($p = 0.011$), in Scenario 3 (rumination in a temporal "nearly happened" event) the group of schizophrenia patients chose the target-counterfactual response significantly less often than did controls ($p = 0.034$). However, there was no statistically significant difference between the groups in CIT Total score ($p = 0.594$).

CFT and Sociodemographic and Clinical Measures in Schizophrenia Patients

The results in **Table 4** suggest that among schizophrenia patients a less frequent generation of counterfactual thoughts (Experiment 2) was negatively associated with all PANSS dimensions (Positive symptoms, $p = 0.007$; Negative symptoms, $p = 0.015$; General symptoms, $p = 0.050$; Total score, $p = 0.011$) and with more than 10 years of illness duration ($p = 0.028$), with this analysis being adjusted by gender, age, and estimated IQ. However, no significant associations were found between performance in Experiment 1 or on the CIT and any of the clinical measures examined, including the daily dose of antipsychotics. None of the sociodemographic characteristics were related to performance on any of the CFT tasks administered.

DISCUSSION

The present study extends previous results of our group by reporting the assessment of counterfactual reasoning in the largest sample to date of schizophrenia patients in symptomatic remission and healthy controls. In addition, potential associations with sociodemographic characteristics, symptomatology, and illness duration have been further examined. As a result, the main finding of the study is that, compared with controls, schizophrenia patients with symptomatic remission significantly generate fewer counterfactual thoughts when faced with a simulated scenario. Regarding the effect of external factors influencing CFT, results also suggest a significant deviation from the normative pattern among patients when counterfactually deriving inferences. However, no significant differences are found regarding the causal attribution pattern. Finally, among patients, deficits in the CFT generation appear to be negatively related to scores on all dimensions of the PANNS, as well as to longer duration of illness.

Compared to what is normally expected in the general population, patients with schizophrenia in a state of symptomatic remission seem to generate significantly fewer spontaneous alternative representations using CFT in the face of a fictional situation with a negative outcome. These findings reinforce the hypothesis that schizophrenia is a mental condition in which patients have difficulties in using conditional reasoning to re-imagine a negative outcome in a positive way, a process that

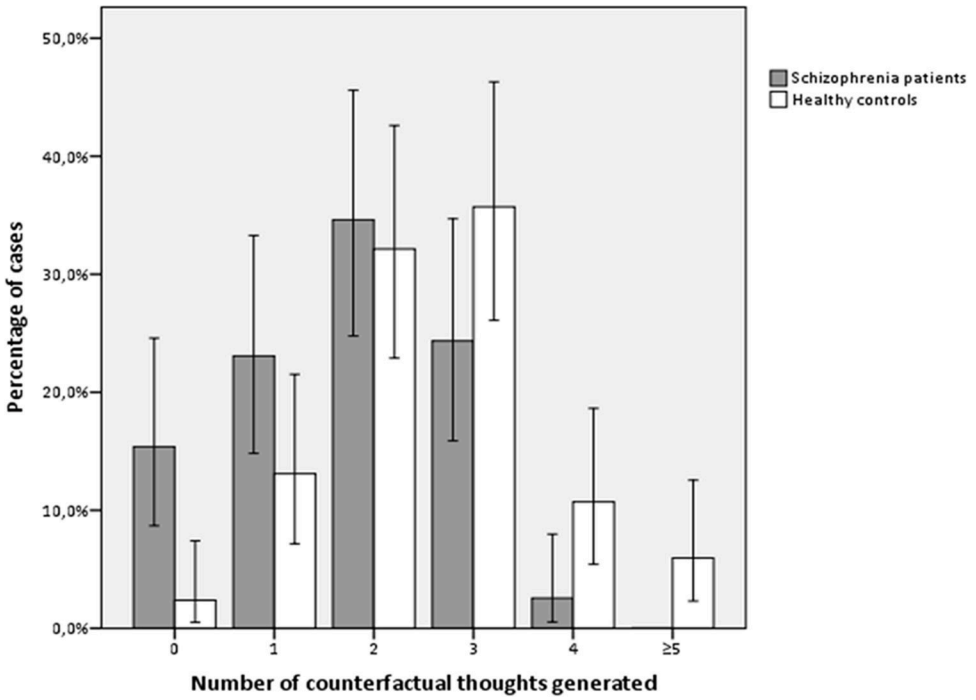

FIGURE 1 | Number of counterfactual thoughts generated by groups of study (Experiment 2).

enables the activation of alternative representations for dealing with reality. Alongside recent findings among unaffected first-degree relatives of schizophrenia patients (Albacete et al., 2016b), the present results also add to our knowledge of cognitive deficits as core features of schizophrenia since these deficits do not seem to be simply the result of symptoms or the pharmacological treatments administered for the illness—i.e., do not seem to share the same underlying pathological process causing the clinical symptoms of the disorder (Gold, 2004; Green et al., 2004).

Interestingly, our data analyses also reveal significant negative associations between CFT generation and scores on the PANSS, including total score and all three symptom dimensions. These results indicate that, although on average PANSS scores were mild, those patients with greater symptom severity tend to generate fewer counterfactual alternatives. This suggests that although these deficits might not be the result of symptoms, they may be influenced by them. This would be in line with previous literature that has related classic symptomatology of the disorder to other neurocognitive deficits (Addington et al., 1991; Shurman et al., 2005; Keefe et al., 2006a).

The results of this experiment also show that schizophrenia patients with longer illness duration are those who tend to generate fewer counterfactual thoughts, suggesting that this deficit does not settle into a stable pattern but, rather, tends to deteriorate over time in schizophrenia. This would be contrary to previous research indicating that cognitive impairment, including non-social, social cognition, and reasoning biases, remains stable over time regardless of changes in clinical state (Heaton et al., 1994, 2001; Rund, 1998; Peters and Garety, 2006; Horan et al., 2012). Our findings therefore appear to warrant further investigation, for instance, by conducting follow-up studies.

Regarding the ability to counterfactually derive inferences, results of the CIT suggest that, compared with controls, the schizophrenia patients react with greater upset in the face of a spatial "nearly happened" event (Scenario 1). Whereas from a clinical point of view this stronger general affective reaction might be related to positive symptoms of the illness such as hostility, from a functional point of view this biased inference generation would lead to difficulties in these patients' ability to deal with interpersonal relationships.

Our analyses also revealed that in comparison with controls, schizophrenia patients react significantly less often with rumination in the face of a temporal "nearly happened" event (Scenario 3). Consistent with previous results reported by our group (Contreras et al., 2016), this tendency to disregard the negative outcome of a social event might be related to negative symptomatology such as blunted affect or emotional withdrawal. This diminished reaction might also be associated with poor psychosocial and vocational functioning among these patients.

Furthermore, the analysis of CIT Total score suggests that schizophrenia patients and healthy controls perform similarly when deriving inferences from CFT. However, it should be noted that the total score of 2/4 found in healthy controls

TABLE 3 | CIT results: descriptive and comparative analysis of the counterfactually derived inferences assessment.

	Schizophrenia patients ($n = 78$)	Healthy controls ($n = 84$)	p-value
Total score, *n (%)*			0.594
0	8 (10.4)	7 (8.3)	
1	17 (22.1)	18 (21.4)	
2	27 (35.1)	29 (34.5)	
3	19 (24.7)	22 (26.2)	
4	6 (7.8)	8 (9.5)	
Total score, *median (IQR)*	2.00 (1.00–3.00)	2.00 (1.00–3.00)	
Scenario 1: *Upset in spatial "nearly happened" event, n (%)*			0.011
Target counterfactual response	29 (37.7)	22 (26.2)	
Non-target counterfactual response	15 (19.5)	7 (8.3)	
Same/can't tell	33 (42.9)	55 (65.5)	
Scenario 2: *Regret in unusual event*, *n (%)*			0.150
Target counterfactual response	34 (44.2)	50 (59.5)	
Non-target counterfactual response	22 (28.6)	17 (20.2)	
Same/can't tell	21 (27.3)	17 (20.2)	
Scenario 3: *Rumination in temporal "nearly happened" event*, *n (%)*			0.034
Target counterfactual response	45 (58.4)	59 (70.2)	
Non-target counterfactual response	24 (31.2)	12 (14.3)	
Same/can't tell	8 (10.4)	13 (15.5)	
Scenario 4: *Judgements of avoidance in unusual event*, *n (%)*			0.840
Target counterfactual response	43 (55.8)	43 (51. 2)	
Non-target counterfactual response	16 (20.8)	19 (22.6)	
Same/can't tell	18 (23.4)	22 (26.2)	

IQR, interquartile range.

TABLE 4 | Multivariate linear regression analysis to evaluate clinic factors associated with the generation of counterfactual thoughts among schizophrenia patients.

Schizophrenia patients	Coeff*	t-value	p-value
Duration of illness (years)	−0.041	−1.857	0.067
<10 years vs. ≥10 years	−0.746	−2.243	0.028
Readmissions			
None vs. 1 episode	−0.008	−0.021	0.983
None vs. 2 episodes	0.200	0.469	0.641
None vs. 3 episodes	0.364	0.908	0.367
Suicide attempts (number of episodes)			
None vs. at least one	−0.087	−0.294	0.770
GAF	0.002	−0.114	0.909
Pharmacological treatment	−0.000	−0.591	0.556
PANSS dimensions			
Positive symptoms	−0.104	−2.783	0.007
Negative symptoms	−0.064	−2.497	0.015
General psychopathology	−0.032	−1.995	0.050
Total score	−0.023	−2.606	0.011

GAF, global assessment of functioning; PANSS, positive and negative syndrome scale; Coeff, coefficients.

**Adjusted by age, gender, and estimated IQ.*

is not consistent with the normative pattern (i.e., a total score of 4/4) originally proposed by Hooker et al. (2000). In fact, previous studies by our group also failed to observe a score of 4/4 among controls, with these subjects tending to score 2 or 3 instead (Albacete et al., 2016b; Contreras et al., 2016). Thus, given that the pattern of response differs significantly between studies not only on total score but also for each scenario, further research is required to elucidate the role of CFT in the generation of cognitive inferences. Importantly, this would entail revising the CIT design and improving test reliability, for instance, by extending the number of scenarios.

Finally, results of the causal order effect' experiment show that influences CFT similarly in both groups, in other words, the response pattern when deciding which of the events is more decisive does not differ between patients and controls. Moreover, and as observed in the general population (Wells et al., 1987), both groups tend to choose the first event as being the most determinant. Contradicting previous findings in a smaller sample of schizophrenia patients who did not meet criteria for symptomatic remission (Contreras et al., 2016), the present results might be cause for optimism since they indicate a normative pattern of causality attribution in schizophrenia.

The present study has a number of shortcomings that should be acknowledged. First, although the number of participants is greater than in previous studies exploring CFT in schizophrenia, an even larger sample might have achieved better statistical power. Second, the case-control design prevents us from drawing conclusions as to whether the CFT impairment observed originates after or before the onset of the illness, although it should be noted that in order to avoid a potential effect of greater cognitive deterioration among older schizophrenia patients, healthy subjects were matched by age, gender, and years of education.

In conclusion, the present study seems to confirm the presence in schizophrenia of impairment in the ability to generate spontaneous counterfactual thoughts. This deficit is present despite the fact that patients are in symptomatic remission, suggesting the independence of this deficit alongside other reported neurocognitive deficits in schizophrenia (i.e., the findings support the consideration of cognitive impairment as being a core feature of the disorder). However, the present results also suggest that clinical factors such as classic symptomatology and illness duration might have a negative impact on the ability to generate counterfactual thoughts. Longitudinal studies might therefore be warranted in order to extend and confirm these findings. It should also be noted that schizophrenia patients deviated from the normative pattern when deriving inferences from CFT in situations involving reactions of regret and rumination in the face of a "nearly happened" event. Finally, the

results also suggest that the causal attribution pattern is preserved among these patients.

Given the potential ecological impact that impaired counterfactual reasoning may have on the day-to-day functioning of these patients (Roese and Olson, 1997), a disruption in the generation of counterfactual thoughts and inferences derived from CFT might be considered a new putative target for future psychosocial or even pharmacological treatment approaches. Further research is required to better describe how these deficits are related to symptomatology and functional outcome in this disorder, for instance by developing new tools of counterfactual inference assessment. Finally, it would also be interesting to explore whether the proposed integrative network of systems supporting CFT is disrupted in schizophrenia by using neuroimaging techniques.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Clinical Research Ethics Committee of the Bellvitge University Hospital with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Clinical Research Ethics Committee of the Bellvitge University Hospital.

AUTHOR CONTRIBUTIONS

AA and FC contributed to the management of the literature searches, design of the study, carried out the cognitive explorations and undertook the statistical analysis. CB, EG, and ÁA contributed in the sample recruitment and psychopathological evaluations. JM supervised the data collection, contributed to the management of the literature searches and assisted with study design. All authors participated in the writing process, read and approved the final manuscript, and are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

FUNDING

This work was supported by the Spanish Ministry of Science and Innovation, the Carlos III Health Institute (PI11/02221) and the University of Barcelona (AA, APIF-UB grants).

ACKNOWLEDGMENTS

The authors thank Cristian Tebé from the Statistical Assessment Service from Bellvitge Biomedical Research Institute-IDIBELL for his role in the statistical analyses and all of the study participants.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

4. 3. Study 3

Counterfactual Reasoning in Non-Psychotic First-Degree Relatives of People with Schizophrenia

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Frontiers in Psychology. 2016 Apr 7:665.

Impact Factor (JCR 2015): 2.463 (Decile 1, Psychology - Multidisciplinary Sciences)

Summary of the results

In general, results from *Study 3* seemed to support the main hypotheses posited by the research group: non-psychotic first-degree relatives of schizophrenia patients showed a subtle alteration of global counterfactual reasoning compared with what is normally expected in the general population. Specific results are detailed below in order of relevance:

1. When faced with a negative fictional scenario, first-degree relatives significantly activated fewer counterfactual thoughts than healthy controls, but more than patients with schizophrenia.

2. When exploring the causal order effect, results suggested no differences between groups regarding the general pattern of response when attributing causality when facing a negative fictional scenario –i.e., all three groups tended to follow the norm by choosing the first event in the sequence as the most decisive.

3. Results from the *Counterfactual Inference Test* (Hooker *et al.*, 2000) revealed that, in overall, the group of relatives did not follow the norm when deriving inferences through CFT. Specifically:

    3a. First-degree relatives were more proficient than healthy controls at making counterfactual-derived inferences in the specific scenarios assessing the effects of unusualness of the situation presented (Scenarios 2 and 4).

4. No significant associations were found between all the counterfactual measures explored and the neuropsychological variables examined.

5. No significant associations were found among relatives and controls between all the counterfactual measures explored and the variables related to level of schizotypy and PLE's examined.

frontiers in Psychology

ORIGINAL RESEARCH
published: 09 May 2016
doi: 10.3389/fpsyg.2016.00665

Counterfactual Reasoning in Non-psychotic First-Degree Relatives of People with Schizophrenia

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OPEN ACCESS

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Specialty section:
This article was submitted to Psychopathology, a section of the journal Frontiers in Psychology

Received: *29 March 2016*
Accepted: *21 April 2016*
Published: *09 May 2016*

Citation:
Albacete A, Contreras F, Bosque C, Gilabert E, Albiach Á, Menchón JM, Crespo-Facorro B and Ayesa-Arriola R (2016) Counterfactual Reasoning in Non-psychotic First-Degree Relatives of People with Schizophrenia. Front. Psychol. 7:665. doi: 10.3389/fpsyg.2016.00665

Counterfactual thinking (CFT) is a type of conditional reasoning that enables the generation of mental simulations of alternatives to past factual events. Previous research has found this cognitive feature to be disrupted in schizophrenia (Hooker et al., 2000; Contreras et al., 2016). At the same time, the study of cognitive deficits in unaffected relatives of people with schizophrenia has significantly increased, supporting its potential endophenotypic role in this disorder. Using an exploratory approach, the current study examined CFT for the first time in a sample of non-psychotic first-degree relatives of schizophrenia patients ($N = 43$), in comparison with schizophrenia patients ($N = 54$) and healthy controls ($N = 44$). A series of tests that assessed the "causal order effect" in CFT and the ability to generate counterfactual thoughts and counterfactually derive inferences using the Counterfactual Inference Test was completed. Associations with variables of basic and social cognition, levels of schizotypy and psychotic-like experiences in addition to clinical and socio-demographic characteristics were also explored. Findings showed that first-degree relatives generated a lower number of counterfactual thoughts than controls, and were more adept at counterfactually deriving inferences, specifically in the scenarios related to regret and to judgments of avoidance in an unusual situation. No other significant results were found. These preliminary findings suggest that non-psychotic first-degree relatives of schizophrenia patients show a subtle disruption of global counterfactual thinking compared with what is normally expected in the general population. Due to the potential impact of such deficits, new treatments targeting CFT improvement might be considered in future management strategies.

Keywords: schizophrenia, counterfactual thinking, reasoning, endophenotype, first-degree relatives

INTRODUCTION

Counterfactual Thinking (CFT) is a specific type of conditional reasoning related to mental simulations of past events generally triggered to a great extent by negative outcomes. In other words, and to quote Van Hoeck et al. (2015, p. 1), CFT refers to the "remarkable ability to infer how an event might have unfolded differently, without directly experiencing this alternative reality." In this way, most people compare the actual result of the event with "what might have been" by generating different hypothetical outcomes "if only" an alternative event had taken place (Byrne, 2016). For instance, in the fictional scenario where John has failed an important test, he could automatically generate a counterfactual thought like, *If I had studied more, I could have passed the test.*

Concerning CFT's neuroanatomical correlates, fMRI studies suggest that prefrontal cortex (PFC) regions are the primary regions activated in people engaged in counterfactual reasoning tasks, although other regions have been found to be related such as the temporal lobes, the left temporal gyrus, and the left cerebellum (Barbey et al., 2009; Van Hoeck et al., 2012). Counterfactual reasoning supports adaptive behavior by enabling us to learn from past experiences (Epstude and Roese, 2008) and by modulating emotional state (Roese and Olson, 1997), promoting creativity (Markman et al., 2007), and supporting future planning and prediction (Smallman and Roese, 2009), in addition to playing a behavior-regulating function that influences behavioral changes and performance improvement (Epstude and Roese, 2008). Furthermore, CFT seems to be related to specific cognitive biases such as the hindsight bias—enhancing memory distortions that contribute to suboptimal decision-making (Roese and Olson, 1996) and to Theory of Mind (ToM) deficits involved in the development of false belief (Byrne, 2016).

Studies of subtle cognitive alterations in unaffected relatives of schizophrenia patients have significantly increased over the last decade in an effort to confirm the hypothesis that these deficiencies might be potential endophenotypes for this disorder (Gottesman and Gould, 2003; Sitskoorn et al., 2004). Contributing to the etiology of schizophrenia (Cardno et al., 1999; Cannon et al., 2000; Byrne et al., 2003), these deficits seem to meet the fifth criterion for endophenotype validation in psychiatry since they are found to a lesser degree in the unaffected relatives of people with this disorder (Gottesman and Gould, 2003). Such deficiencies include alterations in declarative and working memory, sustained attention, verbal fluency, perceptual-motor speed, and certain executive functions (Sitskoorn et al., 2004; Szöke et al., 2005; Snitz et al., 2006). In addition, cognitive biases related to particular symptoms of schizophrenia, such as the data gathering bias known as "jumping to conclusions," have also been described among non-psychotic relatives of patients with schizophrenia (Van Dael et al., 2006; Broome et al., 2007). Regarding social cognition, the data remain inconsistent (Green et al., 2008). Some studies have found evidence of alterations in these probands compared with normal controls (Janssen et al., 2003; Bediou et al., 2007; Lavoie et al., 2013; Cella et al., 2015), whereas other studies have shown no differences at all (Kelemen et al., 2004; Loughland, 2004). Similar deficits have also been observed both in unaffected first-degree relatives high in schizotypy (Chen et al., 1998; Laurent et al., 2000; Vollema and Postma, 2002) and in healthy individuals that have reported psychotic-like experiences (PLEs; Kelleher and Cannon, 2011).

Currently, there is general agreement that neurocognition is a key feature of schizophrenia with deficits in all cognitive domains (Heinrichs and Zakzanis, 1998). Such deficits have already been recorded in the early stages of the disorder (Censits et al., 1997; Keefe et al., 2006; Crespo-Facorro et al., 2011). Thus, given that schizophrenia seems to be related, at least in part, to a PFC dysfunction (Goldman-Rakic, 2011; Jackowski et al., 2012), and that this neurocognitive impairment seems to be the single strongest correlate of these patients' real-world functioning (Green, 1996; Fett et al., 2011), it is not surprising that studies exploring counterfactual reasoning in these patients have emerged over recent years (Hooker et al., 2000; Contreras et al., 2016). Accordingly, the results of such research have revealed disruption in these patients' abilities to generate counterfactual thoughts, to attribute causality through CFT, as well as to counterfactually derive inferences in the face of different fictional social scenarios. The further study of these CFT disruptions in the schizophrenia spectrum has been encouraged since it might help in the understanding of these patients' day-to-day challenges, or eventually provide a new diagnostic tool or even a new target for treatment (Van Hoeck et al., 2015). In keeping with this goal, one possible approach might be through the identification of these cognitive endophenotypes among individuals who have no clinical needs but are at risk for psychosis, such as unaffected first-degree relatives of people with schizophrenia. Research on this topic has become an important area of investigation in recent years not only for providing critical information about the pathophysiology of the disorder but also for its potential to direct early interventions and prevention programs among both schizophrenia patients and these at-risk individuals.

Using an exploratory approach, the current study reports the assessment of CFT in a sample of non-psychotic first-degree relatives of people with schizophrenia. To our knowledge, this is the first time that counterfactual reasoning has been explored among this group and compared to schizophrenia patients and healthy controls. CFT was quantitatively evaluated using different methods of assessment including (1) the generation of counterfactual thoughts, (2) the "causal order effect" on CFT (Wells et al., 1987), and (3) the ability to make counterfactual-derived inferences, assessed using the Counterfactual Inference Test (CIT; Hooker et al., 2000). Potential associations with measures of neurocognition and social cognition, level of schizotypy and PLEs, as well as with any particular socio-demographic characteristic, were further assessed.

MATERIALS AND METHODS

Participants

A total of 141 participants—54 patients with schizophrenia, 43 non-psychotic first-degree relatives, and 44 healthy controls—all fluent in Spanish and between 19 and 66 years of age, were

included in the study after an initial inclusion interview in which an informed consent form was signed and mental and personality disorders were assessed using the structured clinical interview for DSM-IV Axis I Disorders (SCID-I; First et al., 1997) and Axis II Personality Disorders (SCID-II; First et al., 1994). The sample was recruited from the outpatient services of the Psychiatry Department of Bellvitge University Hospital, the Polyvalent Mental Health Unit (Benito Menni CASM), and the Mental Health Unit of L'Hospitalet de Llobregat (Catalan Institute of Health). Potential participants were excluded if they had a history of head trauma involving loss of consciousness, an organic disease with mental repercussions, or an estimated Intelligence Quotient (IQ) below 70. All study procedures were approved by the Clinical Research Ethics Committee of the Ciutat Sanitària de Bellvitge (CEIC Bellvitge).

First-degree relatives—19 parents, 19 siblings, and 5 offspring—of schizophrenia patients of the three collaborating units were also sampled. Family members were excluded if they had a history of a psychotic disorder or substance abuse. All schizophrenia patients met DSM-IV-TR criteria (American Psychiatric Association, 2000), were in remission as defined by Andreasen et al. (2005), and had not undergone electroconvulsive therapy in the last 6 months. Participants with other Axis I disorders were excluded. Healthy control participants were recruited from hospital employees; exclusion criteria were a previous history of personal (Axis I and Axis II) or family psychiatric illness or substance use disorder.

Measures and Procedures

Socio-demographic and Clinical Measures

Socio-demographic data were collected for all participants, including gender, age, years of education, current occupation, and civil status. Laterality was assessed by means of the Edinburgh Handedness Inventory (Oldfield, 1971). Estimated IQ was calculated using a combined score from the Vocabulary and Block Design subtests from the Wechsler Adult Intelligence Scale battery III (Sattler, 2001; Wechsler, 2001).

Symptoms and severity of illness were assessed using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987; Peralta and Cuesta, 1994), the Montgomery–Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979; Lobo et al., 2002), the Clinical Global Impression-Severity Scale (CGI-S; Guy, 1976), and the Scale to Assess Unawareness of Mental Disorder (SUMD; Amador and Strauss, 1990; Ruiz et al., 2008). Level of functioning was assessed with the Global Assessment of Functioning Scale (GAF; American Psychiatric Association, 2000). Pharmacological treatment was recorded, and antipsychotic daily dose equivalents of chlorpromazine were calculated (Kane et al., 2003).

Counterfactual Thinking Evaluation

Counterfactual thinking was examined using a set of three different measures in the following order: (1) the "causal order effect," (2) the generation of counterfactual thoughts, and (3) the ability to counterfactually derive inferences.

To begin with, two experiments framed on the research paradigm originally designed by Wells et al. (1987) were carried out to examine the first two measures. For further information about this procedure, the reader is referred to the work of these aforementioned authors, but, in brief, the procedure consisted of reading aloud to the probands a fictional scenario of four consecutive independent events that resulted in a negative outcome. In order to avoid the first event bias, the researcher randomly changed the order of the events using a 4×4 Latin square design. Thus, the scenario provided the frame for the two experiments described below.

Experiment 1: The causal order effect

In this experiment, participants were asked to choose which one of the four events was the most probable cause of the negative outcome of the scenario—in other words, the event they would select in order to undo the final result. This procedure was based on previous research that has described how the general population usually chooses the first of a chain of events as the main determinant event, even though these events are equal and objectively none is more crucial than the others for the final negative outcome (Segura et al., 2002). Thus, this effect explains how the focus of CFT tends to be influenced by the order in which the information is presented. To complete this experiment, participants had to choose a specific event from the sequence. Those who, even when encouraged, were still unable to choose one of the events, were directly assigned the response type "reasoning blocking." This was done to ensure that these responses were not considered as missing data. The time given to participants to complete this experiment was 60 s. Researchers recorded each participant's answer.

Experiment 2: Generation of counterfactual thoughts

The ability to spontaneously generate counterfactual thoughts for the purpose of avoiding the final negative outcome was assessed by asking the participants to say aloud as many alternatives as possible. These counterfactual thoughts could be original alternatives (e.g., "If only I had called and made a reservation in advance") or alternatives that changed one of the "unfortunate" events (e.g., "If only I hadn't been speeding"). All discrete responses given were recorded by two independent researchers, who filtered which answers were real counterfactual thoughts and which ones were illogical or bizarre (e.g., "I continued sleeping").

Counterfactual Inference Test (CIT)

Originally developed by Hooker et al. (2000), the CIT was administered to measure ability to generate counterfactually derived inferences. This is a multiple-choice, self-reporting instrument designed to evaluate the influence of different specific characteristics of a situation when individuals generate counterfactual inferences. The CIT is based on previous research that described how CFT is enhanced when encountering events with outcomes preceded by unusual rather than typical actions (Kahneman and Tversky, 1982), or events that seem "almost" to have occurred—either spatially or temporally (Kahneman and Varey, 1990). CFT can also influence an individual's affective and judgmental reaction to these situations by enhancing or diminishing these reactions (Kahneman and Tversky, 1982; Kahneman and Varey, 1990).

Thus, the CIT presents four scenarios in which two events with similar outcomes are experienced by two different subjects. However, the circumstances between the events differ such that one of the subjects should think "if only" to a greater extent than the other. For each situation, three possible answers are presented: a target counterfactual response (the option where CFT is activated to a greater extent), a non-target response (the option where CFT is also activated but less intensely), and a "same/can't tell" answer if the participant considers none of the previous options to be suitable (the option where CFT is not activated at all; see **Table 1**). Each scenario in the test is given a maximum score of 1 if the subject chooses the target counterfactual response; if the subject chooses any of the other answers, the score given is zero. The total score, therefore, may range between 0 and 4, with greater values indicating a counterfactual response closer to a normative pattern.

Neuropsychological Evaluation

Cognitive function was assessed using a comprehensive battery of 13 standardized neuropsychological tests, designed to encompass all cognitive dimensions proposed in the MATRICS battery (Green et al., 2004). The tests are summarized in **Table 2**.

Evaluation of Schizotypy and Psychotic-like Experiences

Levels of schizotypy and PLEs were assessed among relatives and controls using the Schizotypal Personality Questionnaire-Brief (SPQ-B; Raine and Benishay, 1995; Spanish adaptation by Mata et al., 2005) and the Community Assessment of Psychotic Experiences-42 (CAPE-42; Stefanis et al., 2002; Spanish adaptation by Fonseca-Pedrero et al., 2012), respectively.

TABLE 1 | The Counterfactual Inference Test (Hooker et al., 2000).

Scenario	Response
(1) Reaction of upset (affective) in response to a spatial "nearly happened" event *Janet is attacked by a mugger only 10 m from her house. Susan is attacked by a mugger 1 km from her house. Who is more upset by the mugging?*	**(a) Janet** (b) Susan (c) Same/Can't tell
(2) Reaction of regret (affective) in response to an "unusual" event *Anna gets sick after eating at a restaurant she often visits. Sarah gets sick after eating at a restaurant she has never visited before. Who regrets their choice of restaurant more?*	(a) Anna **(b) Sarah** (c) Same/Can't tell
(3) Reaction of rumination (judgmental) in response to a temporal "nearly happened" event *Jack misses his train by 5 min. Ed misses his train by more than an hour. Who spends more time thinking about the missed train?*	(a) Ed **(b) Jack** (c) Same/Can't tell
(4) Reaction of avoidance (judgmental) in response to an "unusual" event *John gets into a car accident while driving on his usual way home. Bob gets into a car accident while trying a new way home. Who thinks more about how his accident could have been avoided?*	**(a) Bob** (b) John (c) Same/Can't tell

Typical pattern of responses—that is, the target counterfactual responses—are indicated in boldface (Hooker et al., 2000).

Statistical Analysis

For the descriptive analyses, absolute and relative frequencies were calculated for categorical variables. Continuous variables were assessed using the mean (M) and standard deviation (SD) for normally distributed variables, and the median and range for non-normally distributed variables. To detect differences between groups, Fisher's exact test and χ^2 were used for categorical data, whereas group means were compared using one-way analysis of variance (ANOVA) followed by a Tukey test for *post hoc* analyses. The Kruskal–Wallis test was used for non-normally distributed data. Multivariate linear regression analyses were done to assess significant differences between groups for all CFT measures, adjusted for age, gender, and estimated IQ, as well as to explore potential associations between these measures and variables of neurocognition and social cognition, schizotypy, PLEs, and socio-demographic and clinical characteristics. A value of $p < 0.05$ was considered statistically significant. All analyses were conducted using R 3.1.3.

RESULTS

Socio-demographic and Clinical Characteristics

Socio-demographic characteristics are summarized in **Table 3**. The results of the analyses revealed the group of relatives to be older than the rest of the sample, and the group of patients to have a higher proportion of single and retired individuals, and a lower proportion of women and a lower estimated IQ. Regarding clinical characteristics, the patients exhibited mild levels of symptom severity on the PANSS total score ($M = 65.26$, $SD = 7.80$), on the MADRS ($M = 11.65$, $SD = 6.24$), on the SUMD ($M = 5.20$, $SD = 2.68$), and on the CGI-SCH ($M = 3.30$, $SD = 0.50$). The median GAF score was 70 (range = 50–80); the average length of illness was 16.32 years ($SD = 10.42$); and the mean daily dose of antipsychotic treatment taken was 650.94 mg/day ($SD = 468.75$; chlorpromazine equivalents).

Counterfactual Thinking Evaluation

Experiment 1: The Causal Order Effect

No statistically significant differences were found for this experiment in the general pattern of responses between the first-degree relatives, the schizophrenia patients and the healthy subjects ($\chi^2 = 3.19$, $p = 0.922$; **Table 4**). In addition, the proportion of participants unable to choose any of the four events (that is, the "reasoning blocking" response) was similar between groups ($\chi^2 = 0.40$, $p = 0.820$). Nonetheless, the results showed a tendency among the healthy controls to choose the first event more frequently than the other groups (29.5% versus 27.9% of the relatives and 24.1% of the patients).

Experiment 2: Generation of Counterfactual Thoughts

Figure 1 presents the results of this experiment. *Post hoc* analysis revealed that first-degree relatives generated a significantly lower

TABLE 2 | Neuropsychological Test Battery.

Cognitive domain	Test
Laterality	Edinburgh Handedness Inventory (Oldfield, 1971)
Estimated IQ	Wechsler Adult Intelligence Scale-III, Vocabulary Test (Wechsler, 2001)
	Wechsler Adult Intelligence Scale-III, Block Design Test (Wechsler, 2001)
Attention	Continuous Performance Test-II; CPT (Conners, 2000)
Processing speed	Trail Making Test – Form A (Reitan, 1958)
	Wechsler Adult Intelligence Scale-III, Symbol Coding Test (Wechsler, 2001)
	Stroop Test, word-color (Golden, 1978)
Executive function	Trail Making Test – Form B (Reitan, 1958)
	Stroop Test, word-color interference effect (Golden, 1978)
	Controlled Oral Word Association Test, FAS-Test (Loonstra et al., 2001)
	Test Barcelona, Animal Words (Peña-Casanova, 1990)
	Wisconsin Card Sorting Test, WCST-128 (Heaton et al., 1993)
	Tower of London Test (Culbertson and Zillmer, 2001)
Working memory	Wechsler Adult Intelligence Scale-III, Digit Span Test (Wechsler, 2001)
	Wechsler Adult Intelligence Scale-III, Letter-Number Sequencing Test (Wechsler, 2001)
Verbal memory	California Verbal Learning Test, Spanish version –TAVEC (Benedet and Alejandre, 1998)
Visual memory	Wechsler Memory Scale-III, Visual reproduction Tests I and II (Wechsler, 1997)
Social cognition	Mayer–Salovey–Caruso Emotional Intelligence Test, MSCEIT (Extremera and Fernández-Berrocal, 2009)
	Internal, Personal, and Situational Attributions Questionnaire, IPSAQ (Kinderman and Bentall, 1996)

TABLE 3 | Socio-demographic characteristics of the sample and comparison between groups.

	Schizophrenia patients ($n = 54$)	First-degree relatives ($n = 43$)	Healthy controls ($n = 44$)	p-value
Gender, male: *n* (%)	37 (68.5)	19 (44.2)	21 (47.7)	0.031
Age, years	41.4 (11.1)	50.7 (12.2)	45.6 (12.6)	0.002
Educational level, years	9.7 (2.3)	9.9 (3.5)	10.3 (2.7)	0.502
Employment status: *n* (%)				<0.0001
Employed/Student	5 (9.3)	25 (58.1)	31 (70.5)	
Unemployed	12 (22.2)	12 (27.9)	11 (25.0)	
Retired	37 (68.5)	6 (14.0)	2 (4.5)	
Civil status: *n* (%)				0.000
Single	39 (72.2)	11 (25.6)	13 (29.5)	
Married	10 (18.5)	28 (65.1)	21 (47.7)	
Divorced	5 (9.3)	4 (9.3)	7 (15.9)	
Widowed	0 (0.0)	0 (0.0)	3 (6.8)	
Handedness, right: (%)	87.0	90.7	90.9	0.378
Estimated IQ	94.70 (11.57)	104.56 (11.51)	105.36 (14.50)	0.000

Values presented as means (standard deviation) unless otherwise specified.

number of counterfactual thoughts than the healthy control group ($p = 0.030$). This difference was also observed between the healthy controls and the schizophrenia patients ($p = 0.0001$). However, when adjusted for age, gender, and estimated IQ, these differences maintained only a borderline level of statistical difference ($F = -0.51$, $p = 0.061$). Nevertheless, and as expected, patients generated fewer counterfactual thoughts compared with the other groups ($\chi^2 = 16.15$, $p = < 0.001$). Differences between controls and patients remained significant even when adjusted ($F = -0.79$, $p = 0.004$).

Counterfactual Inference Test

Analyses of group differences on the CIT total score revealed statistically significant differences in favor of the relatives compared with the controls when adjusted for age, gender, and estimated IQ ($F = 0.73$, $p = 0.005$), but not for the patients compared to the controls ($F = 0.19$, $p = 0.446$; **Table 5**). When examining each particular scenario of the test separately, the results revealed that a significantly higher proportion of first-degree relatives chose the target counterfactual response than in the other groups for the specific situations related to regret in the face of an unusual event ($p = 0.047$; Scenario 2) and related to judgments of avoidance also in response to an unusual event ($p = 0.036$; Scenario 4). This difference was also observed in Scenario 1 ($p = 0.013$), but this time in favor of the schizophrenia patients. No significant differences were found regarding Scenario 3 (**Table 6**).

TABLE 4 | The causal order effect (Experiment 1): Descriptive and comparative analysis between groups.

	Schizophrenia patients ($n = 54$)	First-degree relatives ($n = 43$)	Healthy controls ($n = 44$)	χ^2-test (p-value)
Experiment 1: The causal order effect				
Order of the events, *n* (%)				3.19 (0.922)
1st	13 (24.1)	12 (27.9)	13 (29.5)	
2nd	9 (16.7)	7 (16.3)	11 (25.0)	
3rd	10 (18.5)	5 (11.6)	6 (13.6)	
4th	14 (25.9)	12 (27.9)	9 (20.5)	
Reasoning blocking[a]	8 (14.8)	7 (16.3)	5 (11.4)	
1st vs. 2nd, 3rd, 4th, reasoning blocking	24.1/75.9	27.9/72.1	29.5/70.5	0.40 (0.820)

[a]*Unable to choose any event.*

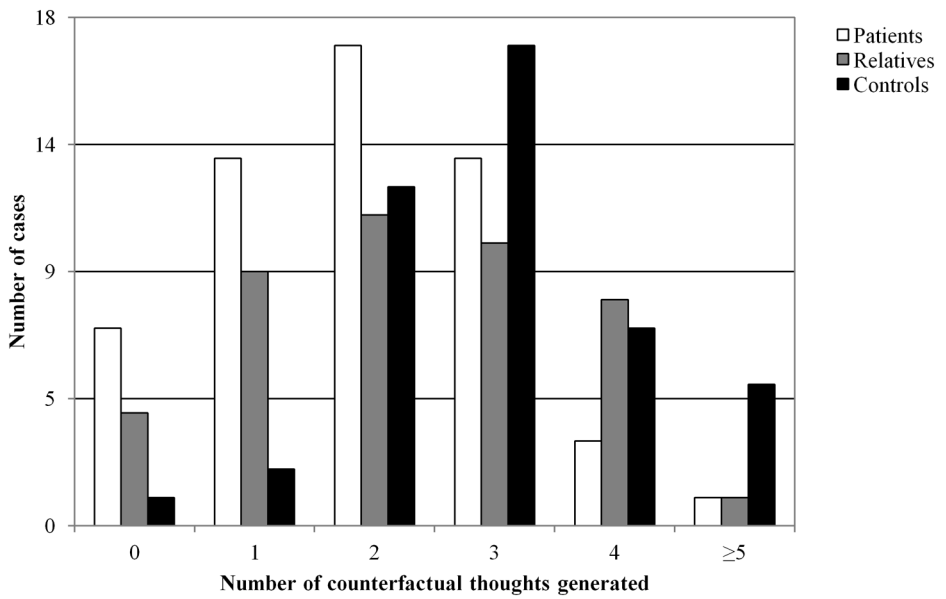

FIGURE 1 | Number of counterfactual thoughts generated by groups in the study (Experiment 2).

TABLE 5 | Descriptive and comparative analysis between groups on the CIT total score.

	Schizophrenia patients ($n = 54$)	First-degree relatives ($n = 43$)	Healthy controls ($n = 44$)	Kruskal–Wallis test (p-value)
Total score, *n* (%)				$\chi^2 = 5.28$ (0.071)
0	7 (13)	4 (9)	6 (14)	
1	12 (23)	9 (21)	13 (30)	
2	19 (36)	9 (21)	15 (34)	
3	10 (19)	13 (30)	8 (18)	
4	5 (9)	8 (19)	2 (5)	

Associations with CFT Measures

The analyses showed no significant associations between CFT measures and any of the potential variables considered, including cognitive performance, schizotypy, and level of PLEs, in any of the three groups studied. Furthermore, among schizophrenia patients, clinical variables, including the daily dose of antipsychotic taken, were not related to CFT performance.

DISCUSSION

Counterfactual thinking is a specific type of conditional reasoning referring to the individual's capacity to infer how an event might have displayed differently without directly experiencing this alternative scenario (Van Hoeck et al., 2015). Counterfactual thoughts are pervasive in everyday life and are involved in other processes such as problem-solving and learning from the experience (Epstude and Roese, 2008). The study of potential cognitive endophenotypes for schizophrenia has significantly increased in recent years in an effort to identify candidate genes associated with susceptibility for schizophrenia that could provide a more reliable index of liability than the illness itself (Gottesman and Shields, 1972; Cannon, 2005). Identifying these potential cognitive endophenotypes among at-risk samples

TABLE 6 | Descriptive and comparative analysis between groups on the CIT scenarios.

	Schizophrenia patients ($n = 54$)	First-degree relatives ($n = 43$)	Healthy controls ($n = 44$)	Statistic	*p*-value
(1) Upset—spatial nearly happened event, *n* (%)				$\chi^2 = 12.24$[a]	0.014
Target counterfactual response	20 (37.7)	10 (23.3)	9 (20.5)		
Non-target response	9 (17.0)	5 (11.6)	1 (2.3)		
Same/can't tell	24 (45.3)	28 (65.1)	34 (77.3)		
(2) Regret—unusual event, *n* (%)				$\chi^2 = 9.60$	0.048
Target counterfactual response	19 (35.8)	26 (60.5)	21 (47.7)		
Non-target response	20 (37.7)	7 (16.3)	8 (18.2)		
Same/can't tell	14 (26.4)	10 (23.3)	15 (34.1)		
(3) Rumination—temporal nearly happened event, *n* (%)				$\chi^2 = 2.91$	0.573
Target counterfactual response	27 (50.9)	25 (58.1)	25 (56.8)		
Non-target response	18 (34.0)	10 (23.3)	9 (20.5)		
Same/can't tell	8 (15.1)	8 (18.6)	10 (22.7)		
(4) Judgments of avoidance—unusual event, *n* (%)				$\chi^2 = 12.24$	0.036
Target counterfactual response	31 (58.5)	31 (72.1)	20 (45.5)		
Non-target response	11 (20.8)	2 (4.7)	7 (15.9)		
Same/can't tell	11 (20.8)	10 (23.3)	17 (38.6)		

Comparisons across groups in the study were made using the χ^2-test unless otherwise specified. [a]*Fisher's Exact Test.*

would not only add knowledge about the pathophysiology of the disorder, but might also provide new guidelines for early interventions and prevention programs in schizophrenia patients and these at-risk individuals (Eack et al., 2010). With this purpose in mind, and based on previous research findings that demonstrated a global CFT impairment in schizophrenia (Hooker et al., 2000; Contreras et al., 2016), the present study assessed this type of reasoning for the first time in a sample of non-psychotic first-degree relatives, and compared them with a group of schizophrenia patients and healthy control subjects. Several striking results are discussed below in order of relevance.

Compared to what is normally expected in the general population, first-degree relatives were less skilful at generating spontaneous alternative representations using CFT in the face of a fictional situation with a negative outcome (Experiment 2). This alteration might be related to previous findings of a broad impairment in executive functions among relatives of schizophrenia patients, including difficulties in the ability to shift sets and to generate new alternatives of classification (Szöke et al., 2005). Moreover, in accordance with the fifth criterion for endophenotype validation, these preliminary results suggest deficits in the generation of counterfactual thoughts as a potential phenotypic marker of schizophrenia (Gottesman and Gould, 2003). Further research using a transdiagnostic approach may be warranted in order to properly examine the specificity of these deficits in schizophrenia and the genetic abnormalities underlying them.

When exploring a higher cognitive level of information processing, results on the CIT suggest that the first-degree relatives were in general more adept at deriving inferences from CFT when compared to the controls. In addition, when analyzing each item of the test in particular, the relatives were more proficient at making counterfactual-derived inferences in the specific scenarios assessing the effect of "unusualness" of the situation presented. This effect, which has previously been demonstrated in the general population, describes how an outcome preceded by an unusual rather than typical action influences CFT by enhancing it—as assessed in Scenarios 2 and 4 of the CIT (Kahneman and Tversky, 1982). Interestingly though, our findings suggest that the unusualness of the situation acted as a more intense CFT trigger for the relatives than for the other groups in the study. That is, the relatives tended to select the target-counterfactual response more frequently than the healthy subjects. Furthermore, a greater reaction of regret and judgments of avoidance was also observed among relatives compared with the controls. Again, this effect has also been observed in healthy controls (Kahneman et al., 1986), but in the present study, it seemed to be more pronounced among first-degree relatives. One possible explanation for both findings could rely on the presence of prominent schizotypy that could predispose these subjects to reacting more suspiciously than the controls. However, the present study explored this potential association using the SPQ-B and the CAPE-42, and no statistically significant results were found. This might be because the relatives that agreed to participate were probably the most compliant and most willing to take part in the research. This may have biased this group, since presumably relatives with prominent suspiciousness, significant interpersonal deficits, or subtle thought disorganization may have been less likely than healthier relatives to collaborate. This might also explain the lack of differences between relatives and controls on the SPQ-B and the CAPE-42 scores, along with the fact that none of the relatives met the criteria for personality disorder.

Furthermore, results on the CIT might be conceptually linked to the study of cognitive biases that play a role in the development and maintenance of delusions in schizophrenia. Specifically, they might be related to the data gathering bias known as jumping to conclusions (e.g., inferring that if Sarah had not gone to a new restaurant she would not have got sick in Scenario 2), which has been observed not only among schizophrenia patients but also in their non-psychotic first-degrees relatives (Van Dael et al., 2006; Broome et al., 2007).

Concerning the causal order effect (Experiment 1), two results should be highlighted. Firstly, the general pattern of response when attributing causality under the effect order was similar between groups, and secondly, all three groups chose the first event in the sequence as the most decisive one. These results conflict with previous results on schizophrenia patients that revealed an alteration in the general pattern of response (Contreras et al., 2016). Framing their ideas in the *mental models theory*, Byrne et al. (2000) suggest that studying the aspects that people use to construct counterfactual alternatives is highly relevant, since these aspects, including causality, "give hints about the 'joints' of reality" in human beings (mental models). Thus, the present findings are more optimistic than previous results, since they show a preserved capacity among patients to attribute causality, which has to be beneficial for these patients' functioning in daily life.

Finally, none of the cognitive functions assessed was related to any of the CFT measures recorded, despite the fact that the neuropsychological test battery was more extensive than in previous research. Consistent with previous findings in schizophrenia (Hooker et al., 2000; Contreras et al., 2016), the present results seem to support Van Hoeck et al.'s (2012) proposal of an integrated network of systems underlying CFT that might cut across different psychological domains. If there is not a distinctive counterfactual reasoning network, it seems logical that no specific neuropsychological test can detect this impairment. In fact, as other authors have already suggested, the present results reinforce the idea that this absence of significance might actually indicate that CFT could be related to more complex reasoning, social cognition and ToM-based abilities (Solca et al., 2015). Studies using other appropriate neuropsychological tests, as well as neuroimaging techniques, might be useful in solving this on-going debate.

The results of the present work need to be interpreted within the context of its limitations. First, as it was a pilot study, it involved a small number of subjects, which may have resulted in a lack of statistical power and greater chances of making a type II error, thus increasing the possibility that the study was not able to detect actual differences between groups. Second, there was potential bias in the representativeness of the first-degree relatives group—those willing to participate were probably the most "healthy" ones. In addition, there was no comparative analysis between types of relatives. However, because of the small sample size, this characteristic was not considered. Moreover, including parents and siblings all together may have made this group older on average than the controls and patients, and this fact might have had an impact on the reported differences. The authors tried to solve this issue by adjusting the results for age of the participants along with other possible confounding variables like gender and estimated IQ.

To our knowledge, this is the first study to report CFT performance in non-psychotic first-degree relatives of patients with schizophrenia. Compared with what is normally expected, relatives presented difficulties when spontaneously generating counterfactual alternatives to face a problem, and had a different pattern of reasoning when counterfactually deriving inferences. These findings represent a step forward in the investigation of counterfactual reasoning as a potential cognitive endophenotype for schizophrenia, and provide a new target for future early interventions and prevention programs not only for schizophrenia patients but also for these at-risk individuals. Further carefully designed family studies that incorporate other psychiatric populations and both molecular and neurobiological measures are still needed.

AUTHOR CONTRIBUTIONS

AA contributed to the management of the literature searches, design of the study, carried out the cognitive explorations, and undertook the statistical analysis. FC contributed in the management of the literature searches design of the study and the psychopathological evaluations. CB, EG, and ÁA contributed in the sample recruitment and psychopathological evaluations. RA-A contributed to the management of the literature searches and assisted with study design. JM supervised the data collection, contributed to the management of the literature searches, and assisted with study design. BC-F supervised the data collection, contributed to the management of the literature searches, and assisted with study design. All authors participated in the writing process, read and approved the final manuscript, and are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

FUNDING

This research was supported by the Spanish Ministry of Science and Innovation, the Carlos III Health Institute (PI11/02221). AA was supported by a trainee research staff grant awarded by the University of Barcelona (APIF-UB grants).

ACKNOWLEDGMENTS

The authors thank Cristian Tebé from the Statistical Assessment Service at Bellvitge Biomedical Research Institute-IDIBELL for his role in statistical analyses, and all of the study participants as well as the staff from the Psychiatry Department, Bellvitge University Hospital.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

4.4. Study 4

Patients with Schizophrenia Activate Behavioural Intentions Facilitated by Counterfactual Reasoning

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PLoS ONE. 2017 12(6): e0178860. [*co-first authors]

Impact Factor (JCR 2015): 3.057 (Quartile1, Multidisciplinary Sciences)

Summary of the results

In general, the results from *Study 4* seemed to support the main hypotheses posited by the research group: by using a novel semantic priming task, schizophrenia patients preserve their capacity to activate intentions as a precursor to behavioural implementation once counterfactual inference is generated, although they appear to be slightly less effective than would be expected in the general population. Specific results are detailed below in order of relevance:

1. Within-group analyses revealed a facilitator effect of counterfactual reasoning when activating behavioural intentions in both groups of study represented by:

    1a. A lower number of incorrect associations made when a counterfactual prime was presented.

    1b. A lower percentage gain in RT difference when a counterfactual prime was presented –i.e., lower time to response correctly when a counterfactual prime was presented.

2. Between-group analyses revealed significantly higher odds of responding incorrectly among schizophrenia patients independently of the prime cue condition –i.e., schizophrenia patients performed slighlty worse than the healthy controls in both experimental conditions (counterfactual and neutral-control).

2a. In addition, schizophrenia patients were capable of learning from experience as the experiment progressed evidenced by decreasing the odds of answering incorrectly.

3. No significant associations were found between all the measures of counterfactual reasoning explored and the neuropsychological variables examined.

4. No significant associations were found between all the measures of counterfactual reasoning explored and the clinical variables examined.

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RESEARCH ARTICLE

Patients with schizophrenia activate behavioural intentions facilitated by counterfactual reasoning

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OPEN ACCESS

Citation: Contreras F, Albacete A, Tebé C, Benejam B, Caño A, Menchón JM (2017) Patients with schizophrenia activate behavioural intentions facilitated by counterfactual reasoning. PLoS ONE 12(6): e0178860. https://doi.org/10.1371/journal.pone.0178860

Editor: Peter John McKenna, Hospital Benito Menni, SPAIN

Received: September 22, 2016

Accepted: May 19, 2017

Published: June 6, 2017

Data Availability Statement: Data are from the PR077/10 study whose authors may be contacted at fcontreras@bellvitgehospital.cat. Fernando Contreras. Bellvitge University Hospital-IDIBELL. The Clinical Research Ethics Committee of Bellvitge (CEIC). Data from the study is available upon request because of confidentiality restrictions. Interested readers can access data contacting with the Clinical Research Ethics Committee of Bellvitge (CEIC) at presidenciaceic@bellvitgehospital.cat.

Abstract

Previous research has associated schizophrenia with an inability to activate behavioural intentions facilitated by counterfactual thinking (CFT) as a step to improving performance. Consequently, these findings suggest that rehabilitation strategies will be entirely ineffective. To extend previous research, we evaluated the influence of CFT in the activation of behavioural intentions using a novel sequential priming paradigm in the largest sample of subjects explored to date.

Method

The main variables assessed were: answer to complete a target task (wrong or correctly), and percentage gain in the reaction time (RT) to complete a target task correctly depending on whether the prime was a counterfactual or a neutral-control cue. These variables were assessed in 37 patients with schizophrenia and 37 healthy controls. Potential associations with clinical status and socio-demographic characteristics were also explored.

Results

When a counterfactual prime was presented, the probability of giving an incorrect answer was lower for the entire sample than when a neutral prime was presented (OR 0.58; CI 95% 0.42 to 0.79), but the schizophrenia patients showed a higher probability than the controls of giving an incorrect answer (OR 3.89; CI 95% 2.0 to 7.6). Both the schizophrenia patients and the controls showed a similar percentage gain in RT to a correct answer of 8%.

Conclusions

Challenging the results of previous research, our findings suggest a normal activation of behavioural intentions facilitated by CFT in schizophrenia. Nevertheless, the patients

Funding: Support was provided by Spanish Ministry of Science and Innovation, the Carlos III Health Institute (PI08/1118) [http://www.isciii.es/]; University of Barcelona (APIF-UB grants) [http://www.ub.edu/web/ub/ca/]. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

showed more difficulty than the controls with the task, adding support to the concept of CFT as a potential new target for consideration in future therapeutic approaches for this illness.

Introduction

Counterfactual thinking (CFT) is a specific type of conditional reasoning manifested as an almost automatic mental representation of alternatives to past events, especially triggered by negative occurrences [1]. These thoughts take the form of "if only" conditional propositions and have an impact on how individuals find meaning in the events that affect them [2]. For instance, in the fictional scenario where John has failed an important test, he might automatically generate a counterfactual thought like *If I had studied harder*, *I could have passed the test*.

As far as the function of CFT is concerned, it seems to play an important role in supporting adaptive behaviour by enabling us to learn from past experiences [3], by modulating emotional states [4], promoting creativity [5] and supporting future planning and prediction [6]. CFT also seems to be related to specific cognitive biases such as the hindsight bias—enhancing memory distortions that contribute to suboptimal decision-making [7]—and to Theory of Mind (ToM) deficits involved in the development of false belief [8].

Thus, although it may sometimes lead to bias, CFT coordinates daily behaviour via course correction, goal cognition, behavioural regulation and performance improvement [3]. For this reason, in 2008, authorities in this field such as Epstude and Roese proposed a functional theory of CFT based on the content-specific pathway concept originally framed in Gollwitzer and Moskowitz's research on how goals influence actions [3,9]. According to this theory, CFT would promote behavioural change following a regulatory sequence divided into three links or steps: following John's fictional scenario, (1) the recognition of a problem that automatically activates the generation of CFT (*I should have studied harder*, Step 1); (2) the activation of behavioural intentions for future similar problems/scenarios (*next time*, *I will study harder*, Step 2); (3) the implementation of corrective behaviours in similar future scenarios (*actually studying harder for the next test*, Step 3). Indeed, previous research has already documented the occurrence of these three steps in the general population [6,10,11].

Cognitive impairment has been endorsed as a core feature of schizophrenia in a growing body of studies. This impairment affects several cognitive domains (with a magnitude of moderate to severe) [12,13], and is already present in the early stages of the disorder [14–16]. In addition, cognitive deficits appear to be independent of the severity of positive symptoms and are only mildly correlated with the severity of negative symptoms [17]. All of which suggests that cognitive deficits in schizophrenia have a different underlying pathological process than those underlying the clinical symptoms of the disorder [18].

Bearing in mind that schizophrenia involves, at least in part, prefrontal cortex dysfunction [19,20], and that this cognitive deficit has been strongly related to real-world functioning in the disorder [21,22], it is not surprising that research on the study of CFT in schizophrenia has increased significantly in recent years. Accordingly, in keeping with the content-specific pathway of CFT, research to date has found global disruption in counterfactual reasoning in Step 1 and Step 2 of the regulatory sequence. Interestingly, the implementation of corrective behaviours (Step 3) appears to be intact in these patients [23]. With regard to these findings, however, it should be noted that although deficits in CFT activation (Step 1) have been widely reported not only in patients with schizophrenia [24–26] but in their unaffected first-degree relatives [27], research into the activation of behavioural intentions (Step 2) is still scarce [28].

Specifically, findings concerning the activation of behavioural intentions (Step 2) in schizophrenia are currently based on a single study carried out by Roese et al. in 2008, in which the facilitator effect of CFT on the activation of behavioural intentions was tested with a semantic priming task developed by these authors using reaction time (RT) as the dependent variable [28]. Fifteen patients with schizophrenia and 13 healthy subjects performed 45 trials where they had to give a yes/no answer to a declaration of intention (i.e., the intention to carry out a specific action in the future). Each trial presented a negative event that was judged using a within-subject sequential priming paradigm in one of three ways: a counterfactual ("should have"), a neutral control (a word-counting judgement) or a no-judgement baseline. Results showed that whereas the healthy controls responded faster to counterfactual judgements relative to control judgements, the patients with schizophrenia's RT did not vary across the different primes—i.e., the CFT trial did not facilitate the activation of behavioural intentions compared with the neutral control trial. The authors concluded that the link between CFT and the generation of behavioural intentions was broken in schizophrenia, stating that "counterfactuals did not activate intentions in patients with schizophrenia (p. 2)" and suggesting that rehabilitation strategies designed to normalize CFT could not have any benefit for these patients.

Roese et al's study [28] would benefit from replication and extension. With this objective in mind, the present study modified the semantic priming task and evaluating the largest sample of patients with schizophrenia and healthy control subjects to date. We hypothesized that both study groups would commit fewer errors and would response faster when confronted with a counterfactual prime than when confronted with a neutral-control prime. It was hypothesized that schizophrenia patients would perform more poorly than the healthy control subjects. If demonstrated, the latter finding suggest the possibility of targeting CFT in future treatment approaches. In addition, potential associations with variables of neurocognition, clinical status and socio-demographic characteristics were explored in the study.

Method

Participants

Seventy-four participants (37 patients with schizophrenia and 37 healthy control subjects) all fluent in Spanish and aged between 19 and 68 were included in the study after an initial inclusion interview in which mental and personality disorders were assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) [29] and Axis II Personality Disorders (SCID-II) [30]. The Clinical Research Ethics Committee of Bellvitge University Hospital (CEIC) approved all study procedures, and all subjects gave written informed consent before inclusion.

All patients with schizophrenia were recruited from the outpatient service of the Psychiatry Department of Bellvitge University Hospital, met DSM-IV-TR criteria [31] and had not undergone electroconvulsive therapy in the last six months. Patients with a diagnosis of bipolar, schizoaffective, delusional or other Axis I disorders were excluded. Healthy control participants were recruited from hospital employees; exclusion criteria were a previous history of personal or family psychiatric illness (Axis I and Axis II).

Participants were excluded if they had a history of substance use disorder as defined according to DSM-IV-TR [31] (with the only exception being nicotine dependence), head trauma involving loss of consciousness, neurological disease or medical illness that could affect brain function, or an estimated Intelligence Quotient (IQ) below 70. A one-to-one matching procedure was employed to match the control group with the schizophrenia patients by sex, age and educational level.

Measures and procedure

Participants attended individual testing sessions lasting an average of four hours. Clinical rating scales, socio-demographic characteristics and cognitive tests were administered by experienced psychiatrists and neuropsychologists.

Socio-demographic and clinical variables were recorded using an in-house standardized medical history. Symptoms and severity of illness were assessed with the Spanish version of the Positive and Negative Syndrome Scale (PANSS) [32,33] and the Clinical Global Impression-Schizophrenia Scale (CGI-SCH) [34]. Level of functioning was assessed using the Global Assessment of Functioning scale (GAF) [35]. Pharmacological treatment was recorded, and antipsychotic (AP) daily dose equivalents of chlorpromazine were calculated [36].

The Spanish version of the vocabulary subtest of the Wechsler Adult Intelligence Scale III battery (WAIS-III) was used to calculate an estimated IQ [37]. Cognitive function was evaluated with the Spanish version of the Brief Assessment of Cognition in Schizophrenia (BACS) [38,39].

Experiment: Activation of behavioural intentions

To assess whether a preceding counterfactual judgement facilitated the activation of a relevant behavioural intention judgement, an experiment was developed using an adaptation of the original sequential priming paradigm designed by Roese et al. [28] (see **Fig 1** for an overview of the procedure). Testing was implemented using desktop computers running DMDX software [40] and consisted of two blocks of 16 trials: first a 2-minute training block, followed by the 10-minute experiment block. The order of presentation of trials was randomized within each block across participants. In this way, all subjects completed 32 judgement trials that were structured in three stages around a hypothetical negative event: first, a description of a negative everyday event appeared on the screen (stage 1) (e.g., "I have missed the train"); two seconds later, a prime cue (stage 2) that could be a counterfactual statement (e.g., "I should have") or a neutral-control statement (a factual-neutral cue such as "It has five words") appeared. The neutral-control prime task was modified from the task used by Roese et al. (2008): while in the original experiment participants executed a word-counting judgement [28], in the current

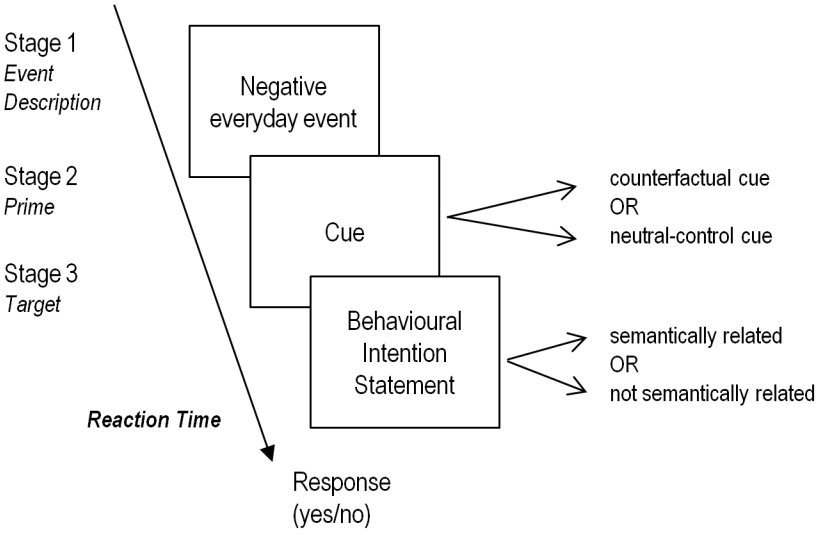

Fig 1. Overview of the sequential priming paradigm adapted from the original sequential priming paradigm designed by Roese et al. (2008) [28].

https://doi.org/10.1371/journal.pone.0178860.g001

study the neutral-control task consisted of reading a statement, as in the counterfactual condition. This ensured that the cognitive load of the procedural work was similar in the two types of task. This stage was followed by a subsequent behavioural intention statement that was either semantically related to the action described previously or not (stage 3) (e.g., "got out of bed sooner" or "washed the car before"). Finally, participants had to press a key on the computer labelled "yes" or "no" to indicate whether the behavioural intention was related to the negative everyday event that preceded it.

Once the experiment was finished, two outcomes were recorded: (1) response to complete the target task (wrong or correct) understood as the associations made by the participants between the first event and the final outcome–e.g., answering "no" when the event and the intention judgement were actually related, or vice versa, and (2) percentage gain in the reaction time (RT) to achieve a correct association or answer whether the prime was a counterfactual or a neutral-control cue. Note that RT to achieve a correct association was defined as the time gap measured in milliseconds from stage 3 and participants' response, and that percentage gain was defined as the difference between RT in the neutral-control prime and RT in the counterfactual prime divided by RT in the neutral-control cue. The decision to use percentage gain rather than raw RT scores was based on previous research findings highlighting a potential arithmetical artefact due to the effect of a general RT slowing in schizophrenia [41]. Specifically, the value for priming will be spuriously inflated in patients with the disorder, if they are slower to respond on both the unprimed and primed versions of the task [42].

Statistical analysis

For descriptive analyses, absolute and relative frequencies were calculated for categorical variables. Continuous variables were assessed using the mean and standard deviation (SD) for normally distributed variables, and the median and interquartile range (IQR) for non-normally distributed variables. To detect differences between groups, Fisher's exact test and χ^2 were used for categorical data, whereas group means were compared using two-tailed Student's T test and Wilcoxon rank sum test.

To evaluate the effect of the prime presented (counterfactual vs. neutral-control), two outcomes were examined. First, the adjusted odds ratio of a wrong association on schizophrenia patients versus healthy controls was estimated using a mixed logistic regression model. Sociodemographic and clinical variables were the potential adjusting variables tested. Secondly, the adjusted effect of being a schizophrenia patient versus a healthy control when assessing the percentage gain in the RT difference was estimated using a mixed regression model, with the same potential adjusting variables being tested. As percentage gain did not follow a normal distribution, a log transformation was performed. Normality was tested graphically by quantile plot and analytically by the Shapiro-Wilks test. For both models, a random subject effect was included to account intra-individual variability on both outcomes among all participants.

Furthermore, as the experiment included 16 repeated trials and a possible learning effect had to be considered, number of trial variable was included in the estimated models with no effect expected. In addition, as the learning effect could differ between patients and controls, the first interaction term was also evaluated. The selection of the model's variables was based on the Akaike Information Criterion (AIC). Fixed effects were tested for statistical significance using the Wald test. Coefficients in the mixed regression model are presented in log scale and odds ratios in the mixed logistic model together with 95% confidence interval and p-values.

Finally, for both outcomes, a second model was estimated for the schizophrenia patients only; this was in order to explore the clinical measures included in the study. Thus, along with the aforementioned potential confounder variables, other clinical variables were included such

as daily dose of AP taken (chlorpromazine equivalents) in mg/day, duration of the illness in years, and scores on the PANSS and GAF scales were tested to adjust the significance of the prime task effect. The analysis of residual and influential values did not identify any covariate pattern with a relevant impact on the goodness of fit statistics, or deviance residual, or in estimating the coefficients model. Data were managed and analyzed using R 3.2.5.

Results

Socio-demographic characteristics are shown in Table 1. There were no differences regarding sex, age, educational level or hand dominance between patients with schizophrenia and healthy controls, but a larger proportion of patients were unemployed/retired and single at enrolment. With regards to neurocognitive performance, the patients had significantly lower scores in all cognitive domains in comparison with the healthy control subjects. No statistically significantly associations were found between any of the experimental measures and neurocognitive performance in either the healthy controls or the schizophrenia patients (these analyses are presented in more detail in S1 Appendix).

In terms of clinical characteristics, the patients exhibited mild levels of symptoms on the PANSS: total score = 74.24 (SD = 16.08), positive dimension = 13.59 (SD = 3.42), negative dimension = 22.35 (SD = 5.94) and general dimension = 38.30 (SD = 8.65).The median GAF score was 60 (IQR = 60–70), mean length of illness was 16.03 years (SD = 9.79) and the mean daily dose of AP treatment taken was 657.13 mg/day (SD = 470.17) (chlorpromazine equivalents).

Experiment: Activation of behavioural intentions

Descriptive data on each prime task condition according to study group is presented in Table 2.

Table 1. Socio-demographic characteristics of the sample.

	Schizophrenia Patients (n = 37)	Healthy Controls (n = 37)	p-value
Male sex, *n (%)*	23 (62.16)	21 (56.76)	0.813[a]
Age (years)	38.49 (10.20)	40.12 (12.52)	0.542[b]
Educational level (years)	10.62 (3.46)	11.57 (3.11)	0.073[c]
Employment status, *n (%)*			0.000[d]
Employed	13 (35.14)	32 (86.49)	
Unemployed/ Retired	23 (62.16)	5 (13.51)	
Student	1 (2.70)	0 (0.00)	
Marital status, *n (%)*			0.020[d]
Single	30 (81.08)	19 (51.35)	
Married	6 (16.22)	15 (40.54)	
Divorced	1 (2.70)	3 (8.11)	
Hand Dominance (right), *(%)*	94.59	97.30	1.000[d]
Estimated IQ	97.57 (11.34)	112.03 (8.93)	0.000[b]

Note. Values presented as means (standard deviation) unless specified otherwise.

[a] χ^2 test

[b] T-test

[c] Wilcoxon rank sum test

[d] Fisher's Exact Test.

https://doi.org/10.1371/journal.pone.0178860.t001

Table 2. Activation of behavioural intentions experiment.

	Counterfactual prime condition	Neutral-control prime condition
Incorrect associations made, *n (%)*		
Healthy controls	26 (4.4)	19 (3.2)
Schizophrenia patients	56 (9.5)	106 (17.9)
RT to correct association (ms), *median (IQR)*		
Healthy controls	1136 (855–1442)	1235 (941–1538)
Schizophrenia patients	1614 (1271–2059)	1808 (1404–2371)

Note. In both prime conditions, the number of observations was 592. ms: milliseconds.

https://doi.org/10.1371/journal.pone.0178860.t002

Response to complete the target task (wrong or correctly): Mixed logistic regression model results. Results from the mixed logistic regression model are summarized in Table 3.

For the *entire sample model*, the odds of responding incorrectly were significantly higher (1.7 times) when a neutral-control prime was presented. Among patients, the odds were 3.9 times higher than among controls after controlling for age, sex and education level. Moreover, a learning effect was found, i.e., for each new trial presented, the odds of making a wrong association were 4% lower. No significant interaction effect was found between type of prime task, study group or number of trials presented.

For the *schizophrenia patients model*, the odds of responding incorrectly were significantly higher (2.4 times) when a neutral-control prime was presented after controlling for age, sex and educational level. Additionally, a learning effect was observed, i.e., for each new trial presented, the odds of making a wrong association were 5% lower. No significant interaction effect was found between type of prime task, study group or number of trials presented. No clinical potential confounder variables presented a significant association, nor improved the model performance.

Percentage gain in the reaction time difference: General linear mixed model results. Results from the general linear mixed model regarding percentage gain in the RT difference are presented in Table 4.

As noted above, percentage gain was measured by dividing the raw reaction time difference by the reaction time to a correct answer under a neutral-control prime. However, to calculate this it was necessary that in each trial the subject answered correctly in both prime conditions. Hence, if a subject answered correctly under the counterfactual prime but not under the

Table 3. Mixed effects logistic regression using right/wrong answer as the dependent variable.

	Entire sample model[a] (n = 74)			Schizophrenia patients model[b] (n = 37)		
	OR	CI 95%	p-value	OR	CI 95%	p-value
Constant	0.03	0.02 to 0.07	<0.0001	0.17	0.08 to 0.36	<0.0001
HC vs. SCZ	3.89	1.99 to 7.58	<0.0001	—		
NC vs. CFT	0.58	0.42 to 0.79	0.001	0.41	0.40 to 0.43	<0.0001
Number of trial	0.96	0.93 to 0.99	0.027	0.95	0.49 to 1.84	0.008
Age (centered)	1.01	0.98 to 1.04	0.468	1.02	0.52 to 2.02	0.654
Sex, male	1.49	0.75 to 2.95	0.250	1.29	0.94 to 1.78	0.615
Educational level (centered)	0.93	0.84 to 1.03	0.183	0.92	0.89 to 0.95	0.273

OR: odds ratio; SCZ: schizophrenia patients; HC: healthy controls; NC: neutral-control prime condition; CFT: counterfactual prime condition.

[a] 2368 observations in 74 clusters.

[b] 1188 observations in 37 clusters.

https://doi.org/10.1371/journal.pone.0178860.t003

Table 4. General linear mixed regression model using percentage gain difference to a right answer as the dependent variable.

	Entire sample model[a] (n = 74)			Schizophrenia patients model[b] (n = 37)		
	beta	CI 95%	p-value	beta	CI 95%	p-value
Constant	4.50	4.48 to 4.60	<0.0001	4.50	4.41 to 4.60	0.000
HC vs. SCZ	-0.04	-0.09 to 0.00	0.070	—		
Number of trial	-0.00	-0.01 to 0.00	0.354	-0.01	-0.01 to 0.00	0.170
Age (centered)	0.00	-0.00 to 0.004	0.082	0.01	-0.00 to 0.01	0.143
Sex, male	0.01	-0.04 to 0.06	0.758	0.03	-0.05 to 0.11	0.451
Educational level (centered)	0.00	-0.00 to 0.01	0.167	0.01	-0.01 to 0.01	0.761

Note. Family Gamma using log as link function. SCZ: schizophrenia patients; HC: healthy controls; NC: neutral-control prime task; CFT: counterfactual prime task.

[a] 994 observations in 74 clusters.

[b] 444 observations in 37 clusters.

https://doi.org/10.1371/journal.pone.0178860.t004

neutral-control prime, or vice versa, the percentage gain was considered as missing. Consequently, taking in account that the percentage of trials presenting a correct response in both prime conditions was 76% among schizophrenia patients and of 93% among controls, the final available sample for the percentage gain model consisted of 994 trials over 1184 potential trials (16 trials in each prime in each group of study).

After adjusting for age, sex and educational level no significant difference between patients and controls was in percentage gain. It should be noted that the expected percentage gain difference in an average participant corresponds to the log of the model's intercept. The percentage gain of a random participant, independently of the study group, was 8%–i.e., the RT when a counterfactual prime was presented was 8% lower in relation to the RT when a neutral-control prime was presented. Accordingly, percentage gain of a random patient was 9% after adjusting for age, sex and educational level in the *schizophrenia patients model*. None of the clinical potential confounder variables assessed presented a significant association.

Finally, for both models, no learning effect was found in this measure across trials in either group.

Discussion

The present study focused on the activation of behavioural intentions facilitated by CFT–the capacity of inferring how an event might have unfolded differently in response to real-world experiences [43]–in the largest sample of patients with schizophrenia and healthy control subjects examined to date. In schizophrenia, it has been proposed that this specific counterfactual skill is disabled [28]. However, these results come from a single study with some methodological concerns; therefore, the present study was designed to re-evaluate these previous findings, using a larger sample and an improved priming paradigm. In addition, potential associations with variables of neurocognition, clinical status and socio-demographic characteristics were explored. Several results were found that merit discussion.

In the first place, it was found that both the patients and the controls made fewer errors and performed faster in the counterfactual semantic priming condition than in the neutral-control priming condition. Hence, the present results support our main hypothesis that patients with schizophrenia would show a counterfactual semantic facilitation, as healthy controls do. Accordingly, as well as confirming previous research in healthy subjects [6], the present study does not support the claim that activation of behavioural intentions facilitated by CFT is disabled in schizophrenia. In fact, as evidenced by a fall in the odds of answering

incorrectly (i.e., response to complete the target task variable), the patients with schizophrenia in this study were capable of learning from experience as the experiment progressed.

One possible explanation for the difference between our findings and those of Roese et al. [28] might be that the sample used in our study (37 patients and 37 controls) was larger than the one used in their study (15 patients and 13 controls). Another explanation might be related to the adaptation made to the original experiment involving changes to the neutral-control prime condition. In Roese et al.'s [28] control condition the participants executed a word-counting judgement which represented a task with significant cognitive demands, and was not comparable to the counterfactual condition task which consisted only of reading a statement. To rectify this problem, in the present experiment the neutral-control condition was modified so that it consisted simply of reading a statement focused on a factual cue rather than executing a cognitive task. The level of difficulty was more similar to that of the counterfactual trial, and the design additionally ensured that participants did not know a priori whether the third message was related to the first event until it appeared on the computer screen.

Secondly, although to our knowledge this is the first time that the potential associations between CFT facilitation of behavioural intentions and clinical, socio-demographic or cognitive measures have been explored, these analyses did not reveal evidence of significant associations with any of these variables. Indeed, the relationship between low and high order cognitive processes is controversial. For instance, whether social cognition and basic cognitive processes are associated is a question not yet adequately answered [44–45]. Thus, similarly, the debate about the observed counterfactual disruption in schizophrenia is the result of a pervasive cognitive impairment or is dependent on a specific deficit in a certain cognitive domain can still be considered to be open. Further research using other neuropsychological measures, for instance, instruments assessing domains of social cognition, might be of interest.

The present study has some limitations that should be acknowledged. Although the sample used was larger than in the one previous study [28], the number of participants remained relatively small. This may have resulted in a lack of statistical power and a type II error, raising the possibility that the study was not able to detect actual differences between groups. Secondly, in order to avoid a potential effect of greater cognitive deterioration in clinical and neurocognitive measures among older schizophrenic patients, healthy subjects were matched by age, sex and educational level, and all analyses were adjusted for these same variables. Thirdly, the study sample did not meet the criteria for stability as defined by Andreasen et al. (2005) [46], although the mean total PANSS score was 74.24 (SD = 16.08) which indicates a relatively low level of current symptoms. Finally, two issues about the experimental design have to be considered: first, this experiment was designed without a baseline (no judgement) condition and second, although the instruction for the participants was to only read the statements, the neutral-control (factual) cues presented (for instance, "it has 5 words") might be counterintuitive for the participants. Further research including these considerations could help to achieve a clearer assessment of the effect of CFT on behavioural intentions activation.

Conclusions

In summary, the findings of this study suggest that patients with schizophrenia preserve their capacity to generate intentions as a precursor to behavioural implementation once CFT is activated. These findings indicate that, in spite of the conclusions of previous research, Step 2 of the CFT content-specific pathway is actually not broken in the disorder. Therefore, in the light of previous studies demonstrating the feasibility of cognitive bias modification programs in the psychotic population [47–49], the present findings may be of interest since from the perspective of targeting counterfactual reasoning deficits in future treatment approaches in order

to improve these patients' reasoning and functional outcome. If, patients with schizophrenia can produce behavioural intentions facilitated by counterfactual judgements, they may also benefit from a specifically cognitive rehabilitation treatment focused on the understanding of negative experiences and the activation of the corresponding corrective intentions. This might help them to regulate and improve their behaviours as well as their future functioning. Further confirmatory studies are needed in order to corroborate the present results.

Supporting information

S1 Appendix. Neurocognitive performance and its association with results from the experiment.
(PDF)

Acknowledgments

The authors thank all the study participants as well as the staff of the Psychiatry Department.

Author Contributions

Conceptualization: FC AA BB.

Data curation: AA CT.

Formal analysis: CT.

Funding acquisition: FC JMM AA.

Investigation: FC AA CT BB AC JMM.

Methodology: FC AA BB.

Project administration: FC AA JMM.

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Supervision: FC AA JMM.

Validation: FC AA CT BB AC JMM.

Writing – original draft: FC AA CT BB AC JMM.

Writing – review & editing: FC AA CT BB AC JMM.

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S1 Appendix. *Neurocognitive performance and its association with results from the experiment*

As presented in **Table S1**, schizophrenia patients obtained significantly lower scores in all cognitive domains than the healthy control subjects.

Table S1. Neurocognitive performance by groups of study.

	Schizophrenia Patients (n=37)	**Healthy Controls (n=37)**	**p-value**
BACS, raw scores			
Verbal memory	34.39 (12.27)	44.16 (6.07)	0.000[b]
Digit sequence	14.62 (4.18)	18.30 (3.38)	0.000[b]
Token motor task	69.08 (15.51)	83.65 (9.14)	0.000[a]
Verbal fluency	28.54 (10.29)	44.51 (8.56)	0.000[a]
Symbol coding	36.22 (14.04)	54.32 (8.39)	0.000[b]
Tower of London	17.81 (2.91)	19.08 (1.66)	0.033[b]

Note. Values presented as means (standard deviation) unless specified otherwise. [a]T-test; [b]Wilcoxon rank sum test; BACS: The Brief Assessment of Cognition in Schizophrenia.

Furthermore, no significant associations were found between any of the cognitive variables assessed and none of the both outcomes measures in the experiment.

This total lack of association with cognitive functioning is not surprising since inferring from CFT, as a higher order process, involves more complex reasoning than other low order cognitive functions such as attention or working memory. Along with the fact that previous research has not found significant correlations between activation of CFT and any of the basic cognitive deficits characteristic of schizophrenia [1–3]. Present results are also supported by recent neuroimaging studies' findings proposing an integrative network of

systems for affective processing, mental simulation and cognitive control in which CFT might be relying on. This proposal considers that counterfactual reasoning might actually be supported by the coordination of multiple information processing systems that together enable adaptive behaviour [4, 5, 6]. Thus, further research could benefit from also including neuroimaging measures other than neuropsychological.

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5. Discussion

The present chapter will summarize and present a general discussion of the findings of this thesis. The discussion will also focus on the implications for future research on the study of neurocognitive impairment in schizophrenia and the development of novel treatment approaches for these patients. Comments on the general limitations and an overall conclusion will be also provided.

5.1. Discussion of Key Findings

5.1.1. Activation of counterfactual thoughts

One of the main findings of the present thesis was the demonstration that, overall, there is an alteration in the ability to activate counterfactual alternatives in schizophrenia. Specifically, results from *Study 1*, *Study 2* and *Study 3* not only revealed schizophrenia patients to generate fewer counterfactual thoughts than healthy control subjects, but also to tend to not be able to activate any counterfactual alternative at all. Importantly, *Study 3* also revealed non-psychotic first-degree relatives to be less skilled than controls in this task, although better than the schizophrenia patients. Thus, in consonance with previous preliminary results (Hooker *et al.*, 2000), the current thesis's findings seem to reinforce the hypothesis that schizophrenia is a mental condition in which patients have difficulties re-imagining a negative outcome in a positive way; a process that enables the activation of alternative representations for dealing with reality. Different hypothesis that can be posited in order to explain this impairment are presented below.

To begin with, two possible explanations emerge from a neurobiological point of view when specifically considering this tendency among schizophrenia patients of not being able to activate any counterfactual alternative at all, and the results among first-degree relatives. Firstly, framed in the study of the psychophysiological bases underlying neurocognitive processes, counterfactual hypoactivation might be related to alterations in neurophysiological measures, such as the prepulse inhibition (PPI) of the startle response. The PPI is a measure

of inhibitory function and time-linked information processing by which a weak sensory stimulus (the prepulse) inhibits the elicitation of the startle response caused by a sudden intense stimulus (Braff *et al.*, 2001). In schizophrenia, a deficient or weak PPI has been reported, reflecting a lack of inhibitory function or sensorimotor gating (Swerdlow *et al.*, 1999). Interestingly, this deficient gating has been correlated significantly with perseverative responses on the WCST (Butler, 1991) and measures of thought disorder (Perry & Braff, 1994), and distractibility (Karper *et al.*, 1996). In this line, we propose the possibility that present counterfactual hypoactivation might be related to these patients' characteristic PPI deficit; specifically, because of its association with greater distractibility rates among these patients.

Secondly, in keeping with this same line of discussion, another interesting proposal to explain the mechanisms underlying the present counterfactual hypoactivation might be based on previous *f*MRI results evidencing a decreased activation of different neural structures in patients engaged in cognitive tasks mediated by these brain structures (Hill *et al.*, 2004; Baas *et al.*, 2008). Thus, it might be possible that this specific counterfactual inability in schizophrenia was in fact related to a hypoactivation of CFT related structures. For instance, structures that previous research has found to be related to counterfactual activation disruption, such as the OFC (Gomez-Beldarrain *et al.*, 2005; Ursu & Carter, 2005). Acting in accordance with this hypothesis, such impairment in the activation of mental simulations might also be related to previous research describing a failure in schizophrenia to deactivate in the medial frontal area, one of the two midline components of the DMN (Pomarol-Clotet *et al.*, 2008a). Previous expert authors on this topic have suggested that DMN dysfunction might account for the cognitive impairment associated with schizophrenia due to a failure to divert physiological resources away from the DMN during cognitively demanding tasks (Libby & Ragland, 2011; Pomarol-Clotet *et al.*, 2008a). Therefore, it is possible that the observed difficulties in the activation of counterfactual mental simulations might somehow be related to dysfunction in this network. Further research is needed in order to shed light on this hypothesis of counterfactual activation being related to brain dysfunction, for instance by using functional neuroimaging techniques in both schizophrenia patients and unaffected relatives.

Thirdly, from a neurocognitive point of view, we hypothesized that this poor ability to activate counterfactual thoughts might be related to performance of schizophrenia patients in any of the neurocognitive domains assessed in this thesis' studies. In fact, we expected to find

significant associations between such counterfactual hypoactivation and specific CFT-related functions that previous research has found to be disrupted not only in schizophrenia patients but in unaffected first-degree relatives as well. Such cognitive domains embrace attention, memory and executive dysfunction including working memory and reasoning deficits (Heinrichs & Zakzanis, 1998; Keefe & Harvey, 2012; Sitskoorn *et al.*, 2004; Szöke *et al.*, 2005). For this, we tested such potential relationships in *Study 1* and *Study 3,* controlling the mean dose of daily antipsychotic being taken to assure that medication was not compromising results on these neuropsychological tests. However, data analyses did not follow the predicted results; none of these studies found a significant result in this direction. Two different explanations can be provided to discuss the present lack of results. From a methodological perspective, maybe other neuropsychological tests more specifically targeting CFT-related structures should had been included. For instance, other instruments related to the vmPFC, such as the Iowa Gambling Task (Bechara *et al.*, 1994). On the other hand, though, as Hooker *et al.* (2000) already proposed in their pilot study, the present results might indicate that the hypoactivation of counterfactual thoughts cannot be reduced to dysfunction of a specific domain but to general cognitive impairment. This proposal would actually be in the line of Van Hoeck *et al.*'s (2015), suggesting an integrative neural networks supporting counterfactual reasoning that subsequently requires the integration of different cognitive functions and psychological processes.

Finally, from a clinical point of view, the possibility that this alteration in the counterfactual activation might actually be the result of the classical symptoms of the disorder can also be considered. For instance, it could be related to conceptual disorganization or lack of spontaneity. However, in conjunction, findings from this thesis' studies do not seem to support this hypothesis due to two different key results: (1) because this deficit was observed among non-psychotic first-degree relatives, although to a lesser degree (*Study 3*), and (2) because it was manifested similarly among those schizophrenia patients meeting criteria for symptomatic remission (*Study 2* and *Study 3*) and those who did not (*Study 1*).

Notwithstanding the above, it has to be mentioned that, although they might not be simply the result of them, difficulties in the activation of counterfactual alternatives appeared to be influenced by symptom severity of the disorder. That is, results from *Study 2* evidenced significant negative associations between counterfactual generation and scores on all the

PANSS scales (including total score and positive, negative and general dimension) despite these patients presenting low levels of current symptoms. In conjunction, the present findings might evidence at least a relatively independence of counterfactual hypoactivation from symptoms. Previous research supports this notion, specifically in relation with the negative symptoms of the disorder (Brissos *et al.*, 2011; Keefe *et al.*, 2006b).

In conclusion, the present thesis results seem to evidence an impoverishment of the counterfactual thought activation in both schizophrenia patients and first-degree relatives, although to a lesser degree in the case of the latter. Different hypotheses from different perspectives have been posited in order to explain the mechanisms underlying such alterations. Accordingly, the results from this thesis' studies seem to suggest a biological basis for the counterfactual hypoactivation in schizophrenia. However, it seems that this fact cannot be explained by other specific cognitive processes impairment or severity of clinical symptoms. Further research is required in order to add knowledge to this field, replicating and extending the present results, for instance by integrating psychophysiological and neuroimaging techniques.

5.1.2. Generation of counterfactual-derived inferences

Another main focus of this thesis has been the assessment of the generation of counterfactual-derived inferences within the frame of the *norm theory* (Kahneman & Miller, 1986). As introduced in Chapter 1 (p.49), this theory explains how the majority of individuals are constrained to specific characteristics of reality as a shortcut mechanism to infer from counterfactuals thoughts. Among this variety of characteristics or factors, the present thesis has evaluated the causal order effect, and the unusualness and proximity of the situation in relation to different affective and judgemental reactions. Overall, the findings seem to suggest that the pattern of counterfactual inference appears to be altered in schizophrenia when certain characteristics of reality are involved. The following paragraphs present a more detailed discussion for each of these results.

5.1.2.1. The causal order effect

As a reminder, the causal order effect refers to the general population's tendency to construct the counterfactual alternative by altering early rather than later events in a causal sequence of

events with a negative outcome (Wells *et al.*, 1987; Segura *et al.*, 2002). Therefore, aiming to add a novel object of study into this field, the present thesis has been the first to date to explore the causal order effect in schizophrenia. Thus, because of their thought disorder, we hypothesized that schizophrenia patients would deviate from the norm by not constructing the counterfactual alternative by altering the earliest event in a chain as would be expected in the general population. However, data analyses from this thesis' studies did not reveal significant differences between patients with schizophrenia and healthy control subjects, and neither with non-psychotic first-degree relatives. Particularly, analyses from *Study 1*, *Study 2* and *Study 3* concisely revealed all three groups of study to alter the first event (i.e., the earliest) rather than the others more frequently when generating the counterfactual inference. Interestingly, results from *Study 1* also revealed altered general pattern of response among patients when deciding which one of the events was more decisive. However, such results were not replicated in *Study 2* and *Study 3*, probably due to the larger samples used in these studies.

In conclusion, the present thesis' findings have demonstrated how, like healthy controls, either patients with schizophrenia and unaffected first-degree relatives tended to attribute causality through counterfactual reasoning by following what Kahneman and Miller defined as the *norm* (1986). Consequently, these results might be cause for optimism since they indicate a normative pattern of causality attribution, which might have a beneficial effect on these patients' daily life functioning.

5.1.2.2. Counterfactual Inference Test

As presented in Chapter 3 (p.80), the CIT (Hooker *et al.*, 2000) was used to explore the ability of the individuals to derive inferences from CFT taking in account two different factors described to influence it: the unusualness and the proximity factors of a situation. At the same time, the CIT also examines the effect of the individual's affective and judgemental reactions in the resulting counterfactual inference (Kahneman & Tversky, 1982a; Kahneman & Varey, 1990). Particular results for the present thesis' studies are discussed in more detail below.

To begin with, data analyses revealed no differences between schizophrenia patients and healthy controls on the CIT-Total score measure (*Study 1*, *Study 2* and *Study 3*). Such

findings seem to suggest that, in general, schizophrenia patients tend to be as adept as the healthy controls when deriving inferences from counterfactual reasoning as measured by the CIT composite score. Interestingly, probably due to the larger samples used in this thesis' studies, these results are challenging those of Hooker *et al.* (2000) in which schizophrenia patients obtained significantly lower mean CIT-Total scores. Thus, the present findings might be cause for optimism like those of the causal order effect experiment, since they indicate a "normative" pattern of counterfactual inference in schizophrenia. However, analyses each of the CIT's scenarios in particular seem to suggest otherwise because of varying results.

Firstly, with regards to the exceptionality of the situation, analyses evidenced schizophrenia patients to significantly select the counterfactual target response when confronted to an unusual event associated to an affective (i.e., regret) reaction (Scenario 2) less frequently than controls. In other words, patients deviate from the general population by altering the usual rather than the exceptional aspect of the situation when constructing the counterfactual alternative (Kahneman & Tversky, 1982a). Interestingly, results also suggested that this "deviated" pattern of response was specifically linked to a diminished regretful reaction to the negative result of the situation. This lower tendency to react with regret might be related to prototypical negative symptoms of the disorder such as blunted affect and emotional withdrawal. However, data analyses did not find any significant associations between these results and symptomatology of the patients. Secondly, when confronting schizophrenia patients to hypothetical situations with a "close" event, analyses evidenced that, when facing a temporally (Scenario 3) "nearly happened" situation, patients tended to select the target or expected counterfactual response less frequently. Similarly as above, patients tended to deviate from the norm, in this case by disregarding the basic perception of nearness to an outcome (Kahneman & Varey, 1990). Specifically, it appears that when confronted with situations with negative results (e.g., getting mugged), schizophrenia patients tend to misperceive the possibility that a better outcome could almost have happened (e.g., not being mugged) –i.e., the possibility to generate counterfactuals focused on the desired (better) outcome becomes unavailable for these patients. Interestingly, this tendency was found to be associated with a diminished reaction of rumination (i.e., judgemental reaction; Scenario 3). Again, it might be possible that this lower tendency to react with rumination might be related to negative symptoms of the disorder. However, data analyses did not find any significant associations with the PANSS negative scale.

Therefore, it appears that data analyses for each of the scenarios are in contradiction with the CIT-Total score: results suggest that when facing social situations with a negative outcome, specific factors of the reality in which the general population tends to rely on when constructing counterfactual inferences are actually having a different effect in schizophrenia patients. Thus, findings from the current thesis not only seem to highlight a propensity in schizophrenia to not adhere to the "normal" habitual mode of reasoning (Kahneman & Miller, 1986; McCloy & Byrne, 2000), but also suggest the unsuitability of Hooker *et al.*'s (2000) proposal of a composite "normative pattern of response" score since it might not adequately reflect the individuals' ability to infer from counterfactuals.

When considering the potential causes underpinning such alterations, one may hypothesize that as with deficits in the counterfactual thought activation, they might be related to neurocognitive dysfunction of this disorder as well. However, neither results from the current thesis' studies, nor those from the previous pilot study found significant results in this direction (Hooker *et al.*, 2000). Interestingly, this absence of results could be suggestive of the involvement of more complex cognitive abilities that have not been explored in the current thesis properly, such as social cognition based abilities. For instance, based on previous studies evidencing counterfactual reasoning to be involved with ToM dysfunction in schizophrenia (Kern *et al.*, 2009), the present results might be related to a disability when mentalizing with the character of the scenario. Further research exploring this link between counterfactual inference and variables of social cognition in schizophrenia could be a logical next step in this field.

Finally, another interesting finding of this thesis is the one derived from *Study 3* suggesting that non-psychotic first-degree relatives stay within the normative pattern when generating counterfactual-derived inferences. In fact, the results not only revealed the relatives to be as skillful as the healthy controls in general, but to be more proficient in the specific scenarios assessing the effect of unusualness of the situation presented (Scenario 2 and Scenario 4). That is, indicating that the exceptionality of the situation acted as a more intense counterfactual inference trigger for the relatives than for the controls. Indeed these findings might suggest some kind of deviation from the norm but in the opposite direction than patients. However, from a functional point of view, the present results indicate that first-degree relatives were actually able to generate counterfactual inferences by following the normative pattern as defined by Kahneman and Miller's *norm theory* (1986). To fully

understand the present findings, further research is needed trying to replicate and extend these results.

In conclusion, the current thesis' findings reinforce the notion that counterfactual inference is altered in schizophrenia, particularly when exceptional and close aspects of reality are related. Thus, there seem to exist a reasoning alteration in schizophrenia that makes patients disregard the "hints" of reality on which the general population tends to rely when engaging in CFT. Such disruption becomes of special relevance when considering how it could be involved in the development and maintenance of delusions in psychosis, and due to its impact on the construction of adaptive counterfactual alternatives, and subsequently, the implementation of future corrective behaviours.

5.1.3. Activation of behavioural intentions

Framed in Epstude and Roese's (2008) proposal of a CFT functional regulatory loop, the aim of *Study 4* was to extend a previous single study suggesting that the link between counterfactual reasoning and the activation of behavioural intentions was dysfunctional in schizophrenia. Interestingly, though, by using a larger sample and a different priming paradigm, findings from *Study 4* challenged previous results evidencing schizophrenia patients to preserve their capacity to generate intentions as a precursor to behavioural implementation once the counterfactual inference was constructed. Specifically, as the healthy controls did, schizophrenia patients tended to commit fewer errors and correctly respond faster when a counterfactual prime was presented. In addition, though, between-group analyses also revealed schizophrenia patients to perform slighlty worse (i.e., committing more errors or incorrect associations) than the controls in both experimental prime conditions, although they were able to learn from past experience as the experiment progressed (i.e., evidenced by a decreasing of the odds of answering incorrectly). In contrast, these findings were not observed with regards to the time to response correctly. Furthermore, none of the neurocognitive functions assessed was found to be associated with performance on this experiment, despite all of them being significantly disrupted among patients. As suggested with counterfactual inference ability, this lack of associations might reflect the involvement of more complex cognitive abilities. In fact, Epstude and Roese (2011) have already proposed the combination of a broad number of cognitive, emotional and motivational processes

supporting the counterfactual regulatory loop. Further research is needed in order to fully understand such relationship.

In conclusion, the present results seem to suggest that, though presenting some difficulties, once they have been able to activate a counterfactual thought and generate an inference from it, schizophrenia patients are able to activate a behavioural intention that could eventually lead to the implementation of a new behaviour, hence, suggesting the suitability of targeting this process in future cognitive rehabilitation programs.

5.2. Implications for Further Research

Findings from the current thesis further characterize counterfactual reasoning impairment in schizophrenia by improving and extending existing preliminary studies on this field. Overall, whereas the abilities to activate counterfactual thoughts and to construct counterfactual inference seem to be altered in this disorder, the ability to activate behavioural intentions through counterfactual reasoning has been found to be preserved. Further, the present thesis provides basis for the study of counterfactual hypoactivation as a new putative cognitive endophenotype for schizophrenia. The implications of these findings for future research in schizophrenia are presented below.

5.2.1. Implications for neuropsychological research

To begin with, the present thesis seems to contribute to the growing literature considering cognitive impairment as a core feature of schizophrenia (Green, 1996), particularly because it provides a basis for the proposal of considering impairment in the ability to activate counterfactual thoughts as a novel primary deficit of the illness. Accordingly, several results seem to support this notion: (1) because it did not seem to be secondary to classic symptoms of the disorder –i.e., it was found among patients with a low level of current symptoms (*Study 1*), and even among patients in a state of symptomatic remission (*Study 2* and *Study 3*), (2) because it seems to persist through the long-term course of the illness –i.e., it was negatively associated with longer duration of the illness (*Study 2*), (3) because the neuroleptic treatment did not seem to have an impact on this deficit (*Study 1*, *Study 2* and *Study 3*), and finally, (4) because it was observed among non-psychotic first-degree relatives of patients with

schizophrenia, although to a lesser degree –i.e., underscoring the heritability of this deficit. Thus, all these results as a whole might suggest that disruption of counterfactual thought activation and psychopathology of the illness are likely caused, at least partially, by distinct pathophysiological processes. Further research is required in order to consolidate the present findings, for instance, trying to replicate and extend our work by studying: (i) patients with a first psychotic episode since this would allow us to control for the effects of confounds such as long-term medication, hospitalization and general chronicity effects; (ii) patients with a longer history of schizophrenia to explore this deficit in all stages of the illness; (iii) patients with other related diagnoses (e.g., within the schizophrenia spectrum disorders or bipolar disorder) to determine the specificity of such impairment; (iv) other individuals at-risk for psychosis or schizophrenia apart from unaffected first-degree relatives; and finally, (v) to design studies within a longitudinal approach in order to fully understand the stability of the present results over time.

Furthermore, it is our impression that the tendency to deviate from the norm when deriving inferences from counterfactual reasoning observed in *Study 1*, *Study 2* and *Study 3* might be somewhat related to the study of cognitive approaches accounting for the development and maintenance of delusions in psychosis (Garety & Freeman, 1999; Moritz & Woodward, 2005). Specifically because such tendency might be enhancing the production of reasoning biases that subsequently could lead to suboptimal decision-making. Such hypothesis can be stated based on previous research evidencing the effect of CFT on some specific cognitive biases in the general population (Roese & Olson, 1996). Further research should try to explore such proposals in more detail, for instance by using neuropsychological tests specifically designed for the assessment of cognitive biases.

Finally, another finding that is worth mentioning is the overall lack of association between any of the counterfactual measures explored and the neurocognitive functions assessed in three of the four the studies. As mentioned previously, contrary to our expectancies and despite that the neuropsychological exploration used was more extensive than in previous research, no significant association was found. These results are similar to those of Hooker *et al.* (2000) who also failed to find such a relationship. Accordingly, these authors proposed that either activation of counterfactual thoughts and generation of counterfactual-derived inferences could not be explained either by a generalized cognitive deficit or a specific cognitive function. Indeed, the relationship between low and high order

cognitive processes is controversial. For instance, whether social cognition and basic cognitive processes are associated is a question that is yet to be adequately answered (Sergi *et al.*, 2007; Ventura *et al.*, 2013). Thus, similarly, the debate about the observed counterfactual disruption in schizophrenia is the result of a pervasive cognitive impairment or is dependent on a specific deficit in a certain cognitive domain can still be considered to be open. Further research using other neuropsychological measures, for instance, instruments assessing domains of social cognition, might be of interest.

5.2.2. Implications for genetic research

Findings from the current thesis might also have relevance in terms of implications for the study of novel putative cognitive endophenotypes for schizophrenia. The importance of identifying such endophenotypes relies on the value they have in illuminating the risk (vulnerability) factors that might be interacting with non-genetic factors to produce the syndrome of schizophrenia. In the case of cognitive endophenotypes, because they could add knowledge to the study of genetic abnormalities underlying cognitive impairment in schizophrenia through the identification of brain dysfunction associated to this impairment (Braff & Freedman, 2002). Therefore, by reporting a deficit in the counterfactual thoughts activation among non-psychotic first-degree relatives, the present thesis may provide a basis for the identification of a novel cognitive endophenotype for this disorder. These results are in line with previous research reporting reasoning alterations in clinically unaffected family members (Kremen *et al.*, 1994; Szöke *et al.*, 2005). Notwithstanding the foregoing, in order to verify this claim, further research exploring the possibility of considering such deficits as a potential phenotypic marker of schizophrenia is needed, particularly if we take into account that *Study 3*'s results only could attempt to meet Gottesman & Gould's (2003) fifth criterion for endophenotype validation. As a reminder, this criterion states that the endophenotype should be heritable, co-segregate with a psychiatric illness, yet be present even when the disease is not (i.e. state independent), and be found in non-affected family members at a higher rate than in the population. Therefore, further research focused on the assessment of each of these conditions should be encouraged, especially because it might facilitate a fuller understanding of how genetic and non-genetic factors interact to produce this devastating illness, hopefully leading to the development of more effective treatments in the future.

5.2.3. Implications for neurobiological research

Importantly, it is the candidate impression that the present thesis' findings might be of value for further research in the field of clinical neuroscience. Particularly because the results from this research might help in the identification of brain anomalies underpinning the hypoactivation of CFT observed in schizophrenia. Thus, with this objective in mind, different proposals for future studies can be posited. Firstly, as mentioned before, it would be interesting to explore deficits in the ability to activate counterfactual thoughts in relation to the psychophysiological measures that might be underlying it. For instance, by exploring the role of PPI on such alterations as has been observed with other cognitive measures in schizophrenia and unaffected first-degree relatives (Karper *et al.*, 1996; Perry & Braff, 1994; Swerdlow *et al.*, 1999). Secondly, studies using functional neuroimaging techniques should become a priority, especially when considering results from previous research describing the main brain structures involved in the counterfactual reasoning process in the general population (Barbey *et al.*, 2009; Gomez-Beldarrain *et al.*, 2005; Ursu & Carter, 2005; Van Hoeck *et al.*, 2013). Thus, it is our suggestion that this line of study could start by exploring each of the three different neural networks included in the integrative proposal by Van Hoeck *et al.* (2015) in schizophrenia patients.

5.2.4. Clinical implications

When considering the implications that the present thesis' findings might have within a clinical perspective, different interesting ideas for future research emerge. First, to further explore the impact of present counterfactual reasoning alterations with schizophrenia patients' functional outcome might of value given the relevance these results could have on the identification of new diagnostic tools or the development of novel treatment approaches. This proposal is based on the general consensus stating the crucial role of CFT supporting adaptive behaviour in the general population (Roese & Epstude, 2017), and previous preliminary findings reporting CFT deficits to be partially mediating social functioning experienced by schizophrenia patients (Hooker *et al.*, 2000). The present thesis studies' used the Global Assessment of Functioning Scale (GAF; American Psychiatric Association, 2000) to explore this dimension, but no significant associations were found. Taking into account previous research suggesting the limitations of the GAF as an adequate tool of functioning assessment (Aas, 2010; Bacon *et al.*, 2002), maybe this lack of results is due to the instrument

used. Therefore, future studies might try to explore this relationship by using psychometric instruments specifically designed to measure functional outcome in severe mental illness, such as the UCSD Performance-Based Skills Assessment (UPSA; Patterson *et al.*, 2001), or specific for schizophrenia such as the Schizophrenia Objective Functioning Instrument (SOFI; Kleinman *et al.*, 2009). In this matter, it also would be of interest to study the role of other variables in the relationship between CFT deficit and functional disability in this disorder. For instance, by exploring the degree to which this association might be exceeded or partially mediated by deficits in social cognition skills. One potential candidate might be the study of ToM skills based on previous research evidencing counterfactuals to be involved in the ability to draw inferences about the intentions, beliefs and feelings of others in social interactions (Kern *et al.*, 2009).

Finally, it is also the candidate's impression that this thesis's findings might also be of value because they could lead to the development of novel treatments approaches for schizophrenia in the future. The necessity of improving treatment in major mental illness is currently undisputed due to the tremendous burden these conditions suppose (Hyman & Fenton, 2003). With this objective in mind, one proposal for new therapeutics in schizophrenia has been targeting cognitive abnormalities based on the recognition of the primacy these deficits as determinants of functional disability of these patients (Gold, 2004; Hyman & Fenton, 2003). However, despite the efforts, benefits of treatment in this direction from both pharmacological and psychosocial perspectives still appear marginal to date (Palmer *et al.*, 2009). Within this context, the rationale for targeting counterfactual reasoning in schizophrenia seems to naturally emerge if we take into account the potential impact that CFT impairment might have on these patients' ability to cope with their day-to-day challenges, and results from *Study 4* suggesting that, despite presenting slight difficulties, schizophrenia patients are able to learn from past experiences and perform as would be generally expected when engaged with a counterfactual reasoning task. Thus, suggesting the suitability of targeting CFT in the future within a cognitive rehabilitation program. However, despite this optimistic outlook, further research is still needed in order to develop an effective treatment strategy targeting counterfactual reasoning deficits to improve these patients' functioning and quality of life.

5.3. Limitations

Findings from the current thesis should be interpreted under certain limitations, which have been previously reported in each study in Chapter 4 (p.91). Nevertheless, the following paragraphs present some limitations that are common throughout the thesis.

Firstly, despite the present studies using larger samples than the ones used in previous research, they still entailed a relatively small number of participants. This could have resulted in a lack of statistical power and greater chances of making a type II error, increasing the possibility that the study was not able to detect actual differences between groups.

Secondly, since it was actually an attempt to simplify experimental materials from previous research (Hooker *et al.*, 2000; Kahneman & Tversky, 1982a; Kahneman & Varey, 1990), lack of validation of the CIT might have limited the present thesis' findings. Specifically, with regards to CIT - total score; in general, healthy controls in the current thesis's studies did not obtain the 4/4 score that would be expected in the general population. Further research is required to revise the CIT design in order to improve the test reliability, for instance, by extending the number of test items.

Thirdly, the fact that *Study 3* was based on the relatives most willing and compliant to participate may have biased this group; presumably because those relatives with prominent suspiciousness or subtle thought disorganization were probably less likely than healthier relatives to collaborate. In addition, further research should try to replicate the present results by exploring siblings solely based on expert authors in this field suggesting that these probands may be better subjects for characterizing the phenotype than the patients themselves, whose multiple deficits may obscure the unique phenotype (Braff & Freedman, 2002).

Finally, another limitation of the thesis is that all of the studies are cross-sectional, which means that nothing is known about the stability of present results across the life-span; to perform longitudinal analyses would be of special relevance due to the results found in *Study 2* suggesting an impoverishment of the counterfactual generation throughout illness duration.

6. Conclusions

Overall, the present thesis adds knowledge to the study of cognitive impairment in schizophrenia by shaping a better understanding of the counterfactual reasoning process in this disorder. The conclusions can be extracted as following:

1. Compared with healthy control subjects, patients with schizophrenia present an **impoverished ability** to **activate counterfactual thoughts**. More specifically:

    a. Schizophrenia patients activate fewer counterfactual thoughts when facing a negative outcome, presenting a tendency to get blocked and not activate any counterfactual alternative at all.

    b. This deficit does not seem to be secondary to classic symptoms of the disorder, although it might be influenced by them.

    c. This deficit seems to persist throughout the long term of the illness.

    d. Underscoring the heritability of this deficit, **non-psychotic first-degree relatives** present a **subtle alteration** in the ability to activate **counterfactual alternatives**. The present thesis may be providing basis for the identification of a novel cognitive endophenotype for schizophrenia.

    e. This alteration does not appear to be related to another specific cognitive dysfunction assessed in the present thesis' studies.

2. Compared with healthy control subjects, patients with schizophrenia tend to deviate from the normative pattern when having to construct **counterfactual-derived inferences** when facing specific characteristics of a situation. More specifically:

    a. Schizophrenia patients present a tendency to deviate from the normative pattern when having to make counterfactual-derived inferences when facing unusual and "nearly happened" hypothetical social situations.

b. This alteration does not appear to be related to another specific cognitive dysfunction assessed in the present thesis' studies.

c. This alteration does not appear to be associated to the clinical features of the disorder assessed in the present thesis' studies.

d. In contrast, schizophrenia patients and non-psychotic first-degree relatives seem to follow the norm when drawing counterfactual-derived inferences under the causal order effect.

3. Compared with healthy control subjects, patients with schizophrenia present a **preserved capacity** to **activate intentions** as a precursor to behavioural implementation **once the counterfactual inference is constructed**. This result indicates that, in spite of there being an impairment in the counterfactual reasoning process in schizophrenia, when it is successfully achieved, the activation of behavioural intentions as a precursor to adaptive behaviour is preserved. More specifically:

   a. Schizophrenia patients commit few errors and respond correctly faster in a semantic priming task once a counterfactual inference is generated.

   b. This process does not appear to be related to another specific cognitive dysfunction assessed in the present thesis' studies.

   c. This process does not appear to be associated to the clinical features of the disorder assessed in the present thesis' studies.

By further characterizing counterfactual reasoning deficits in schizophrenia patients and non-psychotic first-degree relatives, the present thesis represents a step forward in the study of cognitive impairment in this complex and severe disorder. Overall, the present results have reported a hypoactivation of counterfactual thoughts, an alteration in the counterfactual inference process and a preserved capacity to activate behavioural intentions through counterfactual reasoning. Because of the implications that the present findings might have on the development of new diagnostic tools and eventually targets for treatment, the present thesis has also presented several guidelines for future research within different

perspectives of study. Interestingly, this work might be framed in the NIMH's Research Domain Criteria (RDoC) project (Insel *et al.*, 2010). Informed by the current thesis, it is the candidate's view that such an endeavor could have a great impact on the characterization of schizophrenia and on the improvement of cognitive impairment treatment for these patients.

7. Summary in Catalan

Resum en català

1. Introducció

1.1. Esquizofrènia

La esquizofrènia és un dels trastorns psiquiàtrics més greus, complexos i que implica un gran impacte negatiu en la vida dels individus que la pateixen. A nivell epidemiològic, s'estima que la esquizofrènia afecta un promig de 24 milions de persones en tot el món segons la Organització Mundial de la Salut (Piccinelli & Gomez Homen, 1997), afectant al 0,4% de la població mundial, amb una incidència mitja de 15,2 de cada 100.000 persones a l'any (Saha *et al.*, 2005). Pel que fa a la seva etiopatogènia, la esquizofrènia segueix sent a data d'avui una síndrome d'etiologia desconeguda (American Psychiatric Association, 2013). El que sí que podem afirmar amb seguretat però, és que tant els factors genètics com els ambientals són importants (Tandon *et al.*, 2008). És necessari doncs continuar investigant en aquest àmbit per tal de descriure el pes específic de cadascun d'aquests factors, per exemple, a través de l'estudi de potencials endofenotips de la malaltia (Van Os & Kapur, 2009).

Per una altra banda, els avenços en tècniques de neuroimatge de les últimes tres dècades han permès identificar un ampli nombre d'anomalies cerebrals que conformen el nostre coneixement actual sobre les bases neuroanatòmiques de la esquizofrènia. Tot i que cap d'aquestes alteracions pot ser considerada a data d'avui com un marcador diagnòstic del trastorn, actualment sabem que, a nivell estructural, els pacients amb esquizofrènia presenten un volum de la matèria grisa reduït i per contra, un volum ventricular incrementat (Andreasen *et al.*, 1990). A nivell funcional, en general, els resultats assenyalen alteracions al còrtex prefrontal (Keshavan *et al.*, 2008), i més específicament, una menor activació de l'escorça prefrontal dorsolateral a la que s'ha anomenat *hipofrontalitat* (Hill *et al.*, 2004).

Actualment, el deteriorament cognitiu es considera una característica central d'aquest trastorn incloent la presència de dèficits en gairebé tots els dominis neurocognitius i de cognició social (Heinrichs & Zakzanis, 1998; Kern & Horan, 2010). Descrit com un predictor directe del funcionament psicosocial d'aquests pacients (Fett *et al.*, 2011; Green, 1996), aquests dèficits cognitius no només s'observen en les primeres etapes de la malaltia sinó que semblen estar presents fins i tot abans del inici del tractament amb fàrmacs neurolèptics (Saykin *et al.*, 1994; Woodberry *et al.*, 2008). En aquesta línia, l'estudi dels dèficits de raonament i biaixos cognitius que podrien explicar la formació i manteniments dels símptomes psicòtics també s'ha convertit durant la última dècada en una àrea d'investigació rellevant per a la esquizofrènia (Garety & Freeman, 1999; Moritz *et al.*, 2015). D'altra banda, també és important destacar l'estudi d'individus en risc de patir la malaltia, com els familiars de primer grau no afectats, que comparteixen components genètics per al trastorn i que també experimenten alteracions en la funció cognitiva, tot i que en menor grau (Sitskoorn *et al.*, 2004; Snitz *et al.*, 2006; Szöke *et al.*, 2005). Aquest àmbit d'estudi és d'alta prioritat ja que la identificació de les bases biològiques dels dèficits cognitius en la esquizofrènia facilitarà el desenvolupament de futurs tractaments eficaços per promoure la recuperació funcional d'aquests pacients (Byrne *et al.*, 2003; Cannon *et al.*, 2000).

1.2. Pensament contrafactual

Omnipresent en la nostra vida diària, el pensament contrafactual (CFT) és un tipus de pensament condicional encarregat de representar mentalment alternatives a situacions passades que haurien pogut ocórrer però que mai es van produir (Roese, 1997). La generació d'aquests pensaments s'activa principalment davant resultats negatius en forma de preposicions condicionals del tipus "si tan sols" (Byrne, 2016). Per una altra banda, l'habilitat de raonar a través del CFT és considera un subprocés d'aquest i es refereix a la capacitat de fer inferències a través de la generació o activació de pensaments contrafactuals (Van Hoeck *et al.*, 2015). Emmarcat en la *Teoria de la Norma* desenvolupada per Kahneman i Miller l'any 1986, la capacitat d'inferir a través del CFT sembla estar especialment determinada per factors específics de la realitat com la excepcionalitat o la proximitat de la situació, o l'efecte de primacia en una seqüència d'esdeveniments causal (també conegut com l'efecte causal de l'ordre). Pel que fa a les seves bases cerebrals, tot i que aquest complex fenomen psicològic en general sembla estar recolzat per la interacció coordinada de diferents xarxes neuronals (Van

Hoeck *et al.*, 2015), les principals regions activades durant aquest procés cognitiu són àrees del còrtex pre-frontal, com la regió orbito-frontal (Gomez-Beldarrain *et al.*, 2005; Knight & Grabowecky, 1995; Ursu & Carter, 2005).

Des d'un punt de vista funcional, el raonament contrafactual s'ha examinat àmpliament des d'aquesta perspectiva evidenciant múltiples funcions a través de les quals podria estar donant suport a la conducta adaptativa. Aquest repertori inclou l'aprenentatge d'experiències passades (Byrne, 1999), la modulació de l'estat emocional (Roese & Olson, 1997), la promoció de la creativitat (Markman *et al.*, 2007), i el suport a la planificació i predicció futura (Roese, 1999).

Des d'una perspectiva teòrica, integrant els resultats d'investigacions anteriors en aquest camp, Epstude i Roese proposen l'any 2008 la *Teoria Funcional del CFT* basada en la idea que aquests pensaments s'expliquen millor en termes del seu paper en la regulació de la conducta i la millora del rendiment. Així, aquesta teoria es construeix sobre la investigació original de Gollwitzer i Moskowitz (1996) sobre com els objectius influeixen en les accions. Concretament, aquests autors plantegen un bucle de regulació en el qual els pensaments contrafactuals podrien promoure canvis de comportament dividits en tres esglaons o etapes tal i com es presenta en la **Figura 1**.

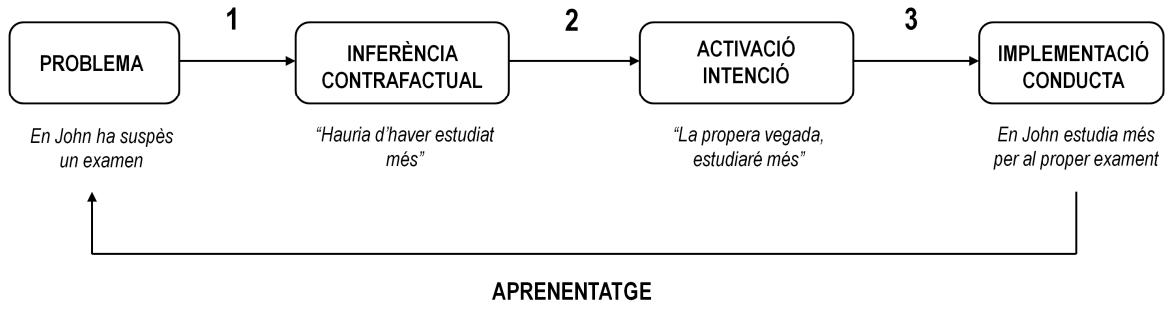

Figura 1. Bucle de regulació conductual a través del raonament contrafactual.
Adaptat de Epstude i Roese, 2008.

Pel que fa a l'estudi del CFT en l'àmbit clínic, l'interès per estudiar alteracions en aquest tipus de raonament en població clínica ha sorgit recentment amb l'objectiu de facilitar la comprensió dels símptomes d'aquests pacients i els reptes del dia a dia que aquesta alteració els podria suposar. Específicament, s'ha proposat que la identificació dels subcomponents alterats en aquest procés podria conduir eventualment a la identificació d'una nova eina

diagnòstica, o fins i tot una nova diana per al desenvolupament de futur tractaments per aquests trastorns (Epstude & Roese, 2008; Van Hoeck *et al.*, 2015). Així doncs, a data d'avui s'han observat dèficits de CFT en pacients amb trastorn obsessiu-compulsiu (Gillan *et al.*, 2014), fòbia social (Kocovski *et al.*, 2005), depressió (Markam & Miller, 2006; Quelhas *et al.*, 2008), la malaltia de Parkinson (McNamara *et al.*, 2003) i de Huntington (Solca *et al.*, 2015) entre d'altres.

1.3. Fonaments del projecte de tesi

Sobre la base que la esquizofrènia està relacionada, almenys en part, amb una disfunció del còrtex pre-frontal i que els pacients que la pateixen mostren alteracions en la presa de decisions i resolució de problemes, no és sorprenent que en els últims anys hagin sorgit estudis explorant dèficits de raonament contrafactual en aquest trastorn, sobretot si tenim en compte el potencial impacte que podrien tenir en el funcionament personal i social d'aquests pacients.

Concretament, només dos estudis han explorat a data d'avui el CFT en esquizofrènia des de dos nivells de processament diferents. En primer lloc, Hooker i col·laboradors van desenvolupar l'any 2000 un estudi centrat en l'avaluació de l'activació de pensaments contrafactuals i generació d'inferències derivades del CFT en una mostra relativament petita de 14 pacients i 12 controls. Mitjançant l'ús de diferents mètodes quantitatius d'exploració, aquest estudi va mesurar la capacitat de generar alternatives contrafactuals, així com l'efecte la proximitat i la excepcionalitat de la situació en el procés de raonament contrafactual usant el *Test d'Inferència Contrafactual* (CIT) desenvolupat específicament per aquest estudi. Els resultats no només van indicar que els pacients generaven menys pensaments contrafactuals que els controls, sinó que també van mostrar una alteració en el patró de generació de inferències contrafactuals dels pacients. Ambdues alteracions es van relacionar amb el deteriorament en el funcionament social dels pacients, però no amb el seu funcionament cognitiu.

En segon lloc, emmarcat en la *Teoria Funcional* d' Epstude i Roese (2008), l'efecte de raonament contrafactual en l'activació de les intencions de comportament va ser explorada per Roese i col·laboradors l'any 2008 mitjançant una tasca de facilitació semàntica desenvolupada per aquests mateixos autors. Amb una mostra de 15 pacients amb esquizofrènia i 13 subjectes controls, l'experiment consistia en 45 assaigs amb un tipus de

resposta sí/no a una declaració de intenció (és a dir, la intenció de fer una acció específica en el futur) en què el temps de reacció es va utilitzar com a variable dependent. Cada assaig presentava un esdeveniment negatiu on la facilitació semàntica o *priming* es podia presentar de tres formes (variables independent): una línia base (és a dir, cap *priming*) , una control-neutra i una contrafactual. Els resultats d'aquest estudi van mostrar que mentre els controls sans responien més ràpid davant els facilitadors contrafactuals, el temps de reacció dels pacients amb esquizofrènia no variava entre la condició contrafactual i la control-neutra. És a dir, el raonament contrafactual no facilitava l'activació de les intencions de comportament en comparació amb l'assaig control-neutra. Per tant, aquests autors van concloure que el vincle entre la inferència contrafactual i la generació d'intencions de conducta estava trencada en la esquizofrènia, concloent que les estratègies de rehabilitació dissenyades per a la normalització del CFT no podien tenir cap benefici per a aquests pacients.

Així doncs, en conjunt, els resultats d'aquests estudis preliminars van proporcionar la base per l'estudi del raonament contrafactual com a una eina útil per aprofundir el coneixement actual que tenim de l'esquizofrènia, els seus símptomes i els reptes diaris al que s'enfronten aquests pacients. No obstant, s'ha de tenir en compte que aquests dos estudis presentaven algunes limitacions metodològiques que podrien estar comprometent els resultats (per exemple, pel que fa a la mida de les mostres o els dissenys experimentals). Per tant, és necessari continuar investigant en aquest àmbit, tractant de caracteritzar adequadament el deteriorament de raonament contrafactual en la esquizofrènia, ja que a la llarga, ens podria conduir a la identificació d'un nou dèficit cognitiu primari de la malaltia susceptible de convertir-se en una futura diana terapèutica per al trastorn.

2. Objectius

L'objectiu general d'aquesta tesi és proporcionar nous coneixements sobre el deteriorament neurocognitiu en la esquizofrènia mitjançant la caracterització dels dèficits de raonament contrafactual en aquest trastorn. Utilitzant diferents mètodes neuropsicològics, la nostra investigació tractarà de descriure millor aquestes alteracions i la seva relació amb el funcionament cognitiu i característiques clíniques del trastorn mitjançant l'avaluació de pacients amb esquizofrènia adults i familiars de primer grau no psicòtics en comparació amb subjectes control sans.

Estudi 1:

- Estudiar les diferències en la capacitat de generar pensaments contrafactuals entre un grup de pacients amb esquizofrènia i un grup de subjectes control sans.
- Estudiar l'efecte de diferents factors que influeixen en la inferència contrafactual en un grup de pacients amb esquizofrènia en comparació amb un grup de subjectes de control sans. El conjunt de factors que s'exploraran inclou (1) l' efecte causal de l'ordre, i la (2) excepcionalitat i (3) proximitat de la situació.
- Estudiar la relació entre les variables relacionades amb el rendiment contrafactual i variables clíniques i de neurocognició d'interès.

Estudi 2:

- Estudiar les diferències en la capacitat de generar pensaments contrafactuals entre un grup de subjectes control sans i un grup de pacients amb esquizofrènia en estat de remissió segons criteris de Andreasen *et al.*, 2005.
- Estudiar l'efecte de diferents factors que influeixen en la inferència contrafactual entre un grup de subjectes control sans i un grup de pacients amb esquizofrènia en estat de remissió segons criteris de Andreasen *et al.*, 2005. El conjunt de factors que s'exploraran inclou (1) l' efecte causal de l'ordre, i la (2) excepcionalitat i (3) proximitat de la situació.
- Estudiar la relació entre les variables relacionades amb el rendiment contrafactual i variables clíniques d'interès.

Estudi 3:

- Estudiar les diferències en la capacitat de generar pensaments contrafactuals entre un grup de familiars de primer grau no psicòtics dels pacients amb esquizofrènia en comparació amb un grup de pacients amb esquizofrènia i un grup de subjectes control sans.
- Estudiar l'efecte de diferents factors que influeixen en la inferència contrafactual entre un grup de familiars de primer grau no psicòtics dels pacients amb esquizofrènia en comparació amb un grup de pacients amb esquizofrènia i un grup de subjectes control

sans. El conjunt de factors que s'exploraran inclou (1) l' efecte causal de l'ordre, i la (2) excepcionalitat i (3) proximitat de la situació.

- Estudiar la relació entre les variables relacionades amb el rendiment contrafactual i variables clíniques i de neurocognició d'interès.

Estudi 4:

- Estudiar diferències en l'activació d'intencions conductuals a través de la inferència contrafactual entre un grup de pacients amb esquizofrènia i un grup de subjectes control sans.
- Estudiar la relació entre les variables relacionades amb el rendiment contrafactual i variables clíniques i de neurocognició d'interès.

3. Metodologia

Com es detalla a continuació, els quatre treballs inclosos en aquesta tesi en realitat s'inclouen dins de dos projectes de recerca diferents del Hospital Universitari de Bellvitge - IDIBELL:

- *Estudi 1* i *Estudi 4* dins del **Projecte 1** (PR077/10). 2010-2011: "El pensament contrafactual en pacients amb esquizofrènia. Associació amb variables clíniques i neurocognitiu."
- *Estudi 2* i *Estudi 3* dins del **Projecte 2** (PR160/12). 2012-2016: "Caracterització de dèficits de raonament contrafactual en pacients amb esquizofrènia i familiars de primer grau en comparació amb els subjectes control sans."

Tots els pacients amb esquizofrènia, així com els familiars de primer grau inclosos en aquesta tesi van ser reclutats a través del servei de consultes externes del Servei de Psiquiatria de l'Hospital Universitari de Bellvitge i dos centres col·laboradors de l'àrea de salut mental de l'Hospitalet de Llobregat: la Unitat polivalent de Salut Mental (Germanes Hospitalaris) i la Unitat de Salut Mental de l'Hospitalet de Llobregat (Institut Català de la Salut). Els subjectes control, van ser reclutats en entorns sociodemogràfic similars. Tots els procediments d'estudi van ser aprovats pel Comitè Ètic d'Investigació Clínica de la Ciutat Sanitària de Bellvitge (CEIC de Bellvitge), i tots els participants van signar el consentiment informat abans d'entrar

a l'estudi corresponent. La **Figura 2** presenta una descripció de les mostres utilitzades en la tesi.

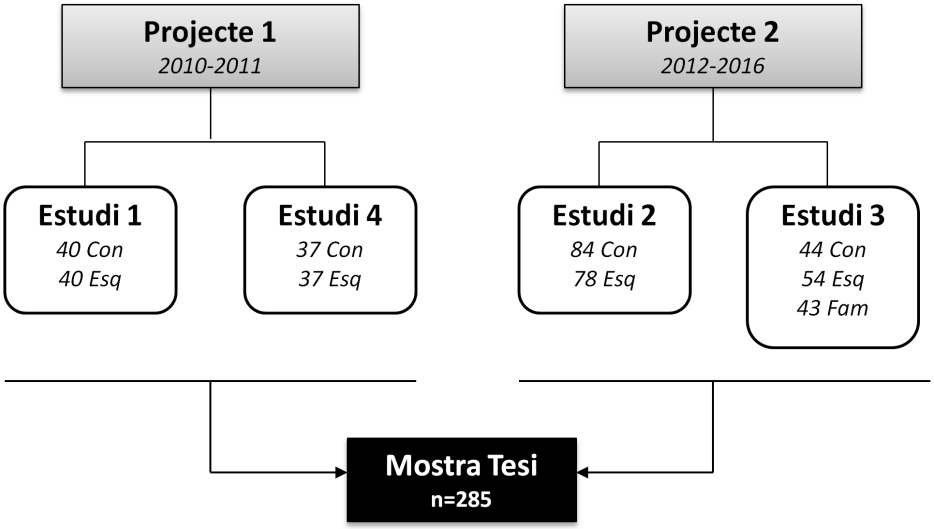

Figura 2. Participants inclosos en cadascun dels estudis de la tesi. Con: controls sans; Esq: pacients amb esquizofrènia; Fam: familiars de primer grau no psicòtics.

3.1. Avaluació del raonament contrafactual

El conjunt de mètodes utilitzats per explorar quantitativament el raonament contrafactual en aquesta tesi es presenta a continuació.

1. **Paradigma de recerca de Wells *et al.* (1987) - *Escenari de William*:** presentació d'un escenari fictici de quatre esdeveniments consecutius independents que donen lloc a un resultat negatiu. A partir d'aquí dos experiments es duen a terme:

   a. **Experiment A:** avaluació de la capacitat de generar alternatives contrafactuals al resultat negatiu de l'escenari.

   b. **Experiment B:** avaluació de l'efecte causal del ordre demanant al subjecte quin dels quatre esdeveniments és el més determinant en el resultat negatiu de l'escenari.

2. **Test d'Inferència Contrafactual - CIT de Hooker *et al.* (2000):** utilitzat per explorar la capacitat dels individus per derivar inferències mitjançant el CFT tenint en compte diferents factors, l'excepcionalitat i la proximitat de la situació.

3. **Experiment C – Tasca de facilitació semàntica:** Adaptant la tasca original de Roese *et al.* (2008), per tal d'avaluar si la inferència contrafactual facilita l'activació d'intenció conductuals.

4. Resultats

Estudi 1: "Counterfactual Reasoning Deficits in Schizophrenia Patients"

1. En comparació amb els controls sans, els pacients amb esquizofrènia van generar significativament menor nombre de pensaments contrafactuals davant d'un escenari fictici negatiu.
2. En explorar l'efecte causal l'ordre, els resultats van suggerir diferències entre els grups en relació amb el patró general de resposta: els pacients amb esquizofrènia van tendir a desviar-se de la norma escollint el primer dels esdeveniments amb menys freqüència que els controls.
3. Els resultats del CIT va revelar que, en comparació amb els controls sans, els pacients amb esquizofrènia no seguien la norma en derivar inferències mitjançant el CFT davant d'ambdós situacions excepcionals i pròximes en el temps.

Estudi 2: "Symptomatic Remission and Counterfactual Reasoning in Schizophrenia"

1. En comparació amb els controls sans, els pacients amb esquizofrènia en estat de remissió simptomàtica van generar significativament menor nombre de pensaments contrafactuals davant d'un escenari fictici negatiu.
    a. Es van trobar associacions negatives entre un pobre generació de pensaments contrafactuals i dues de les variables clíniques analitzades: gravetat dels símptomes i duració de la malaltia.
2. En explorar l'efecte causal de l'ordre, els resultats no van suggerir diferències entre els grups en relació amb el patró general de resposta: els pacients amb esquizofrènia en estat

de remissió simptomàtica van tendir a escollir el primer dels esdeveniments en igual freqüència que els controls.

3. Els resultats del CIT va revelar que, en comparació amb els controls sans, els pacients amb esquizofrènia no seguien la norma en derivar inferències a través del CFT davant de situacions pròximes en temps i espai.

Estudi 3: "Counterfactual Reasoning in Non-Psychotic First-Degree Relatives of People with Schizophrenia"

1. Davant d'un escenari fictici negatiu, els familiars de primer grau no psicòtics van generar significativament menor nombre de pensaments contrafactuals que els controls sans, però més que els pacients amb esquizofrènia.
2. En explorar l'efecte causal de l'ordre, els resultats no van suggerir diferències entre els tres grups en relació amb el patró general de resposta en atribuir la causalitat davant d'un escenari fictici. És a dir, els tres grups van escollir el primer esdeveniment en major proporció.
3. Els resultats del CIT va revelar que, en comparació amb els controls sans, els familiars de primer grau van ser més competents que els controls sans en fer inferències contrafactuals en els escenaris específics que avaluaven l'efecte de la excepcionalitat de la situació.

Estudi 4: "Schizophrenia Patients Activate Behavioural Intentions Facilitated by Counterfactual Reasoning"

1. Els anàlisis intra-grup van revelar un efecte facilitador del raonament contrafactual en activar les intencions de comportament en els dos grups d'estudi representats per:
    a. Menor nombre d'associacions incorrectes al presentar un *priming* contrafactual.
    b. Menor percentatge de guany en el temps de reacció al presentar un *priming* contrafactual.
2. Els anàlisis inter-grup van revelar major probabilitat de respondre de forma incorrecta entre els pacients amb esquizofrènia amb independència del *priming* presentat. És a dir, els pacients van realitzar la prova una mica pitjor que els controls sans en general.

5. Discussió

Els resultats d'aquesta tesi han aconseguit caracteritzar en més profunditat el dèficit de raonament contrafactual en la esquizofrènia millorant i ampliant els estudis preliminars existents en aquest camp. En general, mentre que les capacitats per activar pensaments contrafactuals i per generar inferències a través d'aquests pensaments semblen estar alterats en aquest trastorn, la capacitat d'activar intencions conductuals mitjançant el raonament contrafactual s'ha trobat preservada. De forma rellevant, aquesta tesi també proporciona la base per a l'estudi del deteriorament en l'activació de pensaments contrafactuals com un nou candidat per a ser considerat un endofenotip cognitiu per a l'esquizofrènia.

5.1. Activació de pensaments contrafactuals

Més específicament, un dels resultats més rellevants d'aquesta tesi ha sigut la demostració de que, en general, hi ha una alteració en la capacitat de generar alternatives contrafactuals en l'esquizofrènia. Per tant, d'acord amb resultats preliminars anteriors (Hooker *et al.*, 2000), les nostres troballes reforcen la idea que l'esquizofrènia és una malaltia mental en que els pacients tenen dificultats per tornar a imaginar un resultat negatiu d'una manera positiva; un procés que permet l'activació de representacions alternatives per fer front a la realitat. Diferents hipòtesis que podrien explicar aquest deteriorament inclouen des de la possible relació entre aquest dèficit i la disfunció d'estructures cerebrals relacionades amb el CFT (Gomez-Beldarrain *et al.*, 2005; Ursu & Carter, 2005), la correlació amb dèficits de raonament prototípics de la malaltia (Keefe & Harvey, 2012; Velligan & Bow-Thomas, 1999), o des d'un punt de vista clínic, la possibilitat que aquest dèficit pugui ser el resultat dels símptomes clàssics de la malaltia (Dibben *et al.*, 2009). Desafortunadament, els resultats obtinguts no aporten prou evidències a favor de cap d'aquestes hipòtesis. De fet, respecte a la relació amb la gravetat dels símptomes, els nostres estudis en realitat suggereixen que el dèficit de generació contrafactual no és secundari a aquests ja que s'observen de manera similar en pacients amb esquizofrènia en estat de remissió simptomàtica (*Estudi 2* i *Estudi 3*) i en pacients que no ho estan (*Estudi 1*), així com en familiars de primer grau no psicòtics, encara que en menor grau (*Estudi 3*). Així doncs, per tal de identificar el mecanismes subjacents a aquesta alteració en aquest trastorn, és necessari continuar investigant en aquest àmbit, per exemple, mitjançant estudis de neuroimatge funcional.

5.2. Generació de inferències contrafactuals

Un altre objectiu principal d'aquesta tesi ha estat l'avaluació de la generació d'inferències contrafactuals en el marc de la *Teoria de la Norma* (Kahneman & Miller, 1986). En general, els resultats suggereixen que el patró d'inferència contrafactual sembla estar alterat en l'esquizofrènia, específicament quan certes característiques de la realitat estan involucrades.

5.2.1. Efecte causal de l'ordre

Pel que fa a l'anàlisi de l'efecte causal de l'ordre, no es van trobar diferències significatives entre els pacients amb esquizofrènia i controls sans, i ni amb familiars de primer grau no psicòtics. Per tant, tal i com s'observa en la població general, tant els pacients amb esquizofrènia com els familiars de primer grau no afectats tendeixen a atribuir causalitat a través del raonament contrafactual seguint la norma tal com van definir Kahneman i Miller en la seva *Teoria de la Norma* (1986).

5.2.2. Test d'Inferència Contrafactual

Per començar, els anàlisis estadístics no van revelar diferències entre els pacients amb esquizofrènia i el controls sans en la puntuació Total del CIT (*Estudi 1*, *Estudi 2* i *Estudi 3*). Aquests resultats suggereixen que, en general, els pacients amb esquizofrènia tendeixen a ser tan hàbils com els controls al derivar inferències a partir del pensament contrafactual. No obstant, al analitzar cadascun dels escenaris del CIT per separat, els resultats semblen anar en una altra direcció.

Concretament, l'anàlisi del patró de resposta del pacients en el CIT (Hooker *et al.*, 2000) va revelar una tendència general a desviar-se de la norma davant d'ambdós situacions excepcionals i properes en el temps i espai. Aquests resultats estan d'acord amb els de l'estudi pilot previ en el que els pacients amb esquizofrènia també van ser menys hàbils que els controls al derivar inferències contrafactuals (Hooker *et al.*, 2000). En conclusió però, els resultats d'aquesta tesi han permès demostrar que davant de situacions socials amb un resultat negatiu, els factors de la realitat en els quals la població general tendeix a recolzar-se quan construeixen inferències contrafactual no semblen tenir el mateix efecte en la esquizofrènia. Així, s'evidencia una propensió dels pacients amb esquizofrènia a no adherir-se a la manera habitual "normal" de conducta (Kahneman & Miller, 1986; McCloy & Byrne, 2000). A més a més, aquests resultats també revelen la necessitat de revisar la construcció de la puntuació

Total del CIT, ja que no semblen reflectir adequadament la capacitat dels individus per inferir dels contrafactuals.

Al considerar les possibles causes que sustenta aquesta alteració, es pot plantejar la hipòtesi de que, de manera similar com amb el dèficit en la generació de pensaments contrafactuals, podria estar relacionada amb un disfunció neurocognitiva com per exemple amb dèficits de raonament. No obstant, ni els resultats d'estudis d'aquesta tesi, ni els de l'estudi pilot anterior va trobar resultats significatius en aquesta direcció (Hooker *et al.*, 2000). Aquí es planteja la possibilitat de que capacitats cognitives més complexes que no s'han explorat en aquesta tesi com ara habilitats basades cognició social o biaixos de raonament puguin estar influenciant el procés de raonament contrafactual. Seria interessant doncs, que futures investigacions tinguessin en compte l'ús de proves neuropsicològiques específicament dissenyades per avaluar aquests processos cognitius.

5.3. Activació d'intencions conductuals

Contradient resultats anteriors (Roese *et al.*, 2008), els resultats de l'*Estudi 4* indiquen una capacitat preservada en els pacients amb esquizofrènia a l'hora d'activar intencions conductuals un cop la inferència contrafactual s'ha construït. Concretament, mitjançant l'ús d'una mida mostral més gran i un paradigma de facilitació semàntica més acurat, els anàlisis suggereixen que en la esquizofrènia, la capacitat de generar intencions com a precursor de la implementació de la conducta un cop el raonament contrafactual s'ha aconseguit activar, es troba preservada. La importància d'aquests resultat realment rau en el fet de que si aquesta capacitat no està alterada, aquests pacients es podrien beneficiar d'un tractament de rehabilitació cognitiva específicament centrat en la comprensió de les experiències negatives i l'activació de les intencions correctives corresponents. Això podria ajudar a regular i millorar els seus comportaments, així com el seu funcionament psicosocial. Futures investigacions haurien d'estar orientades en confirmar aquests resultats.

5.4. Implicacions generals per a la recerca

Els resultats del estudis d'aquesta tesi podrien implicacions per al desenvolupament de futures investigacions en diferents àrees de recerca. Per començar, és la impressió de la doctoranda que aquestes troballes podrien ser objecte d'estudi en futures investigacions en el camp de la neurociència clínica. Aquests estudis podrien ajudar en la identificació d'anomalies

cerebrals que sustenten la hipoactivació de CFT observada en la esquizofrènia, mitjançant per exemple, tècniques de psicofisiologia o de neuroimatge funcional.

Des d'un punt de vista neuropsicològic, els resultats d'aquesta tesi contribueixen a la creixent literatura centrada en el deteriorament cognitiu com una característica nuclear de la esquizofrènia (Green, 1996); sobretot en referència al dèficit específic de generació contrafactual com un dèficit cognitiu primari del trastorn. Diversos resultats semblen donar suport a aquesta idea: (1) el dèficit no sembla ser secundari als símptomes clàssics de la malaltia, atès que es va trobar entre els pacients amb un baix nivell dels símptomes actuals (*Estudi 1*), i fins i tot entre els pacients en un estat de remissió simptomàtica (*Estudi 2* i *Estudi 3*); (2) està associat negativament a una major durada de la malaltia (*Estudi 2*), indicant que tendeix a persistir al llarg del curs a llarg termini de la malaltia al contrari d'altres característiques clíniques prototípics del trastorn (Keefe & Eesley, 2006); (3) no està relacionat amb la dosi diària mitjana d'antipsicòtic, suggerint que el tractament amb neurolèptics no estava tenint un impacte en el dèficit; i finalment, (4) tot i que en menor grau, aquest dèficit també es va observar en els familiars de primer grau no psicòtics de pacients amb esquizofrènia. En aquesta línia, un altre resultat que val la pena esmentar és la manca general d'associació entre qualsevol de les mesures de CFT explorades i cap de les funcions neurocognitives avaluades en tres dels quatre estudis. Futures investigacions haurien d'estar orientades a l'estudi més extens d'aquesta relació, per exemple, mitjançant l'ús d'altres mesures de cognició més complexes com dominis de cognició social.

Els resultats d'aquesta tesi també tenen rellevància en termes d'implicacions per a l'estudi de nous endofenotips cognitius per aquest trastorn. La importància d'identificar aquest tipus d'endofenotips es basa en el paper que poden tenir il·luminant els factors de risc (vulnerabilitat) que podrien estar interactuant amb factors no genètics per a produir la síndrome d'esquizofrènia. En el cas d'endofenotips cognitius, per què podrien afegir coneixement en l'estudi del deteriorament cognitiu i les anomalies genètiques subjacents en la esquizofrènia a través de la identificació de la disfunció cerebral associada a aquests dèficits (Braff & Freedman, 2002). No obstant, es necessita més investigació centrada en la possibilitat de considerar el dèficit en la generació contrafactual com un potencial marcador fenotípic d'aquesta malaltia, sobretot si tenim en compte que els resultats de l'*Estudi 3* només compleixen el cinquè criteri per a la validació d'endofenotips en psiquiatria (Gottesman & Gould, 2003).

En considerar les repercussions que els resultats d'aquesta tesi podrien tenir des d'una perspectiva clínica, tres idees interessants emergeixen. En primer lloc, aquesta tendència a desviar-se de la norma en derivar inferències contrafactuals (*Estudi 1*, *Estudi 2* i *Estudi 3*) podria relacionar-se amb l'estudi de processos cognitius subjacents al desenvolupament i manteniment de les idees delirants en la psicosi, com per exemple, en l'estudi del biaixos de raonament (Garety & Freeman, 1999; Moritz & Woodward, 2005). En segon lloc, els resultats d'aquesta tesi també podrien servir de base per al desenvolupament de nous tractaments per a la esquizofrènia agafant com a diana terapèutica la rehabilitació dels dèficits de raonament contrafactual en aquests pacients. Aquesta proposta es basa en el consens general que indica el paper crucial del CFT reforçant la conducta adaptativa en la població general (Roese & Epstude, 2017). Futures investigacions podrien tractar d'explorar aquesta relació mitjançant l'ús d'instruments psicomètrics dissenyats específicament per mesurar el nivell de funcionalitat psicosocial en trastorn mental sever o esquizofrènia (Kleinman *et al.*, 2009; Patterson *et al.*, 2001). Finalment, també creiem que seria interessant explorar les possibilitats de considerar el CFT com un objectiu terapèutic per al tractament d'aquest trastorn. Sobretot tenint en compte els resultats del *Estudi 4* on s'evidencia la capacitat d'aprenentatge del pacients amb esquizofrènia.

5.5. Limitacions

A més dels error estadístic de tipus II, la manca de validació del CIT (Hooker *et al.*, 2000) podria haver limitat els resultats dels estudis. És necessari que en el futur es revisi el disseny d'aquest instrument per tal de millorar-ne la seva fiabilitat, per exemple, augmentant el nombre d'ítems. En tercer lloc, el fet que els familiars de l'*Estudi 3,* al ser els més disposats a participar en la investigació, en realitat pot ser que estiguessin esbiaixant la representativitat d'aquest grup. És a dir, que els familiars més suspicaços o amb una desorganització del pensament subtil, probablement fossin els menys propensos a col·laborar en l'estudi. Finalment, una altra limitació de la tesi és que tots els estudis són de tipus transversal; ens falta informació sobre l'estabilitat dels dèficits de raonament contrafactual al llarg del curs de la malaltia.

6. Conclusions

En general, aquesta tesi afegeix coneixement en l'estudi del deteriorament cognitiu en la esquizofrènia mitjançant la caracterització del procés de raonament contrafactual en aquest trastorn. Les conclusions es poden extreure de la següent manera:

1. En comparació amb els subjectes control sans, els pacients amb esquizofrènia presenten una capacitat empobrida per activar pensaments contrafactuals.

    a. En comparació amb els controls, els familiars de primer grau no psicòtics presenten una subtil alteració en la capacitat d'activar alternatives contrafactuals. Aquesta troballa podria representar la base per a la identificació d'un nou endofenotip cognitiu per a la esquizofrènia.

2. En comparació amb els control sans, els pacients amb esquizofrènia són menys hàbils a l'hora de generat inferències a partir del CFT, especialment davant situacions excepcionals i properes en l'espai i el temps.

    a. Per contra, els pacients amb esquizofrènia semblen seguir la norma quan construeixen inferències contrafactuals sota l'efecte causal de l'ordre.

3. En comparació amb els subjectes control sans, els pacients amb esquizofrènia presenten una capacitat conservada a l'hora d'activar intencions com a pas previ a la implementació de noves conductes un cop la inferència contrafactual s'ha aconseguit generar.

En resum, a causa de les implicacions que els resultats d'aquesta tesi podrien tenir en el desenvolupament de noves eines de diagnòstic, o fins i tot, de nous objectius terapèutics, hem enumerat un sèrie de propostes emmarcades en diferents àmbits d'estudi que podrien servir com a guia en el desenvolupament de futures línies d'investigació centrades en el raonament contrafactual en la esquizofrènia. De forma interessant, aquest futur treball es podria emmarcar en el projecte RDoC del NIMH (Insel *et al.*, 2010). En base als resultats d'aquesta tesi, és opinió de la doctoranda que totes aquestes propostes podrien ajudar a millorar el coneixement actual que tenim de la esquizofrènia i el seu tractament.

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Woodward, N.D., Purdon, S.E., Meltzer, H.Y., & Zald, D.H. (2005). A meta-analysis of neuropsychological change to clozapine, olanzapine, quetiapine, and risperidone in schizophrenia. *International Journal of Neuropsychopharmacology*, *8*(3), 457-472.

Woodward, T.S., Balzan, R., Menon, M., & Moritz, S. (2014). Metacognitive training and therapy: an individualized and group intervention for psychosis. In Lysaker, P.H., Dimaggio, G., & Brüne, M. (Eds.), *Social cognition and metacognition in schizophrenia. Psychopathology and treatment approaches* (pp.179-195). UK: Elsevier Inc.

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Wykes, T., & Spaulding, W.D. (2011). Thinking about the future cognitive remediation therapy—what works and could we do better?. *Schizophrenia Bulletin*, *37*(suppl 2), S80-S90.

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Wykes, T., Reeder, C., Williams, C., Corner, J., Rice, C., & Everitt, B. (2003). Are the effects of cognitive remediation therapy (CRT) durable? Results from an exploratory trial in schizophrenia. *Schizophrenia Research*, *61*(2), 163-174.

Zhang, Q. (2012). *Uncertainties in Counterfactuals: The Determinants and Emotional Consequences of Counterfactual Probability Judgments* (Doctoral dissertation, Durham University).

CURRICULUM VITAE

Àuria Albacete Belzunces

Psychologist

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EDUCATION

2012-2017	**PhD in Clinical Neurosciences** School of Medicine. University of Barcelona. Research project: "Characterization of Counterfactual Reasoning Deficits in Patients with Schizophrenia, Non-psychotic First Degree Relatives in comparison with Healthy Controls" *Supervisors: José Manuel Menchón and Fernando Contreras*
2010-2011	**Master Clinical psychology and Psychotherapy** Blanquerna - Ramon LLull University. *Masters dissertation: Víctor Cabré*
2005-2009	**B.A. Psychology** Universitat Autònoma de Barcelona.

PREVIOUS RESEARCH POSITIONS

2010-2011	**Research Intern** at the Psychopedagogical Intervention and Counseling Service (SAIP). Blanquerna - Ramon LLull University. *Barcelona, Spain.*
2008-2009	**Research Intern** at the Department of Psychobiology and Methodology of Health Sciences. Universitat Autònoma de Barcelona. *Barcelona, Spain.*

TEACHING EXPERIENCE

From 2012	**Collaborator Teacher** in the Bachelor of Medicine from the University of Barcelona to teach in the subject entitled "Psychological Medicine." *Barcelona, Spain.*
March 2015	**Invited talk**: "Counterfactual thinking in schizophrenia, first-degree relatives and healthy controls. Preliminary results." Polyvalent Mental Health Unit. Benito Menni CASM. 2015. *L'Hospitalet de Llobregat, Spain.*

RESEARCH TRAINING

2016 *Oct – Dec*	**Training stay** in the Prevention and Early Intervention Program for Psychosis (*PEPP-Montréal*). Douglas Mental Health University Institute. McGill University. *Montréal, Canada.* *Stay supervisor: Martin Lepage*
2016 *June*	**Training stay** in the Psychiatry Research Unit. Instituto de Investigación Marqués de Valdecilla-IDIVAL. *Santander, Spain.* *Stay supervisors: Benedicto Crespo-Facorro and Rosa Ayesa-Arriola*

GRANTS

2016	**Grant for the finalization of the doctoral thesis** "Ajut Finalització Tesi Doctoral". Supported by Campus de Bellvitge - University of Barcelona. **Grant for the finalization of the doctoral thesis** "Ajut Finalització Tesi Doctoral". Supported by Campus Clínic - University of Barcelona. *RESIGNED* **Mobility research fellow**. McGill University. Montréal, Canada. Supported by Health University of Barcelona Campus (HUBc). **Mobility research fellow.** IDIVAL. Santander, Spain. Supported by University of Barcelona and Fundació Montcelimar.
2012	**PhD fellowship**. APIF-UB Fellowship - Trainee research staff grants for PhD students from the University of Barcelona. *From October 2012 to September 2016.*
2010	**Academic Excellence Fellowship** for master's degree courses. Blanquerna - Universitat Ramon Llull.
2008	**Research Assistant Fellowship** for undergraduate students. Spanish Ministry of Education, Culture and Sport. Spanish Government.

PROFESSIONAL AFFILIATIONS

From 2016	Centro de Investigación Biomédica en Red de Salud Mental-CIBERSAM *Instituto de Salud Carlos III, Ministry of Economy and Competitivity*
From 2010	Official Catalan Association of Psychologists ("Col·legi Oficial de Psicòlegs de Catalunya")

RELEVANT PEER-REVIEWED JOURNAL ARTICLES

2017

- Contreras, F.,* **Albacete, A.**,* Castellvi, P., Caño, A., Benejam, B., Menchón, J.M. (2017). Patients with schizophrenia activate behavioural intentions facilitated by counterfactual reasoning. *PLoS ONE 12(6): e0178860.* [*co-first authors]. Q1. IF: 3.05.

- **Albacete, A.**,* Contreras, F. Bosque, C., Gilabert, E., Albiach, A., Menchón, J.M. (2017). Symptomatic remission and counterfactual reasoning in schizophrenia. *Frontiers in Psychology. 7:2048.* [*co-first authors]. Q1. IF: 2.46.

- Mas, S., Gassó, P., Torra, M., Bioque, M., Lobo, A., González-Pinto, A., …, **PEPs Group.** (2017). Intuitive pharmacogenetic dosing of risperidone according to CYP2D6 phenotype extrapolated from genotype in a cohort of first episode psychosis patients. *European Neuropsychopharmacology – In Press.* Q1. IF: 4.40.

- Mezquida, G., Cabrera, B., Bioque, M., Amoretti, S., Lobo, A., González-Pinto, A., …, **PEPs Group.** (2017). The course of negative symptoms in first-episode schizophrenia and its predictors: A prospective two-year follow-up study. *Schizophrenia Research – In Press.* Q1. IF: 4.45.

- Bernardo, M., Bioque, M., Cabrera, B., Lobo, A., González-Pinto, A., Pina, L., …, **PEPs Group.** 2017. Modelling gene-environment interaction in first episodes of psychosis. *Schizophrenia Research – In Press.* Q1. IF: 4.45.

2016

- **Albacete, A.**, Bosque, C., Custal, N., Crespo, J.M., Gilabert, E., Albiach, A., Menchón, J.M., Contreras, F. (2016). Emotional intelligence in non-psychotic first-degree relatives of people with schizophrenia. *Schizophrenia Research.175: 103-108.* Q1. IF: 4.45.

- **Albacete, A.**, Contreras, F. Bosque, C., Gilabert, E., Albiach, A., Menchón, J.M., Crespo-Facorro, B., Ayesa-Arriola, R. Counterfactual reasoning in non-psychotic first-degree relatives of people with schizophrenia. (2016). *Frontiers in Psychology. 7:665.* Q1. IF: 2.46.

- Contreras, F.,* **Albacete, A.**,* Castellvi, P., Caño, A., Benejam, B., Menchón, J.M. (2016). Counterfactual reasoning deficits in schizophrenia. *PLoS ONE, 11(2), e148440.* Q1. IF: 3.05. [*co-first authors].

- Mas, S., Gassó, P., Lafuente, A., Bioque, M., Lobo, A., Gonzàlez-Pinto, A., …, **PEPs Group**. (2016). Pharmacogenetic study of antipsychotic induced acute extrapyramidal symptoms in a first episode psychosis cohort: role of dopamine, serotonin and glutamate candidate gene. *The Pharmacogenomics Journal. 1-7.* Q1. IF: 3.78.

- González-Pinto, A., González-Ortega, I., Alberich, S., Ruiz de Azúa, S., Bernardo, M., Bioque, M., …, **PEPs Group**. (2016). Opposite cannabis-cognition associations in psychotic patients depending on family history. *PLoS ONE, 11 (8), e0160949.* Q1. IF: 3.05.

- Mezquida, G., Penadés R., Cabrera, B., Savulich, G., Lobo, A., González-Pinto, A., …, **PEPs Group**. (2016). Association of the *brain-derived neurotrophic factor* Val66Met polymorphism with negative symptoms severity, but not cognitive function, in first-episode schizophrenia spectrum disorders. *European Psychiatry, 38: 61-69.* Q1. IF: 3.91.

2015

- Bioque, M., Llerena, A., Cabrera, B., Mezquida, G., Lobo, A., González-Pinto, A., …, **PEPs Group**. (2015). A pharmacovigilance study in first episode of psychosis: psychopharmacological interventions and safety profiles in the PEPs project. *International Journal of Neuropsychopharmacology. 31; 19(4).* Q1. IF: 4.33.

- Cuesta, M.J., Sánchez-Torres, A.M., Cabrera, B., Bioque, M., Merchán-Naranjo, J., Corripio, I., …, **PEPs Group**. (2015). Premorbid adjustment and clinical correlates of cognitive impairment in first-episode psychosis. The PEPsCog Study. *Schizophrenia Research*. 164, 65–73. Q1. IF: 4.22.

- Pina-camacho, L., Del Rey-mejías, Á., Janssen, J., Bioque, M., González-pinto, A., Arango, C., …, **PEPs Group**. (2015). Age at First Episode Modulates Diagnosis-Related Structural Brain Abnormalities in Psychosis. Schizophrenia Bulletin. 42 (2): 344-357. 5–7. Q1. IF: 7.75.

CONFERENCE PRESENTATIONS

- Poster: **Albacete A.**, Contreras, F., Menchón, J.M. *Counterfactual reasoning deficits are related with acute negative symptoms in schizophrenia.* 5th Biennial Schizophrenia International Research Society Conference. 2016. Florence, Italy.

- Poster: **Albacete A.**, Contreras, F., Bosque, C., Menchón, J.M. *Counterfactual thinking is impaired in non-psychotic first-degree relatives of schizophrenia patients.* 5th European Conference on Schizophrenia Research. 2015. Berlin, Germany.

- Poster: Contreras, F., **Albacete, A.**, Custal, N., Menchón, J.M. *Social cognition in schizophrenia, first-degree relatives and healthy controls*. 9th International Conference in Early Psychosis. 2014. Tokyo, Japan.

- Oral presentation: Contreras, F., Castellví, P., Caño, A., Benejam, B., **Albacete, A.**, Menchón, J.M. *Counterfactual thinking deterioration in schizophrenia. Generation, causal order effect and negative symptoms.* 10th International Meeting on the early stages of mental illness. 2012. Santander, Spain.

RESEARCH PROJECTS

Non-funded research projects

2012 — PR160/12: "*Characterization of counterfactual reasoning deficits in schizophrenia patients and first-degree relatives in comparison with healthy control subjects.*" Bellvitge University Hospital-IDIBELL. Role: collaborator. 2012.

2009 — PR077/10: "*Counterfactual thinking in schizophrenia patients. Relationship with cognitive and clinical variables.*" Bellvitge University Hospital-IDIBELL. Role: collaborator. 2009.

Funded research projects

2014 — MN28222: *"A cross-sectional survey and retrospective review of patients with persistent symptoms of schizophrenia to estimate their medical resource utilization and burden of illness"*. Roche Farma, S.A. *Collaborator.*

2013 — 14724A: *"A 28-week, randomized, open-label study evaluating the effectiveness of aripiprazole once-monthly versus paliperidone palmitate in adult patients with schizophrenia"*. H. Lundbeck A/S. *Collaborator.*

2011 — PI11/0222: *"Clinical and neurobiological determinants of second episodes in schizophrenia. A follow-up study of first psychotic episodes"*. Carlos III Health Institute, Centro de Investigación Biomédica en Red de Salud Mental-CIBERSAM. *Collaborator.*

PSY 3011: *"A randomized, multicenter, double-blind, non-inferiority study of paliperidone palmitate 3 month and 1 month formulations for the treatment of subjects with schizophrenia"*. Janssen-Cilag International N.V. *Collaborator.*

2008 — PI08/1118: *"Phenotype–genotype and environmental interaction. Application of a predictive model in first psychotic episodes"*. Carlos III Health Institute, Centro de Investigación Biomédica en Red de Salud Mental-CIBERSAM. *Collaborator.*

AD-HOC PEER REVIEW

Participation as a reviewer for the following journal(s): *The European Journal of Psychiatry*

SCIENTIFIC COURSES (selection)

2017	"*XIV Intensive introduction course to research in neuroscience: cannabis and mental illness*". Carlos III Health Institute, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM). Barcelona, Spain.
2016	"*XIV Jornades de Docència de la Facultat de Medicina i Ciències de la Salut*". Facultat de Medicina i Ciències de la Salut. Barcelona, Spain.
2015	"*I Course in neurocognitive and functional evaluation of patients with severe mental illness*". Carlos III Health Institute, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM). Valencia, Spain.
2014	"*Motivational interviewing. Level II*". Bellvitge University Hospital. L'Hospitalet de Llobregat, Spain.
	"*Motivational interviewing. Level I*". Bellvitge University Hospital. L'Hospitalet de Llobregat, Spain.
2013	"*VIII Intensive introduction course to research in neuroscience: gene-environment interaction in the causation of mental illness*". Carlos III Health Institute, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM). Barcelona, Spain.
	"*VII Intensive introduction course to research in neuroscience: update on research in autism spectrum disorders*". Carlos III Health Institute, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM). Barcelona, Spain.
2011	"*III Intensive introduction course to research in neuroscience: the brain in schizophrenia*". Carlos III Health Institute, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM). Barcelona, Spain.

LANGUAGES

Spanish	*Mother tongue.*
Catalan	*Mother tongue.*
English	*Fluent.* ▪ *Advanced level certificate. Galway Cultural Institute (2011).* ▪ *Cambridge First Certificate in English (2008).*

German	*Basic.* ▪ *A1 Level (2013). Escola Moderna d'Idiomes (EIM). University of Barcelona.*

COMPUTER SKILLS

Operating systems: *Windows 7, Mac OS X.*

Applications: *Microsoft Office, Statistical Package for the Social Science (SPSS), Mendeley reference manager, SAP and Itk-SNAP.*

OTHERS

From 2014	Member of "Ars Medica Orchestra", Col·legi Oficial de Metges de Barcelona. Barcelona, Spain.
2008	Professional Degree in Music. Conservatori Municipal de Música de Barcelona. Barcelona, Spain.

Services to the community/associations:

2010-2011	- Volunteer at "Fundació Formació i Treball", an association that facilitates access to employment for individuals with socio-economic difficulties. Barcelona, Spain. - Volunteer at "Creu Roja Catalunya (Red Cross)", Assamblea comarcal Baix Llogrebat Centre. Barcelona, Spain.

Barcelona, June 2017