Universitat de Girona
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Voices arguing and voices commenting one's action hallucinations: neuropsychological characteristics and evolution. A longitudinal 12 months follow-up study.

END OF TERM PROJECT

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Girona, November 2016

ACKNOWLEDGMENTS

This end of term project could not have been done without the precious knowledge and help of Dr. Domènec Serrano, I wish to express my deepest thanks for providing me his support, guidance and help in carrying out this end of term project.

I would also like to thank the "Unitat d'Hospitalització d'Aguts" of the "Hospital Santa Caterina" for kindly welcoming me during all this time, and especially to Dr. Sara Castellón, Dr. Julio Company, Dr. Albert Ventura and Dr. Núria Rigau for their patience and for opening my eyes to the complexity of the psychiatry.

Thanks to Dr. Teresa Puig for guiding me throughout the project.

And finally I want to thank Lluís Recasens for his dedication and patience.

To my parents,

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1. ABSTRACT

Background: It's known that First Rank Symptoms (FRS) are particularly typical of schizophrenia, although they are not pathognomonic. Some studies have found that there is a high correlation between alienation delusions and voices arguing and voices commenting hallucinations, both of them belonging to FRS that suggests they may have a common pathophysiology. As we know, patients with alienation delusions have a left frontoparietal hypofunction and a right parietal hyperfunction, and patients with auditory verbal hallucinations have an affection of the superior temporal gyrus therefore we could think that people who present voices arguing and voices commenting hallucinations would present a left frontotemporal hypofunction and a compensation through a right temporal hyperfunction.

Aims: To determine whether the patients with voices arguing and voices commenting hallucinations have a dysfunction of the left frontal lobe and the left superior temporal gyrus and a right temporal lobe hyperfunction. And determinate the evolution of these patients after 12 months in terms of psychopathology and social functionality.

Methods: A cohort study will be performed including 210 patients with hallucinations, 79 of them with voices arguing and voices commenting hallucinations and 131 with other auditory hallucinations. Candidate patients will be selected as they are admitted to the "Unitat d'Hospitalització d'Aguts" (UHA) in "Hospital Santa Caterina" (HSC), Girona. Participants will be evaluated during admission and once every three months for twelve-month follow-up period in order to compare the neuropsychological characteristics and the psychopathological and functional evolution.

Keywords: Voices arguing and voices commenting hallucinations, auditory hallucinations, Weschler Adult Intelligence Scale III.

2. ABBREVIATIONS

DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

ICD-10: International Classification of Diseases, 10th revision

fRMI: functional magnetic resonance imaging

VAH: verbal auditory hallucinations

nVAH: non verbal auditory hallucinations

IPL: Inferior Parietal Lobe

FRS: First Rank Symptoms

FRAH: First Rank Auditory Hallucinations

STG: Superior Temporal Gyrus

UHA: "Unitat d'Hospitalització d'Aguts"

HSC: Hospital Santa Caterina

WAIS III: Weschler Adult Intelligence Scale III

SAPS: Scale for the Assessment of Positive Symptoms

PANSS: Positive and Negative Syndrome Scale

CDSS: Calgary Depression Scale for Schizophrenia

YMRS: Young Mania Rating Scale

RSWGcr: Remission Schizophrenia Working Group Criteria

SOFAS: Social and Occupational Functioning Assessment Scale

3. INTRODUCTION:

3.1. Schizophrenia

Schizophrenia is a severe psychiatric disorder that has a profound effect on both the individuals affected and society.

It is present in the 0.7% of the world population. More than 50% of individuals who receive a diagnosis have intermittent but long-term psychiatric problems, and around 20% have chronic symptoms and disability.
Unemployment is staggeringly high at 80–90%, and life expectancy is reduced by 10–20 years (1).

3.1.1. Clinical presentations, signs and symptoms

The core features are positive symptoms (delusions and hallucinations; so-called psychotic symptoms in which contact with reality is lost), negative symptoms (particularly impaired motivation, reduction in spontaneous speech, and social withdrawal), and cognitive impairment (patients have poorer performance than healthy people over a wide range of cognitive functions, although there is much individual variability) (2).

The positive symptoms tend to relapse and remit, although some patients have residual long-term psychotic symptoms. The negative and cognitive symptoms tend to be chronic and are associated with long-term effects on social function.

The first episode of psychosis usually occurs in late adolescence or early adulthood, but it is frequently preceded by a prodromal phase or a so-called at-risk mental state. In some instances, premorbid impairments in cognition or social functioning, or both, can manifest many years before the first psychotic episode. However, in other instances, onset is sudden in previously well-functioning individuals (1).

3.1.2. Diagnosis

In most psychiatric disorders, for the diagnosis there aren't biomarkers and specific diagnostic test, making the diagnosis based on anamnesis and psychopathological exploration.

Schizophrenia, like most of other psychiatric diagnoses, is still a syndromic concept. The diagnoses are usually too wide or too restrictive. On one hand, individuals with schizophrenia vary widely in the predominant symptoms, response to treatment, and the course of evolution and, on the other hand, many psychiatric diagnoses have symptoms in common, and the boundaries between schizophrenia and other disorders are indistinct, as are the boundaries between disorder and wellness.

However, attempts to address this heterogeneity to valid subtypes have repeatedly failed (3).

Even if they are too broad, the DSM-5 and ICD-10 criteria have provided a fairly reliable approach to clinical psychiatric diagnoses, and they are nowadays the most used classifications.

Table 1: Adapted from "Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition" (4)

DSM-5 Criteria for Schizophrenia
A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2), or (3):   1. Delusions.   2. Hallucinations.   3. Disorganized speech (e.g., frequent derailment or incoherence).   4. Grossly disorganized or catatonic behavior.   5. Negative symptoms (i.e., diminished emotional expression or abolition).
B. For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).
C. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion

A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).
D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either 1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or 2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.
E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.
F. If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated).

Table 2: Adapted from the "The ICD-10 Classification of Mental and Behavioral Disorders"(5)

ICD-10 Criteria for Schizophrenia	
a)	Thought echo, thought insertion or withdrawal, and thought broadcasting.
b)	Delusions of control, influence, or passivity, clearly referred to body or limb movements or specific thoughts, actions, or sensations; delusional perception.
c)	Hallucinatory voices giving a running commentary on the patient's behavior, or discussing the patient among themselves, or other types of hallucinatory voices coming from some part of the body.
d)	persistent delusions of other kinds that are culturally inappropriate and completely impossible, such as religious or political identity, or superhuman powers and abilities (e.g. being able to control the weather, or being in communication with aliens from another world).
e)	Persistent hallucinations in any modality, when accompanied either by fleeting or half-formed delusions without clear affective content, or by persistent over-valued ideas, or when occurring every day for weeks or months on end.
f)	Breaks or interpolations in the train of thought, resulting in incoherence or irrelevant speech, or neologisms.
g)	Catatonic behavior, such as excitement, posturing, or waxy flexibility, negativism, mutism, and stupor.

h)	"Negative" symptoms such as marked apathy, paucity of speech, and blunting or incongruity of emotional responses, usually resulting in social withdrawal and lowering of social performance; it must be clear that these are not due to depression or to neuroleptic medication.
i)	A significant and consistent change in the overall quality of some aspects of personal behavior, manifest as loss of interest, aimlessness, idleness, a self-absorbed attitude, and social withdrawal.

3.1.3. Neurobiology

The neurobiology of schizophrenia remains poorly understood. Strong evidence implicates dysfunction of dopaminergic neurotransmission in the genesis of psychotic symptoms, and abnormalities of glutamate signaling might account for the negative and cognitive symptoms. Some brain areas have been linked to specific cognitive dysfunctions (e.g., the prefrontal cortex in working memory impairment), but a widespread and variable involvement of other brain areas and circuits is also likely. Disturbances of synaptic function might underlie abnormalities of neuronal connectivity, possibly through effects on interneurons, but the nature, location, and timing of these events remain unclear. Progression towards schizophrenia can be triggered by postnatal environmental exposures—which might be modulated by genetic factors and environmental factors in early development—and, in some cases, also by oxidative and inflammatory mechanisms (1).

3.2. Hallucinations

Hallucinations are perception-like experiences that occur without an external stimulus.
They are vivid and clear, with the full force and impact of normal perceptions, and not under voluntary control (4, 6).
Hallucinations may occur in a number of different clinical populations including psychiatric patients (e.g., schizophrenia, affective disorders, dissociative disorders, borderline personality disorder, delirium, post-traumatic stress disorder, multiple personality disorder, post-partum psychosis, conversion disorder) and non-psychiatric patients (e.g., cerebrovascular disorder, brain tumor, brain injury, epilepsy, narcolepsy, migraine, Lewy Body Dementia, Parkinson's disease, Alzheimer's disease) (7).

The hallucinations must occur in the context of a clear sensorium; those that occur while falling asleep *(hypnagogic)* or waking up *(hypnopompic)* are considered to be within the range of normal experience. Hallucinations may be a normal part of religious experience in certain cultural contexts (4).

There is also evidence that culture may modulate the phenomenological characteristics of hallucinations. For example, auditory hallucinations seem to be the most frequently reported by schizophrenic patients in the West, in contrast, a number of studies have found that visual hallucinations are a more common type of hallucination in African and Asian countries compared to the West (6).

Neuroimaging studies suggest that hallucinations in a given modality involve areas that normally process sensory information in that modality (6).
In a study that used fRMI to identify differences in brain activation between auditory and somatic hallucinations, found that somatic hallucinations were associated with activation in the thalamus, the primary somatosensory cortex, and posterior parietal cortex, areas classically associated with tactile processing. By contrast, auditory hallucinations were associated with activation in a distinct set of brain areas, particularly the right temporal cortex (8).

3.2.1. Auditory hallucinations

Auditory hallucinations are the most common in schizophrenia and related disorders. They can be defined as auditory percepts which lack an appropriate source in the extracorporeal world.

They are a compelling and distressing feature of the schizophrenic syndrome and studying their phenomenology is of central importance. Given the syndromal diversity and immensely variable outcome of schizophrenia, it may only be by the analysis of specific symptoms rather than global syndromes that a clearer understanding will be gained (9).

As auditory hallucinations defy categorization along the lines of a single theme, it is impossible to present them in the form of a single, overarching classification. Some examples of the guiding principles traditionally used to classify them are content and perceived source.

Classification according to the content:

- **Verbal auditory hallucinations** (VAHs): they may consist of a human or a nonhuman voice, such as an animal voice or a mechanical voice. They may speak in a regular tone of voice, or whisper or shout, and they may be intelligible or unintelligible. When voices are unintelligible, it may be because they sound muffled, faint or far-off, because they are speaking in a foreign language, or because they are masked by other voices or nonverbal sounds.

- **Nonverbal auditory hallucinations** (NVAHs): includes such hallucinated sounds as machine noises, barking, snoring, whistling, music, and nonverbal sounds featuring prominently in tinnitus, such as ringing, hissing, a clear tone, a high-tension wire, buzzing, sizzling, whistling, humming, ticking, clicking, pounding, roaring, pulsating sounds, the sound of the wind or waves upon the shore, an ocean roar, and the chirping of crickets (10).

In both the cases, the perceived content can either change over time or constitute a literal repetition of prior auditory hallucinatory percepts. In the latter case, the term stable hallucination is used.

Classification to their perceived source in space:

- **Internal auditory hallucinations** (coming from inside the head): individuals who experience internal auditory hallucinations generally identify a specific spatial location within the head, often near or behind the ear.

- **External auditory hallucinations** (coming from outside the head).

- **Extracampine hallucination:** may give the impression that they are being heard by body parts such as the knee, the stomach, or the top of the head, which seem to function as acoustic organs (10).

3.2.2. Neurocognitive models

Several possible neurocognitive models of AVH have been proposed. These include (11–13):

- **External misattribution of self-inner speech**: patients with schizophrenia are unable to identify their own thoughts as self-generated and, furthermore, interpret them as intrusive alien voices within their heads.

- **The Aberrant Memory Model:** postulates that AVH result from aberrant memory activation and monitoring, particularly from past traumatic experiences, potentially due to both a failure in inhibition of recall and unintended memory activation. The unintended and out-of-context memory activation is due to dysfunctional prefrontal inhibition, and it may generate intrusive thoughts, which are increased in schizophrenia.

- **'Over-perceptualization' model**: suggests a hyperexcitable state in the primary and secondary sensory regions (11–13).

Some meta-analysis demonstrated that experiencing AHs is associated with increased activity in fronto-temporal areas involved in speech generation and speech perception, but also within the medial temporal lobe, a structure notably involved in verbal memory.

They have seen also the affection of the Inferior Parietal Lobe (IPL) that could play a role in the misattribution of the speech as not being self-generated (12,14).

3.3. First rang symptoms (FRS)

3.3.1. The nature of FRS

Even if we tried to explain separately the phenomenon of hallucinations, the truth is that they are rarely alone in the disorder, and usually appear with the other positive symptoms: delusions and formal thought disorders. There are a lot of theories related to the formation of positive symptoms, and there are some authors who can not separate their physiopathogeny (15).

Although delusions and hallucinations can be found in more than one neurological and psychiatric disorder, there is a specific type that has been identified as typical of schizophrenia: the first rank symptoms, including symptoms related to a particular sense of being passive, be the subject of a control or an external force or agent (16).

Kurt Schneider's insight nearly 80 years ago that schizophrenia could be demarcated from other psychoses by a small set of particular delusions and hallucinations powerfully influenced diagnostic practice.

Schneider referred that FRS are present when "a person's own acts and mental states are not experienced as their own, but as something controlled and influenced" (1971).
Sims (1991) proposed that all first rank symptoms could be conceived of as varieties of *Ichstörung* (ego disturbances or lack of myness): the hallucinations resulting from leaky boundaries between self and non-self, and hence one's thoughts became invested with an alien and objective quality; delusional perception illustrating the converse, with what was actually an external, neutral event being imbued with personal meaning (17).

Table 3: Schneider's first rank symptoms (according to Mellor, 1970) (17).

Schneider's first rank symptoms.	
1. *Audible thoughts*	Voices speaking thoughts aloud. "Echo de la pensée"
2. *Voices arguing*	Two or more hallucinatory voices discussing the subject in the third person
3. *Voices commenting on one's action*	Voices describing subject's activities as

	they occur
4. *Influence playing on the body somatic Passivity*	Experience of bodily sensations imposed by external agency
5. *Thought withdrawal*	Thoughts cease and subject simultaneously experiences them as removed by external force
6. *Thought insertion*	Thoughts have quality of not being own, ascribed to external agency
7. *Thought broadcasting*	Thoughts escape into the outside world where they are experienced by others
8. *Made feelings*	Feelings do not seem to be own, attributed to external force
9. *Made impulses*	Drive or impulse seems to be alien and external
10. *Made volitional acts*	Actions and movements felt to be under outside control
11. *Delusional perception*	Normal perception has private and illogical meaning

3.3.2.   Diagnostic and prognostic implications

FRS have been the subject of much debate with a focus on the role they have played in diagnostic systems and on their psychopathological and prognostic importance.

The sensitivity and specificity of the FRS in schizophrenia is different depending on the studies: The prevalence of FRS in schizophrenia has differed in various studies and cultural contexts from 25.4% to 88%. However, FRS have been observed in mental disorders other than schizophrenia, and even in the normal population. Although the numbers have varied from 1% to 32%, the prevalence of FRS in non-schizophrenic patients is significantly less than seen in schizophrenia patients (7,17).

The prognostic implications of FRS remain equivocal. Some maintain that FRS is associated with poor prognosis (18,19), while others argue that FRS have no prognostic implications (20). Rosen et al. found in a prospectively follow-up during 20 years that the presence of FRS

at the acute phase represents more severe type of psychotic symptoms as they predict the absence of later recovery in schizophrenia (21).

3.3.3. AVHs in First Rank Symptoms

It is clear that seven of the 11 FRS do involve a lack of myness, but the three sorts of auditory hallucinations are not completely explained with a lack of myness.

Some authors found that auditory verbal hallucinations (AVH) could result from an inner speech generation disorder, whereby one's own inner speech is attributed to others (22).

For speech generated by one's own brain, schizophrenia patients exhibit an experiential disorder whereby speech that is usually experienced in the inner space could be experienced in outer space, and vice versa. So, patients could occasionally experience their inner speech in outer space.

Therefore, schizophrenics who experience 'voices' blur external and internal space, as if the boundaries between these were porous, is further evidence of the central role of anomalous spatiality in these psychopathological phenomena. One is therefore drawn to the conclusion *independently* by an anomalous sense of spatiality (23).

Phenomenologically, AVHs are quite heterogeneous in nature: varying from first to second to third person commentary; from brief utterances of simple sounds or single words to full conversations; consisting of voices (the average is three) from familiar, personal and repeated to the unknown; from passive discussions to issuing commands; and from pleasant or complimentary to—far more commonly—unpleasant and distressing (11).

Due to this heterogeneity, just some of the AVH are included in the FRS, and those are the audible thoughts, voices arguing and voices commenting on one's action.
The presence of First-Rank Auditory Hallucinations (FRAH) in patients with schizophrenia is between 42 and 55% (24).

3.3.4. Correlation between alienation delusions and voices arguing/ voices commenting hallucinations

It is known that the brain works as a whole, so we can't talk about single disturbances. Consequently the schizophrenia symptoms could be caused by the compensation of certain brain dysfunctions.

As commented before, hallucinations are usually accompanied by delusions. In terms of FRS, there is a special correlation between alienation delusions (thought withdrawal, thought insertion and thought broadcasting) and the voices arguing and voices commenting hallucinations. Among patients with alienation delusions, the 61% presented also voices commenting one's action and the 59% presented voices arguing.
We also observe an association between both auditory hallucinations, since the 77% of the patients with voices commenting one's action present voices arguing hallucinations too (16). Concluding that they may have a common pathophysiological mechanism.

Direct electrical stimulation of the Superior Temporal Gyrus (STG) has been reported to elicit auditory hallucinatory experiences. Also, functional imaging studies have demonstrated involvement of the right temporal cortex in processing prosody making inference from what is said, as well as generating an emotional response to its content which have a direct relevance to the hallucinatory experience (25).

Patients with alienation delusions have been seen to present a left frontoparietal dysfunction and a right parietal hyperfunction (16). There is also an affection of the left temporal lobe, but knowing that there is a strong correlation between alienation delusions and voices arguing and voices commenting hallucinations we could think that the hypofunction of the temporal lobe is due to the hallucinations.

4. JUSTIFICATION

People suffering from schizophrenia present a heterogenic variety of clinical, which questioned the utility of the criteria used until nowadays to define and characterize the pathology, because it is difficult to identify a well delimited entity which allows us to research appropriately in terms of etiology and pathophysiology (26).

Several times there have been several attempts to characterize specific symptoms of schizophrenia, and among them the Kurt Schneider's one with the First Rank Symptoms. In an intuitive way, based on the clinical observation, he proposed them as relevant in the characterization of the pathology. Hallucinations have a special importance among FRS (17).

Since some years ago, it has been observed the need of understanding the schizophrenic disorder as a global lesion, but that can be characterized by other more specific disturbances in different brain areas that are known to be interconnected through neural networks.

For that reason, from the symptoms' clusters that we supposed to be linked to a specific disturbance in a cerebral area, we should be able to associate neuropsychological disturbances with the same area (12,14). Thus, there would be a common dysfunction for all the schizophrenic patients and some specific characteristics which would allow us to explain some particular phenotypes.

The results in some subtests of neuropsychological tests, such as WAIS-III, are related with the functioning of some cerebral areas. So, even though they are not designed for this function, they would be useful to detect neuropsychological disturbances that are present in patients with voices arguing and voices commenting hallucinations.

We know that there is a strong correlation between alienation delusions and voices arguing and voices commenting hallucinations. In this project we will search if they have common brain anatomical dysfunctions (at the left inferior parietal lobe and Superior Temporal Gyrus (STG)) that cause a compensation in some brain regions (right parietal lobe and STG), so that we could consider them a specific entity between the schizophrenia disorder.

We also would like to know if this specific entity has a significant difference in the evolutionary characteristics in a psychopathological and cognitive level.

5. HYPOTESIS

5.1. Main hypothesis

- Patients with voices arguing and voices commenting one's action hallucinations have a dysfunction in the left frontal lobe and left superior temporal gyrus and a hyperfunction of the right temporal lobe.

5.2. Secondary hypotheses

- Patients with voices arguing and voices commenting one's action hallucinations have a worse recovery of the positive symptoms than patients experiencing other auditory hallucinations.

- The functional recuperation at 12 months is worse in patients with voices arguing and voices commenting one's action hallucinations than in patients experiencing other auditory hallucinations.

6. OBJECTIVES

6.1. Main objective

– To determine whether the patients with voices arguing and voices commenting one's action hallucinations have neuropsychological characteristics according to the WAIS-III test different from patients with other auditive hallucinations, consisting in a dysfunction of the left frontal lobe and the left superior temporal gyrus and a hyperfunction of the right temporal lobe.

6.2. Secondary objectives

– To determine whether the evolution of the positive symptoms at 12 months of the patients with voices arguing and voices commenting one's action hallucinations is worse than the evolution of the patients experiencing other auditory hallucinations according to the Remission Schizophrenia Working Group Criteria (RSWGcr).

– To determine whether the functional recuperation at 12 months according to the SOFAS test of the patients with voices arguing and voices commenting hallucinations is worse than the recovery of the patients experiencing other auditory hallucinations.

7. METODOLOGY

7.1. Study design

Cohort study. Longitudinal, observational, analytic and prospective.

7.2. Study population

The study subjects will be all the patients who ingress in the "Unitat d'Hospitalització d'Aguts" (UHA) at the "Hospital Santa Caterina" (HSC) with the diagnosis of schizophrenia according to the DSM-5 diagnostic criteria.

7.2.1. Inclusion criteria

1. Diagnosis of schizophrenia according to DSM-5 criteria

2. Presence of voices arguing and voices commenting hallucinations without auditory hallucinations.

3. Presence of auditory hallucinations without voices arguing and voices commenting hallucinations.

4. Absence of concurrent psychiatric diagnoses or affective episode.

5. Presence of a relative or another informant during the duration of the study with a minimum of weekly contacts with the patient.

6. Informed consent.

7.2.2. Exclusion criteria

1. Determination in urine of the following toxics: opiates, cocaine, cannabis and amphetamines in the week prior to the administration of tests.

2. Intellectual disability determined according to DSM-5 criteria.

3. Presence of neurological diseases and other disorders that can present with cognitive impairment (Parkinson's, Dementia, Korea ...).

4. Background of head trauma with loss of consciousness collected in the clinical history.

5. Sensory deficits (auditory and visual) of sufficient magnitude to interfere with the administration of the tests.

6. Impossibility to track during the study.

7. Presence of delirium according to DSM-5.

7.3. Sampling

7.3.1. Sample selection

The sampling method will be consecutive sequential (non-probabilistic). The sample recruitment will take part in the UHA of the HSC in Girona, as we will include all the patients diagnosed with schizophrenia according to the UHA protocol who meet the criteria attended.

After being diagnosed, all the patients will receive the information about the possibility of enter in a study to assess the neuropsychologic, psychopatologic, and functional characteristics of the schizophrenia and, if they want to participate, they will sign the informed consent (Appendix 1).

7.3.2. Sample size

The EPIDAT calculator was used to achieve our sample size. To achieve a statistical power of 80% to detect a minimum difference of 2 points in the block design's subtest on the contrast of the null hypothesis H_0: $\mu_1 = \mu_2$ through the bilateral Student-t test for two independent samples, assuming a 5% significance level and a joint standard deviation of 5 points, it is necessary to include 131 patients with auditory hallucinations and 79 patients with voices arguing and voices commenting hallucinations. Thus, our sample will include 210 subjects.

From previous studies we know that 16% of the patients with schizophrenia present voices arguing and voices commenting hallucinations without auditory hallucinations, and 23% present auditory hallucinations without voices arguing and voices commenting hallucinations (16).

In the UHA of the HSC there are approximately 1200 hospitalizations every year and it is supposed that 40% are diagnosed of schizophrenic disorder. This data makes it possible for the sample selection to be carried out to term in 1 year (≈480 patients).

7.4. Study Variables

7.4.1. Independent Variable

Scale for the Assessment of Positive Symptoms (SAPS): it includes 6 types of hallucinations. Through the application of this variable, we will achieve the creation of two groups, one with patients experiencing voices arguing and voices commenting one's action hallucinations, and the second one with other auditory hallucinations.

7.4.2. Dependent Variable

Weschler Adult Intelligence Scale III (WAIS-III): we are going to apply this test that includes 13 subtests (vocabulary, similarities, information, comprehension, arithmetic, digit span, letter-number sequencing, picture completion, block design, matrix reasoning, digit-symbol coding, symbol search, picture arrangement) to determinate which parts of the brain are affected in both study groups, as we know that this subtests have a correlation with neuroanatomical disturbances.

7.4.3. Covariates

- **Age at the diagnosis of schizophrenia.**
- **Years from the diagnosis of schizophrenia**: measured in months.
- **First episode:** Yes/Not
- **Gender**: male/female.

- **Sociodemographic variables:** These co-variables will be determined in the clinical interview.
  - *Education*: less than high school; high school degree; college degree; graduate degree.
  - *Marital status*: married; in a partnership; single; separated; divorced; widowed.
  - *Employment situation*: employed; unemployed; student; retired.
  - *Ethnic group*: Caucasian; Black; "Latino"; Asian; others.
- **Intelligence**: WAIS-III total score.
- **Substances consumption:** Yes/ Not.
- **Schizophrenic symptoms severity:** global punctuation of the PANSS.
- **Previous treatment:** Yes/ not
- **Adherence to treatment:** 0% adherence; 0-25% adherence; 25-50% adherence; 50-75% adherence; 75-100% adherence; 100% of the prescribed doses.
- **Depressive symptoms severity**: score of the Calgary scale.
- **Maniac symptoms severity**: score of the Young scale.
- **Remission of symptoms**: according to Remission Schizophrenia Working Group Criteria (RSWGcr). Yes (punctuation $\leq$ 3 for each item); not (punctuation > 3 for each item)
- **Social functioning**: punctuation at the Social and Occupational Functioning Scale (SOFAS), with an evaluation the previous year at a basic level and after 12 months.

7.5.   Measuring instruments

7.5.1.   *Scale for the Assessment of Positive Symptoms (SAPS)* (27). (Appendix 3)

It was created by NC Andreasen in 1984 and collect 30 schizophrenia symptoms that are grouped in hallucinations, delusions, bizarre behavior, and positive formal thought disorder. Each group includes the evaluation of specific symptoms and a global item that represents the evaluator determination of the general severity in the group symptoms.

Those are the SAPS items:

1. **Hallucinations**: auditive hallucination, voices commenting, voices arguing, somatic or tactile hallucinations, olfactory hallucinations and visual hallucinations.

2. **Delusions**: persecutory delusions, delusions of jealousy, delusions of guilt or sin, grandiose delusions, religious delusions, somatic delusions, delusions of reference, delusions of being controlled, delusions of mind reading, thought broadcasting, thought insertion and thought withdrawal.

3. **Bizarre behavior**: clothing and appearance, social and sexual behavior, aggressive and agitated behavior and repetitive or stereotyped behavior.

4. **Positive formal thought disorder**: derailment (loss of association), tangentiality, incoherence, illogicality, circumstantiality, pressure of speech, distractible speech and changing (a pattern of speech in which sounds rather than meaningful relationships govern word choice).

All the items have a punctuation from 0 to 5. 0 points means that the symptom (or group of symptoms) is absent and 5 points means that the symptom (or group of symptoms) is severe. The total composite score is between 0 and 125 depending on the symptoms group and the total score oscillates between 0 and 20.

7.5.2. *Positive and negative syndrome scale (PANSS)* (28). (Appendix 4)

It was created by Kay et al. in 1987 to measure the severity of the psychopathology in young adults who suffered schizophrenia, schizoaffective disorder and other psychotic disorders, giving importance to the positive and negative symptoms.

The PANSS includes three scales and 30 items: 7 items constitute a positive scale (delusions, conceptual disorganization, hallucinations…), other 7 a negative scale (blunted affect, emotional withdrawal, poor rapport…) and 16 constitute a general psychopathology scale (somatic concern, anxiety, guilt feelings…).
Each item is rated from 1 to 7 depending on the severity of the symptom (1 is absent and 7 is extreme).

7.5.3. *Weschler Adult Intelligence Scale III (WAIS-III)* (16,29). (Appendix 5)

Is one of the most used psychometric instruments for the evaluation of the intellectual capacity in people who is older than 18. This instrument and his subtests are widely used in

the clinical evaluation and in the research in patients with schizophrenia. It gives a measurement of the verbal intelligence and the non verbal intelligence.

The WAIS-III contains 13 subtests organized in four groups which are verbal comprehension scale, working memory scale, perceptual reasoning scale and processing speed scale:

- **Verbal comprehension:** is a measure of the acquired verbal knowledge and the verbal reasoning.

  - **Vocabulary:** is about giving definitions to the words. Is particularly sensitive to the left hemisphere lesions, especially at the temporal lobe.
  - **Similarities:** it consists telling which are the similarities between two objects. Is a damage indicator at the left hemisphere and a decline in its score is associated with left frontal and temporal lesions and also bilateral frontal lobe compromise.
  - **Information:** is about orally answering to questions about some information. A decline in the score indicates a left hemisphere lesion, especially in that cases where all the verbal tests have a low punctuation too.
  - **Comprehension:** it consists to answer questions that require an understanding of concepts and social practices and it also has items that assess the abstract reasoning and the conceptualization through the ability to interpret proverbs. It is especially vulnerable to the left hemisphere commitment.

- **Working memory:** it's a measure that includes the temporal storage and the concurrent processing of the information.

  - **Arithmetic:** there are arithmetic problems to resolve in a limited time. A low score in this subtest makes us think about a possible memory, concentration or memory function disease.
  - **Digit span:** is about repeating a numeric sequence first in a direct order and then in reverse order. The first one evaluates the attention and the immediate auditive memory, and the second is a good measure of the work memory of the patient.
  - **Letter-number sequencing:** the evaluator reads a numbers and letters combination to the subject who has to remember first the numbers and then the letters in ascending order. It evaluates the work memory and the attention.

- **Perceptual reasoning:** is a measure of the visuospatial and visuoconstructive processing and the non-verbal reasoning.

  - **Picture completion:** the patient looks at some pictures and has to indicate which part of the picture is missing. It needs the participation of the right posterior cortex and the left parietal lobe in the task resolution.

  - **Block design:** it consists in asking the subject to replicate models or drawings of two colors designs with blocks. A low score is associated with right and left parietal damage. The patients with left lesions have a difficulty in the identification of the intern details in the design, and the patients with right lesions have an altered visuospatial conceptualization of the design.

  - **Matrix reasoning:** the subject should look at a matrix with a section missing and has to identify the correct one between 5 possible options. It measures abstract and fluid reasoning.

- **Processing speed:** is a measure of the ability to process visual information quickly.

  - **Digit symbol coding:** <u>Codification</u>: consists in coping symbols associated with numbers with a limit time of 120 seconds. <u>Incidental learning</u>: the subject should remember the symbols when the number is given to them, and to draw as much symbols as he/she remembers. Is a very sensitive test for cerebral damage, regardless location.

  - **Symbol search:** the subject should determine which of two target symbols fits to some of the symbols of a group. It evaluates the information processing speed and the attention research.

  - **Picture arrangement:** it consists in ordering a group of cards to create a logical history. A low score in this subtest is usually associated to a right temporal lesion. However, patients with a frontal lesion can also present a low punctuation due to the tendency to elaborate hypothesis in an impulsive way. It is also a test to the diffuse brain damage.

7.5.4. *Calgary Depression Scale for Schizophrenia (CDSS)* (30).

The CDSS (Addington et al 1990) was developed to evaluate the comorbid depressive symptoms specifically in patients who suffered schizophrenia, as the depression scales like

Hamilton scale wasn't reliable because some of the items could overcome the negative symptoms of schizophrenia.

It has 9 items: depressed mood, hopelessness, self-depreciation, guilty ideas of reference, pathological guilt, morning depression, early wakening, suicide ideas and observed depression. Each item has some questions and some descriptive answers for the evaluation, and its score is from 0 (absent) to 3 (severe). The total punctuation can be from 0 to 27: a score ≥ 5 could indicate a high risk of major depressive disorder. However, the depressive disorder has to be confirmed through a clinical exam.

7.5.5. *Young Mania Rating Scale (YMRS)* (31). (Appendix 6)

It was published in 1978 by Young et al. It is used to measure the severity of the maniac symptoms and the psychopharmacs' effect in the maniac severity.

The YMRS has 11 items that punctuate from 0 to 4 and has descriptions associated to each severity level, even though there are 4 items (irritability, speech, content and aggressive behavior) that punctuate from 0 to 8 to compensate the lack of collaboration observed in severe patients. Total score reaches 60: 13 (minimum severity), 20 (low severity), 26 (moderate severity) and 30 (important severity).

7.5.6. *Remission schizophrenia working group criteria (RSWGcr)* (32)*.

It has 9 items chosen from the PANSS including positive symptoms: delusions (P1), conceptual disorganization (P2) and hallucinatory behavior (P3); negative symptoms: blunted affect (N1), social and emotional withdrawal (N4) and lack of spontaneity (N6); and general psychopathology symptoms: mannerisms and posturing (G5), unusual thought content and lack of insight (G12).

The working group consensus defined a score of mild or less (item scores of ≤ 3) simultaneously on all items as representative of an impairment level consistent with symptomatic remission of illness (using the 1-7 range for each item).

7.5.7. Social and occupational functioning scale (SOFAS) (16,33). (Appendix 7)

It is focalized exclusively on the level of social and working functioning of the individual and it is not directly influenced by the general severity psychopathologic symptoms of the patient. The SOFAS evaluation takes in account any impairment in social or work functioning that is due to general medical conditions. It has a global punctuation from 1 to 100 where as higher score better performance.

In the first visit we are going to register the maximum functioning level in the previous year before the hospitalization, and the evaluation after 12 months will ascertains the maximum functional capacity in the previous month.

7.6. Data collection

All the data will be collected in 6 meetings, with 3 months between them, in face-to-face interviews, after the patients' agreement to participate in the study.

Data obtained from participants at baseline and during the following visits will be registered in the Case Report Form (Appendix 2) and, according to this form, data will be reported in the study database. The process of filling in the forms will be repeated in follow-up visits.

In the first appointment, an exhaustive evaluation of demographic and clinical data will be obtained, to ensure the collection of the measures of the independent and dependent variables as well as those of the co-variables. Information will be obtained by asking both the patient and relatives, in order to increase the collected data reliability.

The sociodemographic variables and the intelligence quotient will be asked only in the first meeting.

The WAIS and the SOFAS tests will be made only in the first and the last meeting, and the RSWG criteria will be asked only in the last meeting.

8. STATISTICAL ANALISYS

Statistical analysis will be performed using Statistical Package for Social Sciences (SPSS) for *Windows®*.

8.1. Univariate analysis

The SAPS score will be considered as a binary categorical variable (presence of voices arguing and voices commenting hallucinations / presence of other auditory hallucinations). The WAIS-III score will be considered as a quantitative variable as we are going to take the mean score of the patients in the different subtests.

In the same way, most of the covariates will be treated as quantitative with the exception of gender, sociodemographic variables, substance consumption, first episode, previous treatment and RSWGcr that will be treated as cathegorical variables.

The cathegorical variables will be described using frequencies and percentages while the quantitative variables will be described by mean ± standard deviation (when normal distribution) or median and interquartile range (if variables without normal distribution).

8.2. Bivariate analysis

Comparison between the presence or absence of voices arguing and voices commenting hallucinations (independent variable) and the scores in the different WAIS-III subtests (dependent variable) will be carried out using Student-t test or Mann-Whitney test as the first one is a cathegorcal variable and the second one is a quantitative variable.

8.3. Multivariate analysis

A binary logistic regression model will be used to quantify the multivariate-adjusted risk of presenting voices arguing and voices commenting hallucinations. The models will include the variables of age at the diagnoses, years from the diagnosis, first episode, gender, education, marital status, employment situation, ethnic group, intelligence, substances consumption, schizophrenic symptoms severity, previous treatment, adherence to treatment, Calgary scale score, Young scale score, RSWGcr and SOFAS score as independent variables.

Results will be expressed as absolute numbers and percentages, means, standard deviations, hazard ratios, and 95% confidence intervals (95% CI). Statistical tests will be considered to be significant for a two-tailed p-value <0.05.

9. ETHICAL CONSIDERATIONS

Before carrying out the study, the research protocol will be presented to the ethics committee, CEIC (Clinical Research Ethics Committee) from "Institut d'Assistència Sanitária de Girona".

This study is designed in accordance to the human rights and to the ethical tenets defined on the World Medical Association Declaration of Helsinki of "Ethical Principles for Medical Research Involving Human Subjects" of 2013.

The participants will be informed of the research's purpose and structure by the psychiatrist and psychologist and will also be given an information sheet that details the information transmitted beforehand. Subjects will be invited to participate voluntarily by the signature of the informed consent.

This study guarantees the confidentiality of the patient's data as the Case Report Form will only use the medical record number and not the participant's name. Clinical history information, names and surnames will remain anonymous when collecting data from the database and publishing results.

Confidentiality of participants' personal data will be in accordance to "Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal".

Study Participants have the right to access, modify, oppose or remove their personal data contained in the file at any time.

10. STUDY LIMITATIONS

- We use a consecutive sampling method where all the sample is from the hospital, what means that the subjects have severe symptoms, and the patients with less severity are excluded. So, we could make a selection bias.

- The neuropsychological tests (WAIS), used to evaluate the cognitive deficiencies as a correlate of cerebral disorders, aren't enough focalized in one particular area and assess these changes globally (in work memory, executive function…). May be they don't give a specific and well delimited information about de affected area.

- This study is a prospective cohort and as is typical in this type of studies, is very time consuming and expensive. Furthermore, the large duration of the study may account to higher dropout rates, either by death, geographical reasons (change of address) or lack of attendance (withdrawals to follow-up biases). To avoid sample losses, we will call each patient one week before each meeting as a remainder.

- There are different covariates that can modify the WAIS results producing a confounding bias. This limitation will be minimized by the use of a multivariate analysis to adjust the results for the confounding factors.

11. WORK PLAN AND CHRONOGRAM SCHEME

This study will be performed in 3 years and 3 months. The activities sequence carried out by the research team is gathered in 7 phases:

STAGE 1. Study setting-up - 3 months (September 2016- November 2016)

The principal investigator will make a literature review, will propose objectives and hypothesis, develop a methodology and a draft of the protocol design. This protocol will be presented to a group of "Facultat de Medicina de la Universitat de Girona" teachers, and it will require also the acceptance of the CEIC.

STAGE 2. Coordination phase - 2 months (December 2016- January 2017)

In this phase, the protocol will be presented to the rest of the research team and they will agree an execution plan. The work team will consist of one main investigator (a psychiatrist) three more psychiatrists, one psychologist and one qualified statistician. The study objectives will be shared, as well as its methods of data collection and the timeline.

Every three months, a coordination meeting will be held and data quality controls will be performed with the aim of evaluating the collected data consistency.

STAGE 3. Participant's recruitment - 12 months (February 2017- January 2018)

It will take place the inclusion of patients from the UHA, until the sample size will be achieved. During the first visit, the information sheet and informed consent will be facilitated to the patients.

The patients' recruitment will be carried out to term until the sample size is completed or the 12 months period ends (where, according to the data available, we can predict we will have all the members needed).

STAGE 4. Data collection – 24 months (February 2017- January 2019)

This stage starts when the first participant is recruited and ends one year after the last patient is included and data is registered in the study database according to the Case Report Form for each participant.

The data will be collected in the appointments between the participants and the health professionals. The psychologist will be in charge of the neuropsychological tests. The professionals will fill out the Case Report Form with all the information recruited from the interviews and the tests.

In order to evaluate participants once every 3 months, after the first evaluation during the hospitalization, the principal investigator will have to schedule the three-monthly visits for all patients in their respective centers, which will coincide as much as possible with one of the visits that patients will have already programmed. Subjects' evaluation will be performed by the several investigators and collaborators, applying the same visits chronogram to all them.

Appointment 1: In this meeting, the patient will answer the questions reflected in the Case Report Form. They will do all the tests of the study except the RSWGcr.
Appointments 2- 7: The PANSS, SAPS, Calgary, Young and SOFAS tests will be done again. The patients will be asked also by the treatment adherence. 7
Appointment 8: all the tests will be answered again, including the RSWGcr.

To avoid sample losses, one week before each appointment, the participant will receive a phone call and a text message that will act as a reminder.

 STAGE 5. Data analysis - 1 month (February 2019)

After processing the database, all data collected will be analyzed by the statistician using the already mentioned methods and using the appropriate software. Firstly, a descriptive and bivariate analysis will be conducted and, secondly, a multivariate analysis using a multiple lineal regression will be performed.

STAGE 6. Results interpretation and final report elaboration - 3 months (March 2019-May 2019)

All the statistical results will be analyzed and interpreted by the investigation team and they will perform the final discussion and conclusions of the study.

STAGE 7. Publication and dissemination - 6 months (June 2019- November 2019)

The final results of this study will be published and disseminated in prestigious scientific journals.
It will be presented to "JAMA Psychiatry", formerly known as "Archives of General Psychiatry".
The results will be then presented in a national specialty congress: "XXIII Congreso Nacional de Psiquiatria".

Chronogram

	2016			2017					2018		2019					
	Sep- Oct	Nov	Dec	Jan	Feb-Apr	May-July	Aug-Oct	Nov-Dec	Jan	Feb-Dec	Jan	Feb	Mar	Apr	May	Jun- Nov
Stage 1																
Study sign up	▓	▓														
Final project design and writing	▓	▓														
CEIC revision and approval		▓														
Stage 2																
Team meetings			▓	▓												
Stage 3																
Patients recruitment					▓	▓	▓	▓	▓							
Stage 4																
Appointments 1- 8					▓	▓	▓	▓	▓	▓						
Team meetings					▓	▓	▓	▓	▓	▓						
Stage 5																
Data analysis												▓				
Stage 6																
Results interpretation													▓	▓		
Final report writing															▓	
Stage 7																
Results publication																▓
Final report dissemination																▓

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12. CLINICAL AND HEALTHCARE IMPACT

People who suffer from schizophrenia have a really heterogeneity in the clinical presentation, that have questioned the utility of the criteria used during a long time, as they cannot be correlated with a common physiopathology and etiology.

This study tries to make a subcharacterization of the patients with schizophrenia according to the presence or the absence of voices arguing and voices commenting hallucinations, and a correlation between them and the neuropsychological changes, to better understand the physiopathology of the schizophrenia.

We know that the alienation delusions (thought withdrawal, thought insertion and thought broadcasting) have a strong correlation with voices arguing and voices commenting hallucinations, as well as we also know that those delusions have a hypofunction of the left frontal and temporal lobe and a hyperfunction of the right parietal lobe (16).

Therefore, from results obtained in this study we are going to do a subgroup into the schizophrenia disorder that will allow us to better understand the physiopathology, so it will be able to paving the way for future new treatment strategies, more specific for the patient.

13. BUDGET

EXPENSES	BUDGET PROPOSAL		
	QUANTITY	COST PER UNIT (€)	COSTS (€)
PERSONAL COSTS			
Investigation team	5 investigators	0 €	0 €
MATERIAL AND SERVICES			
Statistician	120 h	35 €/h	4200 €
Questionnaires, scales, and informed consent	(21 units/participant) X 210 participants	0.20 €/unit	4410 €
PUBLICATION AND DISSEMINATION			
Publication			1000 €
Conferences			
• *Inscription fee*	5 investigators	600 €	3000 €
• *Accommodation*	5 investigators	140 €	700 €
• *Travel*	5 investigators	75 €	375 €
TOTAL			**13.685 €**

Before starting the study it is necessary to ensure the financing.

The psychiatrists and psychologist working for the program will not receive a compensation for their work in this study, as they are employees of the UHA where all the patients are recruited, and the tests and questionnaires done to the subjects are common and useful in the habitual clinical practice.

In the same way, all in personal meetings performed during the whole duration of the study neither suppose additional expenses, because these will be performed in the same HSC.

Finally, all the validated questionnaires and scales that will be applied to patients are available in all centers, meaning that their cost is mainly associated with printing expenses.

14. REFERENCES

1. Owen MJ, Sawa A, Mortensen PB. Schizophrenia. 2016;6736(15):1–12.

2. Joyce EM, Roiser JP. Cognitive heterogeneity in schizophrenia. Curr Opin Psychiatry. 2007;20(3):268–72.

3. Owen MJ. New approaches to psychiatric diagnostic classification. Neuron. 2014;84(3):564–71.

4. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Arlington. 2013. 87-118 p.

5. WHO. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. 1992. 78-79 p.

6. Larøi F. The Phenomenological Diversity of Hallucinations: Some theoretical and clinical implications. Psychol Belg. 2006;46(1–2):163–83.

7. Saddichha S, Kumar R, Sur S, Sinha BN. First rank symptoms: concepts and diagnostic utility. Afr J Psychiatry. 2010;13(February):263–6.

8. Shergill SS, Cameron LA, Brammer MJ, Williams SC, Murray RM, McGuire PK. Modality specific neural correlates of auditory and somatic hallucinations. J Neurol Neurosurg Psychiatry. 2001;71(5):688–90.

9. Carter DM, Mackinnon A, Howard S, Zeegers T, Copolov DL. The development and reliability of the Mental Health Research Institute Unusual Perceptions Schedule (MUPS) : an instrument to record auditory hallucinatory experience. Schizophr Res. 1995;16(2):157–65.

10. Kinderman P. Auditory hallucinations. Tidsskr Nor Psykologforening. 2007;44(5):548–54.

11. Tracy DK, Shergill SS. Mechanisms Underlying Auditory Hallucinations-Understanding Perception without Stimulus. Brain Sci. 2013;3(2):642–69.

12. Pouchet A, Pins D, Ph D, Thomas P, Ph D. in Schizophrenia : A Coordinate-Based Meta-Analysis. :73–81.

13. Palaniyappan L, Balain V, Radua J, Liddle PF. Structural correlates of auditory hallucinations in schizophrenia: A meta-analysis. Schizophr Res. 2012;137(1–3):169–73.

14. Kühn S, Gallinat J. Quantitative meta-analysis on state and trait aspects of auditory

verbal hallucinations in schizophrenia. Schizophr Bull. 2012;38(4):779–86.

15. Fletcher PC, Frith CD. Perceiving is believing: a Bayesian approach to explaining the positive symptoms of schizophrenia. Nat Rev Neurosci. 2009;10(1):48–58.

16. Serrano D. Fenotips delirants en pacients amb esquizofrènia: carecterització clínica i evolució als 6 mesos. Universitat Autònoma de Barcelona; 2016.

17. Cutting J. First rank symptoms of schizophrenia: their nature and origin. Hist Psychiatry. 2015;26(2):131–46.

18. Taylor MA, E B, L B, Bellak L, Hurvich M, Gediman H et al, Robins E GS, K S, et al. Schneiderian First-Rank Symptoms and Clinical Prognostic Features in Schizophrenia. Arch Gen Psychiatry. 1972 Jan 1;26(1):64.

19. Kendell RE, Brockington IF, Leff JP, CG H, Reid JR FJ, Feighner JP, Robins E, Guze SB et al, et al. Prognostic Implications of Six Alternative Definitions of Schizophrenia. Arch Gen Psychiatry. 1979 Jan 1;36(1):25.

20. Thorup A, Petersen L, Jeppesen P, Nordentoft M. Frequency and predictive values of first rank symptoms at baseline among 362 young adult patients with first-episode schizophrenia. Schizophr Res. 2007 Dec;97(1–3):60–7.

21. Rosen C, Grossman LS, Harrow M, Bonner-Jackson A, Faull R. Diagnostic and prognostic significance of Schneiderian first-rank symptoms: A 20-year longitudinal study of schizophrenia and bipolar disorder. Compr Psychiatry. 2011;52(2):126–31.

22. David AS. The cognitive neuropsychiatry of auditory verbal hallucinations: an overview. Cogn Neuropsychiatry. 2004;9(1–2):107–23.

23. Stephane M, Kuskowski M, McClannahan K, Surerus C, Nelson K. Evaluation of inner-outer space distinction and verbal hallucinations in schizophrenia. Cogn Neuropsychiatry. 2010 Sep;15(5):441–50.

24. Shinn AK, Heckers S, Öngür D. The special treatment of fi rst rank auditory hallucinations and bizarre delusions in the diagnosis of schizophrenia. Schizophr Res. 2013;146(1–3):17–21.

25. O'Daly OG, Frangou S, Chitnis X, Shergill SS. Brain structural changes in schizophrenia patients with persistent hallucinations. Psychiatry Res - Neuroimaging. 2007;156(1):15–21.

26. Shapleske J, Rossell SL, Chitnis XA, Suckling J, Simmons A, Bullmore ET, et al. A

computational morphometric MRI study of schizophrenia: effects of hallucinations. Cereb Cortex. 2002 Dec;12(12):1331–41.

27. Andreasen NC. Scale for the Assessment of Positive Symptoms (SAPS). Iowa City: Univerity of Iowa; 1984.

28. Kay SR, Fiszbein A OL. The Positive and Negative Syndrome Scale for schizophrenia. Schizophr Bull. 1987;13(2):261–76.

29. Hill BD, Elliott EM, Shelton JT, Pella RD, O'Jile JR, Gouvier WD. Can we improve the clinical assessment of working memory? An evaluation of the Wechsler Adult Intelligence Scale-Third Edition using a working memory criterion construct. J Clin Exp Neuropsychol. 2010;32(3):315–23.

30. Addington D, Addington J, Atkinson M. A psychometric comparison of the Calgary Depression Scale for Schizophrenia and the Hamilton Depression Rating Scale. Schizophr Res. 1996;19(2–3):205–12.

31. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry. 1978 Nov;133:429–35.

32. Andreasen NC, Carpenter WT, Kane JM, Lasser RA, Marder SR, Weinberger DR. Remission in schizophrenia: Proposed criteria and rationale for consensus. Am J Psychiatry. 2005;162(3):441–9.

33. Morosini PL, Magliano L, Brambilla L, Ugolini S, Pioli R. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. Acta Psychiatr Scand. 2000;101(4):323–9.

15. APPENDICES

Appendix 1: Information sheet and informed consent

FULL D'INFORMACIÓ AL PACIENT

Benvolgut/a,

Li agraim molt el seu interès en participar en aquest estudi. Abans d'acabar de decidir si desitja participar-hi, és important que entengui perquè es vol dur a terme aquesta recerca i que involucrarà. Si us plau, llegeixi detingudament la informació següent i pregunti a l'investigador si hi ha alguna cosa que no li queda clara o si necessita més informació.

Títol de l'estudi:

Veus que comenten i veus que conversen: característiques neuropsicològiques i evolució dels pacients. Estudi longitudinal de seguiment a 12 mesos.

Propòsit de l'estudi

L'esquizofrènia és un trastorn molt heterogeni amb una gran varietat de presentacions clíniques així com també en l'evolució.

Alguns dels símptomes més característics de l'esquizofrènia són els deliris i les al·lucinacions, entre d'altres. S'ha vist que hi ha una gran relació entre la presència de deliris d'alienació (robatori del pensament, inserció l pensament, difusió del pensament) i les al·lucinacions en forma de veus que comenten i veus que conversen.

Amb aquest estudi es vol investigar si els pacients amb veus que conversen i veus que comenten presenten les mateixes alteracions a nivell cerebral que els pacients que presenten deliris d'alienació. Així com també comprovar si els pacients amb aquest tipus d'al·lucinacions presenten diferències a nivell de l'evolució clínica.

En què consistirà la meva participació?

Els pacients seran entrevistats en el moment que entrin a l'estudi, per tal d'elaborar una història clínica (antecedents personals i familiars) i fer una avaluació psiquiàtrica completa. Per fer aquesta avaluació, cada participant haurà de respondre una sèrie de qüestionaris que seran proporcionats i avaluats per l'equip mèdic. Aquesta primera fase es realitzarà a l'Hospital Santa Caterina, mentre que els participants estan ingressats a la Unitat d'Hospitalització d'Aguts.

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En els següents 12 mesos, els participants tindran una visita mensual amb el seu psiquiatre. Aquestes visites coincidiran amb algunes de les visites habituals que cada pacient ja tingui concertada amb el seu psiquiatre, independentment de si hagués entrat o no a l'estudi. Durant aquesta visita mensual, els pacients hauran de respondre també algun qüestionari com ho van fer a l'inici de l'estudi.

Confidencialitat:

Les dades personals dels participants són totalment confidencials, d'acord amb la Llei Orgànica 15/1999 de 13 de desembre, de Protecció de Dades de Caràcter Personal. Només tindran accés a aquestes dades l'equip investigador i personal autoritzat.

Per més informació:

En cas de dubte, o si desitja més informació podrà parlar amb el principal investigador, el qual li proporcionarà un contacte el dia de la primera entrevista.

Participació voluntària:

La participació en aquest estudi és voluntària. Vostè pot decidir si vol o no formar part d'aquest treball.

Després de firmar aquest document és igualment lliure de sortir de l'estudi en qualsevol moment sense haver de donar cap explicació. Sortir de l'estudi no afectarà de cap manera la relació amb els psiquiatres i psicòlegs de la unitat. Si decideix sortir de l'estudi abans de que l'acabi la recol·lecció de dades, les seves dades li seran retornades o seran destruïdes.

FULL DE CONSENTIMENT INFORMAT

Jo (nom i cognoms): _____

- He llegit detingudament i he entès tot el full d'informació que se m'ha entregat, i he tingut la oportunitat de fer preguntes.

- L'entrevistador m'ha explicat de manera detinguda tot el procediment.

- Entenc quin serà el meu paper com a participant a l'estudi.

- Entenc que les meves dades seran tractades d'una manera estrictament confidencial.

- Entenc que la meva participació a l'estudi és voluntària i que en qualsevol moment puc abandonar-lo sense haver de donar cap explicació.

Per tant, accepto voluntàriament participar en l'estudi "Veus que comenten i veus que conversen: característiques neuropsicològiques i evolució dels pacients. Estudi longitudinal de seguiment a 12 mesos".

Signatura del participant o tutor/s legal/s   Signatura de l'entrevistador

_____   _____

Girona, _____ de _____ del 201 __

Appendix 2: Case report form

CASE REPORT FORM

Patient number: _____

SOCIODEMOGRAPHIC FEATURES (fill-up only in the first meeting)

- Birth date: _____ / _____ / _____

- Gender: Male ☐   Female ☐

- Education:

  Less than highschool ☐   Highschool degree ☐

  College degree ☐   Graduate degree ☐

- Marital status:

  Married ☐   In a partnership ☐   Single ☐

  Separated ☐   Divorced ☐   Widowed ☐

- Employment status:

  Employed ☐   Unemployed ☐

  Student ☐   Retired ☐

- Ethnic group:

  Caucasian ☐   Black ☐   "Latino" ☐

  Asian ☐   Others ☐

CLINICAL FEATURES

- Intelligence quotient (WAIS):_____ (fill-up only in the first meeting)

- Substance consumption: Yes ☐   Not ☐

- Age at the diagnoses of schizophrenia: _____

- Years from the diagnoses of schizophrenia: _____

- First episode: Yes ☐   Not ☐

- Previous treatment: Yes ☐   Not ☐

- Adherence to treatment:

  0% ☐   0-25% ☐   25-50% ☐

  50-75% ☐   75-100% ☐   100% ☐

- PANSS score: _____

- Presence of voices arguing and voices commenting hallucinations: Yes ☐   Not ☐

- Presence of auditory hallucinations: Yes ☐   Not ☐

- Calgary scale score: _____

- Young scale score: _____

- SOFAS score:_____(fill-up only in the first and last meeting)

- RSWG score:_____(fill-up only in the last meeting)

- WAIS-III results: (fill-up only in the first and last meeting)

  <u>Verbal comprehension</u>:

  Vocabulary score: _____   Similarities:_____

  Information: _____   Comprehension: _____

  <u>Working memory</u>:

  Arithmetic: _____   Digit span: _____

  Letter-number sequencing: _____

  <u>Perceptual reasoning</u>:

  Picture completion: _____   Block design: _____

  Matrix reasoning: _____

  <u>Processing speed</u>:

  Digit-symbol coding: _____   Symbol search: _____

  Picture arrangement: _____

Appendix 3: Scale for the Assessment of Positive Symptoms (SAPS)

| 0=None | 1=Questionable | 2=Mild | 3=Moderate | 4=Marked | 5=Severe |

1-12 dupl

0. CARD NUMBER [_ _] 13-14

1. HALLUCINATIONS

1 **Auditory Hallucinations** [_] 15
The patient reports voices, noises, or other sounds that no one
else hears.

2 **Voices commenting** [_] 16
The patient reports a voice which makes a running commentary
on his behavior or thoughts.

3 **Voices Conversing** [_] 17
The patient reports hearing two or more voices conversing.

4 **Somatic or Tactile Hallucinations** [_] 18
The patient reports experiencing peculiar physical sensations in the body.

5 **Olfactory Hallucinations** [_] 19
The patient reports experiencing unusual smells which no one
else notices.

6 **Visual Hallucinations** [_] 20
The patient sees shapes or people that are not actually present.

7 **Global Rating of Hallucinations** [_] 21
This rating should be based on the duration and severity of the
hallucinations and their effects on the patient's life.

2. DELUSIONS

8 **Persecutory Delutions** [_] 22
The patient believes he is being conspired against or persecuted
in some way.

9 **Delusions of Jealousy** [_] 23
The patient believes his spouse is having an affair with
someone.

10 **Delusions of Guilt or Sin** [_] 24
The patient believes that he has committed some terrible sin or
done something unforgivable.

11 **Grandiose Delusions** [_] 25
The patient believes he has special powers or abilities.

| 0=None | 1=Questionable | 2=Mild | 3=Moderate | 4=Marked | 5=Severe |

12 **Religious Delusions**   [_]   26
The patient is preoccupied with false beliefs of a religious nature.

13 **Somatic Delusions**   [_]   27
The patient believes that somehow his body is diseased,
abnormal, or changed.

14 **Delusions of Reference**   [_]   28
The patient believes that insignificant remarks or events refer
to him or have special meaning.

15 **Delusions of Being Controlled**   [_]   29
The patient feels that his feelings or actions are controlled by
some outside force.

16 **Delusions of Mind Reading**   [_]   30
The patient feels that people can read his mind or know his thoughts.

17 **Thought Broadcasting**   [_]   31
The patient believes that his thoughts are broadcast so that he
himself or others can hear them.

18 **Thought Insertion**   [_]   32
The patient believes that thoughts that are not his own have
been inserted into his mind.

19 **Thought Withdrawal**   [_]   33
The patient believes that thoughts have been taken away from
his mind.

20 **Global Rating of Delusions**   [_]   34
This rating should be based on the duration and persistence of
the delusions and their effect on the patient's life.

3. BIZARRE BEHAVIOR

21 **Clothing and Appearance**   [_]   35
The patient dresses in an unusual manner or does other strange
things to alter his appearance.

22 **Social and Sexual Behavior**   [_]   36
The patient may do things considered inappropriate according
to usual social norms (e.g., masturbating in public).

23 **Aggressive and Agitated Behavior**   [_]   37
The patient may behave in an aggressive, agitated manner,
often impredictably.

0=None	1=Questionable	2=Mild	3=Moderate	4=Marked	5=Severe

24 **Repetitive or Stereotyped Behavior**
The patient develops a set of repetitive actions or rituals that he
must perform over and over.   [_] 38

25 **Global Rating of Bizarre Behavior**
This rating should reflect the type of behavior and the extent to
which it deviates from social norms.   [_] 39

4. POSITIVE FORMAL THOUGHT DISORDER

26 **Derailment**
A pattern of speech in which ideas slip off track onto ideas
obliquely related or unrelated.   [_] 40

27 **Tangentiality**
The patient replies to a question in an oblique or irrelevant manner. [_] 41

28 **Incoherence**
A pattern of speech that is essentially incomprehensible at times.   [_] 42

29 **Illogicality**
A pattern of speech in which conclusions are reached that do
not follow logically.   [_] 43

30 **Circumstantiality**
A pattern of speech that is very indirect and delayed in
reaching its goal idea.   [_] 44

31 **Pressure of Speech**
The patient's speech is rapid and difficult to interrupt; the amount
of speech produced is greater than that considered normal.   [_] 45

32 **Distractible Speech**
The patient is distracted by nearby stimuli which interrupt his
flow of speech.   [_] 46

33 **Changing**
A pattern of speech in which sounds rather than meaningful
relationships govern word choice.   [_] 47

34 **Global Rating of Positive Formal Thought Disorder**
This rating should reflect the frequency of abnormality and the
extent to which this affects the patient's ability to communicate.   [_] 48

Appendix 4: Positive and Negative Symptoms Scale (PANSS)

ESCALA DE LOS SINDROMES POSITIVO Y NEGATIVO (PANSS)
Adaptación española de V. Peralta y M. J. Cuesta

Nombre del paciente _____ Número _____
Entrevistador _____ Periodo de observación _____ Fecha _____

	A	D	L	M	MS	S	E
SINDROME POSITIVO (PANSS-P)							
1. Delirios	1	2	3	4	5	6	7
2. Desorganización	1	2	3	4	5	6	7
3. Comportamiento alucinatorio	1	2	3	4	5	6	7
4. Excitación	1	2	3	4	5	6	7
5. Grandiosidad	1	2	3	4	5	6	7
6. Suspicacia/perjuicio	1	2	3	4	5	6	7
7. Hostilidad	1	2	3	4	5	6	7
SINDROME NEGATIVO (PANSS-N)							
1. Embotamiento afectivo	1	2	3	4	5	6	7
2. Retraimiento afectivo	1	2	3	4	5	6	7
3. Contacto pobre	1	2	3	4	5	6	7
4. Retraimiento social	1	2	3	4	5	6	7
5. Dificultad en el pensamiento abstracto	1	2	3	4	5	6	7
6. Ausencia de Espont. y fluidez en la conversación	1	2	3	4	5	6	7
7. Pensamiento estereotipado	1	2	3	4	5	6	7
PSICOPATOLOGÍA GENERAL (PANSS-PG)							
1. Preocupaciones somáticas	1	2	3	4	5	6	7
2. Ansiedad	1	2	3	4	5	6	7
3. Sentimientos de culpa	1	2	3	4	5	6	7
4. Tensión motora	1	2	3	4	5	6	7
5. Manierismos y posturas	1	2	3	4	5	6	7
6. Depresión	1	2	3	4	5	6	7
7. Retardo motor	1	2	3	4	5	6	7
8. Falta de colaboración	1	2	3	4	5	6	7
9. Inusuales contenidos del pensamiento	1	2	3	4	5	6	7
10. Desorientación	1	2	3	4	5	6	7
11. Atención deficiente	1	2	3	4	5	6	7
12. Ausencia de juicio e "introspección"	1	2	3	4	5	6	7
13. Trastornos de la volición	1	2	3	4	5	6	7
14. Control deficiente de impulsos	1	2	3	4	5	6	7
15. Preocupación	1	2	3	4	5	6	7
16. Evitación social activa	1	2	3	4	5	6	7

Hoja de puntuación de la PANSS (continuación)

Appendix 5: Weschler Adult Intelligence Scale III (WAIS-III).

Appendix 6: Young Mania Rating Scale (YMRS)

Young Mania Rating Scale (YMRS)

GUIDE FOR SCORING ITEMS:

The purpose of each item is to rate the severity of that abnormality in the patient. When several keys are given for a particular grade of severity, the presence of only one is required to qualify for that rating.

The keys provided are guides. One can ignore the keys if that is necessary to indicate severity, although this should be the exception rather than the rule.

Scoring between the points given (whole or half points) is possible and encouraged after experience with the scale is acquired. This is particularly useful when severity of a particular item in a patient does not follow the progression indicated by the keys.

1. **Elevated Mood**
   0 Absent
   1 Mildly or possibly increased on questioning
   2 Definite subjective elevation; optimistic, self-confident; cheerful; appropriate to content
   3 Elevated; inappropriate to content; humorous
   4 Euphoric; inappropriate laughter; singing

2. **Increased Motor Activity-Energy**
   0 Absent
   1 Subjectively increased
   2 Animated; gestures increased
   3 Excessive energy; hyperactive at times; restless (can be calmed)
   4 Motor excitement; continuous hyperactivity (cannot be calmed)

3. **Sexual Interest**
   0 Normal; not increased
   1 Mildly or possibly increased
   2 Definite subjective increase on questioning
   3 Spontaneous sexual content; elaborates on sexual matters; hypersexual by self-report
   4 Overt sexual acts (toward patients, staff, or interviewer)

4. **Sleep**
   0 Reports no decrease in sleep
   1 Sleeping less than normal amount by up to one hour
   2 Sleeping less than normal by more than one hour
   3 Reports decreased need for sleep
   4 Denies need for sleep

5. **Irritability**
   0 Absent
   2 Subjectively increased
   4 Irritable at times during interview; recent episodes of anger or annoyance on ward
   6 Frequently irritable during interview; short, curt throughout
   8 Hostile, uncooperative; interview impossible

6. **Speech (Rate and Amount)**
   - 0 No increase
   - 2 Feels talkative
   - 4 Increased rate or amount at times, verbose at times
   - 6 Push; consistently increased rate and amount; difficult to interrupt
   - 8 Pressured; uninterruptible, continuous speech

7. **Language-Thought Disorder**
   - 0 Absent
   - 1 Circumstantial; mild distractibility; quick thoughts
   - 2 Distractible, loses goal of thought; changes topics frequently; racing thoughts
   - 3 Flight of ideas; tangentiality; difficult to follow; rhyming, echolalia
   - 4 Incoherent; communication impossible

8. **Content**
   - 0 Normal
   - 2 Questionable plans, new interests
   - 4 Special project(s); hyper-religious
   - 6 Grandiose or paranoid ideas; ideas of reference
   - 8 Delusions; hallucinations

9. **Disruptive-Aggressive Behavior**
   - 0 Absent, cooperative
   - 2 Sarcastic; loud at times, guarded
   - 4 Demanding; threats on ward
   - 6 Threatens interviewer; shouting; interview difficult
   - 8 Assaultive; destructive; interview impossible

10. **Appearance**
    - 0 Appropriate dress and grooming
    - 1 Minimally unkempt
    - 2 Poorly groomed; moderately disheveled; overdressed
    - 3 Disheveled; partly clothed; garish make-up
    - 4 Completely unkempt; decorated; bizarre garb

11. **Insight**
    - 0 Present; admits illness; agrees with need for treatment
    - 1 Possibly ill
    - 2 Admits behavior change, but denies illness
    - 3 Admits possible change in behavior, but denies illness
    - 4 Denies any behavior change

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Appendix 7: Social and occupational functioning scale (SOFAS)

Escala de evaluación de la actividad social y laboral (EEASL)

La actividad social y laboral debe considerarse dentro de un espectro continuo que va desde un nivel excelente a un deterioro evidente y completo. Debe incluirse el deterioro debido a impedimentos físicos o a trastornos mentales siempre y cuando causa y efecto estén relacionados directamente. No se consideran los efectos derivados de la falta de oportunidades o de otras limitaciones ambientales.

Código (**Nota:** Deben utilizarse los códigos intermedios cuando sea posible, p. ej., 45, 68, 72)

100	Actividad superior en un amplio abanico de actividades.
91	
90	Actividad buena y efectiva en todas las áreas.
81	
80	Ligero deterioro de la actividad social, laboral o escolar (p. ej., conflictos interpersonales poco frecuentes, retrasos escolares transitorios).
71	
70	Algunas dificultades en la actividad social, laboral o escolar, aunque en líneas generales puede considerarse correcta; el individuo mantiene algunas relaciones interpersonales significativas.
61	
60	Moderadas dificultades en la actividad social, laboral o escolar (p. ej., pocos amigos, conflictos con colegas o colaboradores).
51	
50	Seria afectación de la actividad social, laboral o escolar (p. ej., no tiene amigos, le resulta difícil mantener un empleo).
41	
40	Deterioro importante en diversas áreas, por ejemplo, las relaciones laborales, escolares o familiares (p. ej., el hombre deprimido que evita a sus amigos, se muestra negligente con la familia y es incapaz de obtener un empleo; el niño que se pelea frecuentemente con otros más pequeños, se muestra contestatario en casa y fracasa en el colegio).
31	
30	Incapaz de actividad en la mayor parte de las áreas (p. ej., se pasa el día en la cama; no tiene trabajo, casa ni amigos).
21	
20	A veces no puede mantener la mínima higiene personal y es incapaz de vivir de forma independiente.
11	
10	Incapacidad permanente para mantener la mínima higiene personal. No puede hacer nada sin perjudicarse a sí mismo o a los demás o sin una dosis considerable de apoyo externo (p. ej., cuidado y supervisión de una enfermera).
1	
0	Información inadecuada.