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Functional brain correlates of auditory verbal hallucinations in schizophrenia: a design of an fMRI study testing perceptual and cognitive models.

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ABSTRACT

Auditory verbal hallucinations (AVHs, or ‘hearing voices’) are a cardinal symptom of schizophrenia, and yet, their biological basis has not been fully determined. As of now, theories that attempt to disentangle the origins of AVHs can be separated into two main types (or models): perceptual *versus* cognitive. The former has considered AVHs to be due to malfunction in perceptual processing, namely an abnormal activation in the auditory cortex, as well as having a top-down cognitive influence. The latter considers AVHs to be due to one of two cognitive processes: the misinterpretation of intrusive memories (which posit that AVHs are the result of a breakdown in the processes monitoring the source of memories) or to the malfunction of inner speech (which posits that AVHs are due to dysfunction of speech monitoring). The current study aims to propose an adequate experimental design of a prospective fMRI study that will test both the perceptual and cognitive approaches allowing to fill the gaps in the general framework for AVHs. Firstly, to test the perceptual model, an experimental design borrowed from Fuentes-Claramonte and colleagues (2021) will be adapted, with a modification controlling for motor activity. To test one side of the Cognitive Model, the theory of intrusive memory, the experimental paradigm that has been created by Fuentes-Claramonte and colleagues (2019) and validated by Martin-Subero and colleagues (2021) will be adapted to test *schizophrenic patients with AVHs*, which has not been done before. It will elicit negatively valenced autobiographical memories, which has been shown to activate parts of the default mode network, a circuit thought to be impaired in schizophrenia. Thirdly, to test the other side of the Cognitive Model, namely the theory of inner speech, an experimental paradigm will be proposed called the Rhyming task, a phonological encoding task that is known to activate brain regions involved in subvocal rehearsal and short-term storage of information. However, because the stimuli for this task is lacking for the Spanish population, a pilot study (an online survey) was conducted, presenting healthy participants with pairs of objects (created partly from a personalized corpus), and asked them to do three tasks: to decide whether the names of both objects rhyme; provide the name of each object; and rate the object on a 1 to 5 Likert scale for the purposes of determining emotional valence. The results of the pilot study guided the selection of the appropriate stimuli for the prospective imaging study. The proposed fMRI study tackles the biological basis of AVHs from different perspectives, helping to improve patients' lives that are touched by this cardinal symptom, and thus enabling future research to sculpt appropriate clinical intervention thanks to pinpointing the exact biological basis of hearing voices.

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“We all carry the seeds of greatness within us, but we need an image as a point of focus in order that they may sprout.”

Epictetus as interpreted by Lebell (2007, p. 95).

Such “images as a point of focus” play the most important role in one’s life, as without them one is made up of missing pieces – and I am lucky enough to have a few that watered my seeds for them to sprout.

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To my family: you have given me many fruits: those of perseverance, faith, strength, and without your most cherished one, constant support, I would not be here today. Although it seems that words cannot express the depth of my gratitude, it is still through language that I hope to try to meet you on the bridge to your heart: *Dziękuję wam bardzo za wszystko*¹.

To my beloved father - the lighthouse that always guided me to the shore: your light shall be eternally missed. *This thesis is dedicated to you.*

¹ Polish to English translation: *Thank you so much for everything.*



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ABBREVIATIONS

ACC	Anterior Cingulate Cortex
ALE	Activation Likelihood Estimation
AM	Autobiographical Memory
AMI	Autobiographical Memory Interview
AVH	Auditory Verbal Hallucination
BOLD	Blood Oxygen Level Dependent
DMN	Default Mode Network
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
EEG	Electroencephalography
EMG	Electromagnetic
fMRI	Functional Magnetic Resonance Imaging
GLM	General Linear Models
IQ	Intelligence Quotient
MTG	Middle Temporal Gyrus
MTL	Medial Temporal Lobe
PAC	Primary Auditory Cortex
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PTSD	Post-Traumatic Stress Disorder
ROI	Region of Interest
SD	Standard Deviation
SMA	Supplementary Motor Area
STG	Superior Temporal Gyrus
VH	Visual Hallucination

1. INTRODUCTION

“Always deters me from the course of action I was intending to engage in, but it never gives me positive advice.”

*Socrates on his purported auditory verbal hallucinations
as told by Plato (Long, 2009, p. 64)*

Hearing voices, or experiencing auditory verbal hallucinations (AVHs), is one of the main symptoms of schizophrenia, and occurs in about 70% of patients (David, 1999; McCarthy-Jones, 2012). Despite its clinical significance, the biological basis underlying AVHs is undetermined, and the findings portrayed by scientific literature remain inconclusive till this day.

The present multidisciplinary framework (from Psychiatry to Cognitive Science) has mainly taken two approaches to explain the origins of AVHs.

The first approach proposes that hallucinations appear as a result of *abnormal activity* in the primary auditory cortex, the brain region that processes auditory perception, leading to the perception of these voices that characterize the symptom. This theory has received mixed experimental support, as some single studies and meta-analyses have found activation in the auditory cortex during AVHs (Dierks et al., 1999, Lennox et al., 1999; Kompus et al., 2011), while others have not (Silbersweig et al., 1995; Lennox et al., 2000; Copolov et al., 2003; Diederer et al. 2010; Hoffman et al., 2011; Fuentes-Claramonte et al. 2021; Jardri et al., 2011; Kühn and Gallinat, 2012); Zmigrod et al., 2016).

The second approach proposes that hallucinations arise from two distinct cognitive processes. The first is a theory of the misinterpretation of *intrusive or traumatic memories*, which posits that AVHs are due to the malfunction in “the processes monitoring the source of memories” (Seal et al., 2004, p. 53). The second is a theory on *the malfunction in inner speech*, particularly *short-term verbal memory*. However, as of now, there are very few studies that have attempted to test this model, and thus a complete answer is still lacking.

For these exact reasons, the current study aims to establish the building blocks needed to test the biological basis of AVHs in a prospective fMRI study. This shall be done in the following way.

Firstly, I will embark upon a review of the available literature by briefly diving into the phenomenological basis of AVHs, where I look at the structure and content of such hallucinations. Next, I outline how such studies on AVHs are conducted, by explaining different design approaches and focusing on one technique in particular, known as the ‘symptom capture’ technique, which compares brain states or activation patterns in periods of time when a schizophrenic patient hallucinates and when said patient does not.

Once this brief background is provided, I then elaborate on the methodology and findings of individual studies and meta-analyses that have targeted *the Perceptual Model*. Throughout my review, I will show that studies which have implemented the symptom capture technique have mixed findings with regards to the genesis of brain activation whilst schizophrenic patients experience AVHs. Because of this factor, we propose implementing an experimental paradigm, *the Symptom Capture Paradigm*, which has been formulated by Fuentes-Claramonte and colleagues (2021). Essentially, patients are to indicate when they experience AVHs by pressing a button with their right index finger, and they are also to indicate when they perceive real speech by pressing a button with their left index finger. Numerous previous studies have been posed with some limitations, one in particular being the confounding effect of motor activity on brain activation during AVHs. To counteract this limitation, we propose a modification that controls motor activity by asking participants to press two buttons with both their index fingers when they are not experiencing AVHs. In this way, the influence of motor activity during button press will be nullified.

Following this, I move to *the Cognitive Model*, where I begin by discussing the two dominant theories: the misinterpretation of intrusive or traumatic memories, and the malfunction of inner speech. I provide a theoretical background for both by reviewing a handful of available studies that have attempted to test this particular model. For each cognitive theory, we propose an experimental paradigm. For the former theory, we propose implementing the *Autobiographical Recall Task*, an experimental paradigm created by Fuentes-Claramonte and colleagues (2019) and validated by Martin-Subero and colleagues (2021). It tests whether there are any alterations linked to hallucinations and the intrusiveness of traumatic memories. For the latter theory, I will focus on the

Rhyming Task, which involves internal speech, in which subjects must determine whether two words rhyme or not. As this task involves processes of phonological coding that involve internal speech and short-term verbal memory, it can test whether there are inner speech alterations linked to hallucinations, namely whether patients with hallucinations experience an altered processing of inner speech, or if there is alteration in brain activation in the inner speech task whilst patients are experiencing AVHs. It is worth noting, however, that because no previous study has used rhyming pairs in Spanish, this pilot study attempts to design this stimuli.

For this reason, I focus on the design of the above-mentioned Rhyming Task in Section 3, and explain how we created and validated the stimuli, as well as providing the chosen stimulus pairs that will be used in the prospective fMRI study.

In the last Section, I end with a discussion and conclusions on the prospective fMRI study as well as the pilot study by pointing out the advantages and potential limitations of both the prospective fMRI study and pilot study, as well as the possible direction of future research and our speculation.

With all that in consideration, only by first thoroughly building a set of foundations, specifically the experimental design that will take AVHs apart, can the presence of heard illusory voices be ultimately understood as being due to abnormal auditory activity, intrusive or traumatic memories or alterations in inner speech. By identifying the basis of AVHs, the key can be found to designing new treatments, such as neuromodulation techniques, aimed at acting on the precise brain areas involved - therefore having a direct impact on this symptom. Thanks to this, the development of interventions to treat a specific symptom or set of symptoms is a further step towards personalized medicine which, in a disease as heterogeneous as schizophrenia, is imperative in adjusting treatments to the needs of each patient. All this is endeavored so that the maximum clinical improvement is obtained, minimizing potential health risks and other adverse effects.

2. LITERATURE REVIEW

2.1. The Phenomenological Basis of AVHs

From figures like Socrates to Sigmund Freud, auditory verbal hallucinations (AVHs) do not spare anyone on their warpath. Following contemporary psychiatric classifications, AVHs are considered a characteristic symptom of a range of psychotic and mood disorders as in, for instance, schizophrenia (McCarthy-Jones, 2012). This particularly disabling mental disorder comprises “a collection of signs and symptoms of unknown aetiology, predominantly defined by observed signs of psychosis” (Insel, 2010, p. 187). Although the peak onset age of schizophrenia is said to be in early adulthood (Li et al., 2009), only recently has it been considered as a neurodevelopmental disorder (Insel, 2010). When considering AVHs in schizophrenia, the first question that arises is regarding their phenomenological basis. In order to cover some explanatory ground, here is a demonstration of a few examples of AVHs:

Example (1): “You're not crazy, she tells me. *I* love you, she tells me. You're going to change the world, she tells me (laughs). You really don't believe me, she tells me. It's weird but it's like that, she tells me. Jose, she tells me again. I have always loved you. Don't be ashamed. You have them all freaking out. Jose, again, repeats a little, you know? Really, even if you don't believe me.” [Transcription of a patient's AVHs by Tovar et al., (2019)]

Example (2): “*You* killed your father and you want to kill your sister, you want to stay in power, you want to kill your mother, you want to hurt everyone around you. Because you're bad, you're cruel. You are a very bad person (...) You're disgusting. You want to take power. You want to kill everyone. You want to destroy the whole world” [Transcription of a patient's AVHs by Tovar et al., (2019)]

Example (3): “*He* is an astronomy fanatic. Here is a taste of his own medicine. He is getting up now. He is going to wash. It is about time” - “ [Transcription of a patient's AVHs by Frith (1992, p. 66)].

AVHs are also considered to be “perceptual experiences that occur in the absence of a triggering external sensory stimulus” and are “perceived to originate from another

agency” (Hugdahl et al., 2008, p. 2; Waters et al., 2006, p. 66; Woodruff, 2004; Nayani & David, 1996). Thus, *Examples (1) - (3)* of AVHs must not be thought of as the individual’s imagination running wild, but as significant elements of their realities of the world that accompany them every step of their way.

In most cases, AVHs are perceived as human voices external to the individual, spoken most commonly in second-person, as seen in *Examples (1) and (2)*, or in third-person, as seen in *Example (3)* (Tovar et al., 2019; McCarthy-Jones, 2012). In other instances, AVHs have been said to be “more like ideas than external sensations”, “soundless voices, absolutely silent and could not be heard” (McCarthy-Jones, 2012, p. 108). It must be underlined, however, that schizophrenic patients *do not* tend to confuse AVHs with the voices of real individuals or of their own thoughts (McCarthy-Jones, 2012; Mullen, 1997; Hoffman et al., 2008). What is more, the vocalizations of these hallucinations may be clear, mumbling, whisper-like, or shouting, and their location variable — coming to the patient internally (i.e. located in the brain, body, belly, feet), externally, or both (McCarthy-Jones, 2012; Nayani & David, 1996; Moritz & Laroi, 2008; Copolov et al., 2004). The number of voices depends on the patient, ranging from only hearing a single voice to a multitude of them (Tovar et al., 2019; Nayani & David, 1996; McCarthy-Jones, 2012). Furthermore, the content of such voices is diffuse and can range from being very positive, such as in *Example (1)*, to being very negative, such as in *Example (2)* in terms of valence, and said voices can discuss a range of topics, such as in *Example (3)*.

Based on *Examples (1) - (3)*, it can be said that these voices have a distinctive linguistic profile. A recent study by Tovar and colleagues (2019) explored the formal linguistic aspects of AVHs in 18 patients with either schizophrenia or schizo-affective disorder. The first fundamental factor found was that ‘voice talk’ is on a *personal level*, whereby “speech participants or other objects of the immediate context are the subject of the utterance” rather than on an *impersonal level*, whereby voices describe “facts about the world relatively independent of the speech content” (Tovar et al., 2019, p. 8). For instance, in *Example (2)* the voices speak of the patient, their mother, and “everyone around them”. Thus, AVHs mostly concern aspects of the patient’s life that are ‘close to home’, as opposed to external world events. Furthermore, the authors (2019) also discovered that their voice sample encompassed parataxis, which is “language with a strong tendency to be reduced to the single sentence level, lacking connectivity and embedding” as exemplified in *Example (1)*: “[Don't be ashamed.] [You have them all

freaking out.] (...) [Really, even if you don't believe me]”. In addition, the content of “voice talk” is normally noted to be free of semantic or syntactic error, which may be due to “the low grammatical complexity of such speech” as seen in all the above-mentioned examples (Tovar et al., 2019, p. 15). As such, the details of the phenomenology of AVHs do not just concern the content of what patients hear, but also the linguistic profile of hearing voices as well, which should always be considered in analysis, as there is much more to consider than is immediately apparent.

On another note, even though it has been mentioned that the voice-hearer can separate the voices from the real world, they can have properties which make them seem to have their own sense of agency that is separate from the patient’s intentions (McCarthy-Jones, 2012). There are instances in which voices are in pursuit of self-preservation and try to persuade the patient, for example, to avoid antipsychotic medication, collaboration in treatment and other forms of aid. At times, if the patient refuses to comply with their commands, the voices bully them. As a result of this process, there is a variability in the degree of command that patients have over the voices, and consequently patients are, at times, engaged in battles of power or dominance. Such a push-and-pull relationship is demonstrated in the following examples:

Example (4): “It makes me feel like a Spanish fly. It makes me feel bad. I could not block them out. There was not anything I could do about it. They make me feel bad just the same” (Modell, 1958, p. 451).

Example (5): “I did not know but I did not want to listen. It was just the sound of a certain person’s voice that gave me pleasure. I was scared when it all first started so I was trying to blank them out and I kept pushing them back because I did not want to hear them. I just did not want to and I kept blocking my ears. I was scared. I really was” (Modell, 1958, p. 452).

Example (6): “When I make mistakes she is right with me. She (*voice 1*) gets too impatient with me, and I try to figure out something all by myself. I am trying to make a clothespin apron, and she is right there with me and she is trying to tell me what to do. The fellow (*voice 2*) leaves me alone. She is a little but too overanxious. I want to be left alone. If I asked her for help, it would be different but I do not want her bothering me” (Modell, 1958, p. 452).

Based on these examples, it can be stated without any doubt that the voices which the patient experiences are *not* imagined, but instead are abnormal perceptions - a part of their reality, which reflects the inherent subjectiveness of the situation. This in turn

precisely demonstrates the significant role that AVHs can play in a patient's life: they are detrimental, as such individuals experience a loss of “basic human needs”, including but not limited to: privacy, homeostasis, hope, motivation, social relationships, self-esteem, autonomy, professional opportunities, respect, or freedom (McCarthy-Jones, 2012). Moreover, individuals experiencing AVHs not only suffer from a loss of consensual reality in which they feel as if they are no longer living in the same world as the rest of society (Dilks et al., 2010; Mauritz & van Neijel, 2009; Jarosinski, 2008; McCarthy-Jones, 2012), but they also lose their own sense of self.

Unfortunately, those that experience such voices are in a way prisoners of their own minds. Despite the widespread affliction of schizophrenic individuals hearing voices, little is understood regarding the biological origins of such hallucinations, and thus, the ‘optimal’ form of therapy for such patients has still not been fully laid out.

2.2. Brain Activation Correlates Underlying AVHs

In order to delineate the neurobiological basis of this phenomenon, the following subsection aims to shed light on how brain activation correlates with underlying AVHs.

With the advent of bountiful technological advancements, many studies have undertaken functional neuroimaging. This has lent a helping hand in determining the concrete brain activation patterns during AVHs, which would not have been detectable to such an extent by other techniques (i.e. EEG) - this is in part due to the high spatial resolution of functional neuroimaging techniques, such as Functional Magnetic Resonance Imaging (fMRI for short) or Positron Emission Tomography (PET for short). The former is a neuroimaging technique that “depicts changes in deoxyhemoglobin concentration consequent to task-induced or spontaneous modulation of neural metabolism” (Glover, 2011, p.1). The latter is a neuroimaging technique that measures “physiological function by looking at blood flow, metabolism, neurotransmitters *and* radiolabeled drugs” (Berger, 2003, p. 1449). Together these neuroimaging techniques provide the opportunity to conduct two types of studies that may provide a detailed portrayal of brain activation whilst experiencing AVHs.

One set of studies attempts to measure brain activity precisely during the occurrence of AVHs. These are the so-called *symptom capture* studies, also known as *state studies*, and are conducted on the basis of a *within-subject design* in which there is a comparison made between brain states or activation patterns in periods of time when a schizophrenic patient hallucinates and when the same patient does not (Kühn & Gallinat,

2012). Such studies have been used to examine *the perceptual model*, whose hypothesis is that the mechanism responsible for AVHs is abnormal auditory perception in auditory brain regions, such as the primary auditory cortex. The second type of study, known as *trait studies*, are conducted on the basis of a *between-subjects design* in which there is a comparison made between brain states or activation patterns of one group of schizophrenic patients who hallucinate with another group of schizophrenic patients that do not have this symptom or a group of healthy controls (Kühn & Gallinat, 2012). The comparison between groups can be done either in resting state, or when exposing the participants to an experimental task that involves processes presumably linked to AVHs, such as sound or speech perception (thus targeting *the perceptual model*) or tasks involving language and memory (thus testing *the cognitive model*) (Allen et al., 2008). As these studies attempt to measure brain activity dedicated to cognitive processes “underlying the disposition to hallucinate”, their hypothesis is that the mechanisms responsible for AVHs are due to the inability to detect speech monitoring (inner speech theory), or to the activation of traumatic memories (intrusive memory theory) (Allen et al., 2008, p. 179). Thanks to the fact that whole brain analytical processes are implemented across the above-mentioned studies, deciphering which particular model is the building block of AVHs can be discreetly determined.

On a methodological level, the most common approach² used to capture AVHs in functional neuroimaging studies is known as the *button press*. This method allows subjects to press one or two buttons with one or both hands to indicate the onset, duration, or diminishing of their hallucinations (i.e. Silbersweig et al., 1995; Dierks et al., 1999; Lennox et al., 1999, 2000; Diederer et al., 2010; Hoffman et al., 2011; Fuentes-Claramonte et al., 2021). This approach became utilized post-hoc Serafetinides et al. (1986), who demonstrated that manually reporting AVHs is a much more viable method than verbally reporting AVHs, as had been done in electrophysiological studies, the results of which are, for the most part, inconclusive (i.e. Marjerrison et al., 1968; Stevens et al., 1979; Stevens & Livermore, 1982). Despite the fact that the indication of AVHs in

² It must be noted that there are other approaches to capturing AVHs which are not as common as the button press approach. The first, known as *random sampling*, is a discontinuous acquisition method, “in which many fMRI volumes are acquired at random intervals” during the experiment (Leroy et al., 2017, p. 2; i.e. Shergill et al., 2000a). The second, known as *independent component analysis*, “allows the co-activated brain regions to be separated without predefined temporal model of brain activity” (Leroy et al., 2017, p. 2; van de Ven et al., 2005; Jardri et al., 2007, 2009; Jardri et al., 2013). However, because the proposal of this thesis is in part based on the button press approach, emphasis will only be placed in this particular approach.

functional neuroimaging studies is based on self-reports, it has been rigorously shown that patients are highly accurate at providing feedback to unexpected auditory stimuli in an fMRI environment, demonstrating the ability to capture similar unexpected AVHs with similar accuracy (e.g. van de Ven et al., 2005; Sommer et al., 2008; Diederer et al., 2013; van Lutterveld et al., 2013; Foucher, 2013; Jardri et al., 2013; Leroy et al., 2017).

As the Perceptual Model deserves the same level of scrutiny, it shall be examined henceforth.

2.2.1. The Perceptual Model

The forthcoming section targets *the Perceptual Model*, which maintains that AVHs are genuinely perceptual, that is, that they arise as a result of pathological activity in auditory perception regions of the brain. This theory has come together through a multitude of studies across time (of which only a select few shall be mentioned) whose approach was to understand and investigate AVHs exploratorily, their primary aim being to capture and compare brain activation during the experience of AVHs or lack thereof. Accounting for this premise, what must be kept in mind is that rather than there *first* being a model that all studies followed, what took place was common exploration that *then* formed the model.

2.2.1.1. Aberrant Perception Theory

Human reality is constructed ‘brick by brick’ by perception, which is a set of complex processes that cooperate to determine one’s experience and one’s reaction to a given stimulus in one’s environment. The neural engine processes incoming information from the environment, or in other words, engages in bottom-up processing. This type of processing stimulates the brain’s receptors, thanks to which a given percept is created by “recombining features from sensory input” (de Boer et al., 2019, p. 2772; Engel et al., 2001). This particular framework is the starting point of all perception, as without it, the neural engine would not have information to process to begin with. The brain is not a ‘blank’ slate, but is instead equipped with existing knowledge about previous experience which is set into play by having certain expectations about the world, or in other words, it engages in top-down processing. This type of processing allows for “a faster processing of sensory information” (de Boer et al., 2019; Fenske et al., 2006; O’Callaghan et al., 2017). Worth noting is the constant dynamic interplay between both types of processing which sculpts an *accurate* perception of the world (de Boer et al., 2019; Stocker &

Simoncelli, 2006). Conversely, *any imbalance* prompts the opposite: errors in perception in which certain percepts become activated without any external stimulation from the environment.

On this basis, one principal mechanism that has been thought to be behind the underlying foundation of AVHs is the phenomenon of “*aberrant perceptions* generated in the auditory regions”, particularly in *the primary auditory cortex* (PAC for short), as presented in **Figure 1** (Jardri et al., 2011, p. 73; Kompus et al., 2013; Ćurčić-Blake et al., 2017). The PAC “is located in the superior plane of the superior temporal gyri called Heschl’s gyrus” (Ćurčić-Blake et al., 2017, p. 13; Zatorre et al., 2002). It is responsible for primary sound perception and processing. It then sends further information down to the secondary auditory cortex (consisting of the superior temporal gyrus (STG for short) and middle temporal gyrus (MTG for short)) (Ćurčić-Blake et al., 2017). Finally, thanks to the thalamus, the information travels up to the higher-order areas involving language, allowing for a full processing of the original auditory percept (Belin et al., 2000; Zatorre, et al., 2002, 2007; Javitt & Sweet, 2015; Ćurčić-Blake et al., 2017). Consequently, it is hypothesized that “AVHs that form even stronger sensory experiences accordingly, activate the auditory cortex (including the left STG), which houses the linguistic auditory perception regions of the brain” (Ćurčić-Blake et al., 2017, p. 13; Allen et al., 2012; Woodruff et al., 1995, 1997).

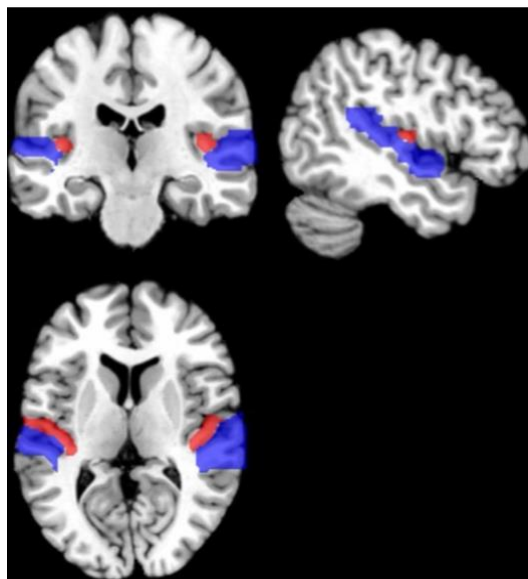


Figure 1. *The Primary Auditory Cortex* (PAC for short) presented on a brain template by Kompus et al. (2013, p. 2). PAC occupies a large portion of Heschl's gyrus (or the transverse temporal gyrus) (red), and is surrounded by the superior temporal gyrus (blue).

The idea that hallucinations arise from the auditory regions originally comes from Kraepelin (1913), who suggested that AVHs could be due to irritative neural activity in the auditory cortex. Additionally, Penfield & Perot (1963) stimulated the temporal lobe in epileptic patients, particularly the STG, which resulted in the patients having auditory hallucinations that consisted of “either a voice, voices, music or meaningful sound”, of which hearing a voice or voices was most commonly experienced (McCarthy-Jones, 2012, p. 193; see also Mahl et al., 1964). Interestingly, when other areas beneath the temporal cortex are stimulated, such as the left amygdala region or the anterior hippocampus, AVHs are not experienced (Ferguson et al., 1969). This lays out the premise for the idea that in order to understand AVHs, the key brain areas responsible for *auditory perception* should be taken into consideration.

One of the earliest PET studies, conducted by Silbersweig and colleagues (1995), did not find significant brain activation in the auditory cortex when comparing a group of 5 schizophrenic patients with AVHs and a single case of a schizophrenic patient who experienced both AVHs and visual hallucinations³ (VHs for short). The subjects’ task was to press a button throughout the process of experiencing their hallucinations while their cerebral blood flow was recorded. On a group level, the patients that only experienced AVHs were found to only have activation in: subcortical nuclei, particularly the thalamus and ventral striatum; limbic and paralimbic structures, such as the hippocampus, parahippocampal and cingulate gyri; and the orbitofrontal cortex (Silbersweig et al., 1995, p. 176). The authors (1995) posit that such activation in these interconnected structures may be responsible for modulating the hallucinations that the patients experience. No significant activation was found in the PAC, however (Silbersweig et al., 1995). Conversely, the single patient with both AVHs and VHs showed activation in “visual *and* auditory/linguistic association cortices as part of a distributed cortical-subcortical network” (Silbersweig et al., 1995, p. 176). Such a differentiation in brain activity presents not only how varied the two sensory hallucinations are, but also the nature of individual versus group analyses (Silbersweig et al., 1995; Shergill et al., 2000a).

Following the path laid out by Silbersweig et al. (1995), Dierks and colleagues (1999) conducted an fMRI study and tested 3 paranoid schizophrenic patients with

³ Visual hallucinations are visual perceptions that one experiences without external stimuli. For instance, this particular patient saw “moving, colored scenes with rolling, disembodied heads, and simultaneously heard the heads speaking to him, giving him instructions” (Silbersweig et al., 1995, p. 176).

transitory AVHs who were asked to indicate the onset of their AVHs by pressing a button with their left hand, and continue pressing it until the end of their hallucinations in two conditions. The first consisted of the patients being in a resting state. The second consisted of the patients being presented with spoken text which was played backwards and presenting them with “a modulated tone of 2000 Hz”, during which all patients were to indicate their AVHs (Dierks et al., 1999, p. 615). When experiencing AVHs, the authors found significant activation in Heschl’s gyrus, the posterior STG, the MTG, the frontoparietal operculum, the hippocampus, the amygdala as well as the sensorimotor cortex. According to the authors (1999, p. 617) such activation increased “when the patient signalled the onset of an episode of hallucination, remained at a high level during that episode, and returned to baseline levels immediately after the patient had signalled the hallucination ended”. Furthermore, when comparing the experience of AVHs and acoustic and tonal stimulation, the highest correlation of the BOLD signal was found in Heschl’s gyrus “at the same location” in both, suggesting a mutual location for their genesis (Dierks et al., 1999, p. 617).

Next in this sequence of studies, Lennox and colleagues (1999) tested one paranoid schizophrenic with AVHs who was to press a button as an indication of both the onset and end of his AVHs in an fMRI state study. In the time periods associated with AVHs, the authors (1999, p. 644) found significant activation in the right MTG; bilateral STG; right middle and inferior frontal gyri, right ACC; right cuneus; and the primary motor cortex (related to the manual response). Worth mentioning is that the strongest activation was not found in the primary auditory cortex, but rather in the MTG, part of the *secondary* auditory cortex. In a follow-up fMRI study, the same research group (2000, p. 17) asked four schizophrenic patients with AVHs to press the left button for the onset of their hallucination, and the right button for the end of the hallucination. The authors demonstrated that whilst experiencing hallucinations, significant activation was found “in the left and right STG, left inferior parietal and left middle frontal gyrus” (Lennox et al., 2000, p. 15). As this study implemented a different methodology for the button press when compared to previous studies, the authors argue that it serves as an advantage in the technical aspect of the analysis as there is less contamination in image acquisition. Together, Lennox and colleagues (1999, 2000) place emphasis on the role of brain regions responsible for auditory perception in the origins of AVHs.

A lack of activation in the primary auditory cortex during AVHs was found by Copolov et al. (2003), who compared 7 schizophrenic patients with hallucinations and 1

patient with schizoaffective disorder with hallucinations, 7 schizophrenic patients without hallucinations, and 8 healthy controls. The first group of participants was to press a button with their right index finger during the onset and duration of their AVHs, whilst the second and third groups of participants were presented with auditory stimuli that “consisted of multi-speak babble, a crowd noise, in which many human voices could be heard talking about different topics with no one dominating” and were instructed to also press a button with their right index finger as an indication that they perceived the stimulus (Copolov et al., 2003, p. 141). Interestingly, pure exposure to human speech in the second and third group crucially revealed “bilateral activation of the superior temporal gyri, involving the primary and association auditory areas (...) and bilaterally in the superior temporal gyri”, as well as other areas (Copolov et al., 2003, p. 143). For those patients that experienced AVHs, however, the areas of significant activation were localized in “the right medial frontal region, most probably reflecting a combination of anterior cingulate and cingulum activity (...) lateral surface of the right prefrontal cortex, the left posterior STG, and the right posterior MTG (...) left hippocampal formation” and so on, yet no such activity was demonstrated in the auditory cortex (Copolov et al., 2003, p. 146-147).

A different fMRI study by Diederer and colleagues (2010) tested 24 psychotic patients with AVHs, and made a comparison of brain activation between them squeezing a balloon as an indication of onset of AVHs and 15 healthy individuals squeezing a balloon randomly across trials. The patients presented significant activation during their AVHs in the bilateral language areas, predominantly in “bilateral insula and inferior frontal gyrus (including Broca’s homologue) as well as the MTG, STG, and supramarginal gyri” (Diederer et al, 2010, p. 430-431). What is more, 6 seconds prior to the onset of hallucinations, 15 out of the 24 patients showed significant “deactivation in the left parahippocampal gyrus” - an area involved in memory recollection⁴ (Diederer et al., 2010, p. 432). Subsequently, the authors conclude the presence of AVHs can be mainly found in bilateral language areas.

Following Diederer et al. (2010), Hoffman and colleagues (2011) aimed at improving the “understanding of the chain of brain events leading to AVHs”. For this reason, the authors (2011) compared 11 patients with either schizophrenia or

⁴ The fact that brain regions responsible for memory recollection become activated prior to AVHs is an interesting finding and shall be discussed further on in Section 2.2.2.1..

schizoaffective disorder with AVHs and 10 patients with similar diagnoses but without AVHs. Prior to hallucinating, the first group showed significant activation in both the left inferior frontal gyrus, and right posterior MTG and STG, as well as a decrease in the left temporal regions of interest (ROIs) pointing to the relevance of speech processing brain areas in triggering AVHs. Similarly to Diederer et al. (2010), a decrease in activation was also found in the right parahippocampal gyrus amongst other areas.

Recently a study by Fuentes-Claramonte et al. (2021) has rigorously re-examined the activation pattern of AVHs by modifying a version of the symptom capture paradigm. The authors (2021) tested 15 patients with either schizophrenia or schizoaffective disorder experiencing AVHs and 15 patients with schizophrenia or schizoaffective disorder without AVHs. In brief, the group of patients with AVHs were asked to indicate experiencing AVHs by pressing a button with their right index finger. Moreover, patients were also asked to indicate with their left index finger their perception of a sample of actual spoken language with characteristics similar to AVHs, which was tailored to each patient individually prior to the experiment. As the second group of patients did not experience AVHs, they only took part in the second part of the fMRI task, using as stimuli on an individual basis the spoken language fragments assigned to a patient from the first group that was as similar as possible in terms of age, sex, and estimated premorbid intelligence quotient (IQ).

The authors (2021) found that experiencing a hallucination was not associated with auditory cortex activity, but with other brain regions, particularly Broca's areas and Wernicke and their counterparts in the right hemisphere, as well as the precentral gyrus and the supplementary motor area, bilaterally. In comparison, listening to actual language activated the superior temporal cortex bilaterally, in addition to the same frontal and parietal regions activated during the AVH experience. The results are shown in **Figure 2**. A caveat of this study is that motor activity may have confounded the results, because brain activity linked to the act of button pressing could not be separated from brain activity due to the experience of AVHs (Fuentes-Claramonte et al., 2021). Furthermore, the experimental blocks for both experiencing hallucinations and perceiving real speech were not separated either. In order to reconcile this discrepancy, further studies should aim at creating a paradigm that distinctly disentangles them in order to be able to isolate AVH-related activation from motor activity (Fuentes-Claramonte et al., 2021).

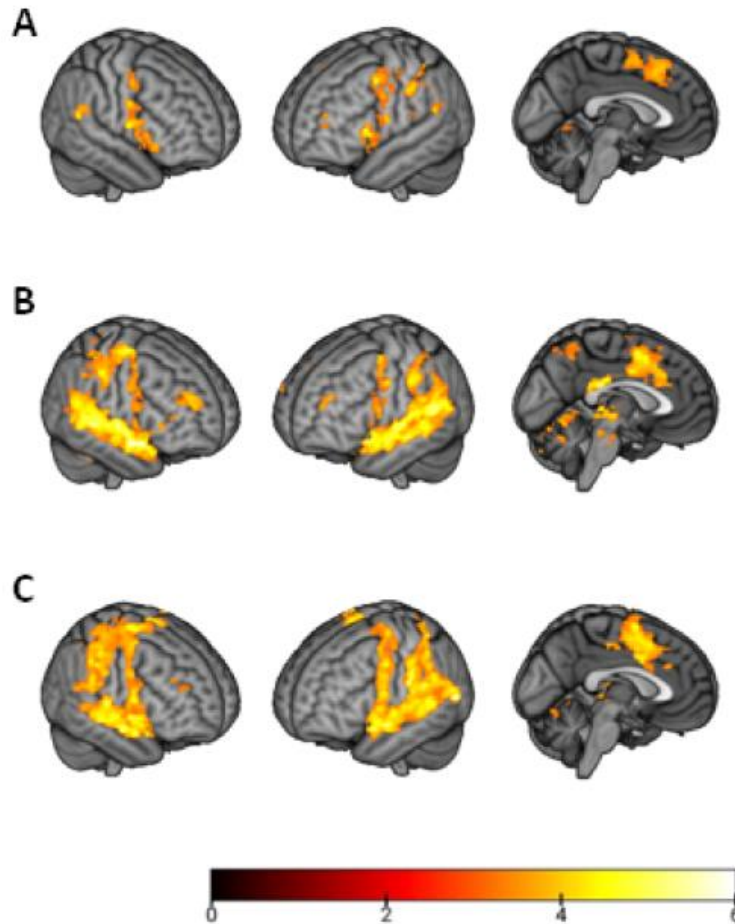


Figure 2. Group brain activation patterns during the symptom-capture task borrowed from Fuentes-Claramonte et al. (2021). (A) depicts group activation maps for patients with hallucinations during their AVHs. (B) depicts group activation maps for patients with hallucinations during real speech presentation. (C) depicts activation maps for patients without hallucinations during real speech presentation. The color bar presented below depicts Z values.

Further in-depth meta-analyses, which include the above-mentioned studies, have found AVH-associated activations in cortical regions to lay *outside* the auditory regions, shedding light on the fact that a much more complex mechanism than just abnormal activation of the auditory perception regions may be involved.

The first meta-analysis was conducted by Jardri and colleagues (2011), consisting of 10 PET and fMRI studies. The authors (2011) implemented the meta-analytic procedure known as *activation likelihood estimation* (ALE), which “models the convergence of activation coordinates across studies and generates statistical maps of consistent brain activity” to trace the spatial localization of the activation patterns most frequently replicated during AVHs (Zmigrod et al., 2016, p. 2). When AVHs were experienced, significantly increased activation likelihoods were found in “a bilateral

neural network, including the Broca's area, anterior insula, precentral gyrus, frontal operculum, MTG, STG, inferior parietal lobule, and hippocampus and parahippocampal region" (Jardri et al., 2011, p. 73). To conclude, despite the widespread activation in language-related areas, no such significant activation was found in the PAC when AVHs are experienced.

In the second meta-analysis, Kühn and Gallinat (2012) compared 12 functional state and 8 trait studies by implementing ALE. For the state studies, convergent patterns of activation were observed "in bilateral inferior frontal gyrus, bilateral postcentral gyrus, left parietal operculum that is part of the left inferior parietal lobule" (Kühn & Gallinat, 2012, p. 781). Even after the authors (2012) decreased the threshold, no significant convergence was found in the STG. For the trait studies, convergent patterns of activation were observed in "left STG, left MTG, ACC, left premotor cortex" (Kühn & Gallinat, 2012, p. 781). With such findings, this meta-analysis does not lend credence to the theory of AVHs being due to abnormal neuronal activity in the auditory cortex, but rather implicates speech production areas.

The third meta-analysis, executed by Kompus and colleagues (2011), gathered data from fMRI and PET studies and employed ALE. The aim of this meta-analysis was to compare brain activations across studies in which patients experienced AVHs "in the absence of a corresponding external stimulus" and when patients were exposed to "external auditory stimulus" (Kompus et al., 2011, p. 3364). The authors (2011, p. 3362) found that "the areas of significant convergence of *increased activation* when experiencing auditory hallucinations included a cluster in the STG, corresponding to left PAC, extending to parietal operculum", and the left primary sensory/motor cortex, as well as other areas (to a lesser extent) such as "left insula, left posterior hippocampus, right MTG, right inferior parietal lobule, opercular part of the right inferior frontal gyrus and rostral portion of right superior frontal gyrus". Additionally, the left primary auditory cortex was also implicated in the auditory stimulation tasks, yet its activation was *decreased* in schizophrenic patients when compared to healthy controls, pointing to a deficit in auditory processing. Based on this, the authors (2011, p. 3365) concluded that both such a deficit in auditory processing and experiencing AVHs share common mechanisms in speech perception areas, which may point to "competition between internally generated and externally originating neural activity in the auditory cortex for the attentional resources in hallucinating individuals".

The fourth meta-analysis, consisting of 14 studies, done by Zmigrod and colleagues (2016), aimed to examine both AVHs and VHs in not only schizophrenia, but also other clinical and non-clinical populations (i.e. psychotic disorders, Parkinson's disease, Alice in Wonderland syndrome⁵, Charles Bonnet syndrome⁶). A distinct pattern of activation was found for both AVHs and VHs, with some areas of overlap indicating that hallucinations of different sensory modalities have little brain activity in common (Zmigrod et al., 2016). Most importantly, during AVHs, large clusters of activation were observed in the “bilateral somatosensory cortex, bilateral insula, STG, Broca's area and its right hemisphere homologue, and in Wernicke's area/secondary auditory cortex, (...) left hippocampus/parahippocampal gyrus, the right motor cortex” and so on (Zmigrod et al., 2016, p. 5). In comparison, significant activation for VHs was found in “extrastriate visual areas around the ventral lingual and fusiform gyri” demonstrating a distinction between brain regions associated with AVHs versus VHs (Zmigrod et al., 2016, p. 5). Although activity was found in speech production areas and the secondary auditory cortex (and others) during AVHs, this analysis may overgeneralize brain activation across groups, as a variety of both clinical and nonclinical studies were converged, rather than just those of schizophrenic patients. As of now, the degree to which AVHs in schizophrenia (or psychosis) mirrors AVHs in other populations remains unknown (i.e. Frith and Dolan, 1997; Waters et al., 2006; McCarthy-Jones, 2012; Choong, et al., 2007; Diederer et al., 2012).

The conclusions of the data presented points to a commonality: brain activity whilst experiencing AVHs is inconsistent in the sense that the same brain regions, particularly those involved in auditory perception, are not activated across all studies. By putting together the data from single case studies to meta-analyses, the most common brain regions that have been found to be involved in AVHs are: the *PAC* (including *Heschl's gyrus* (Dierks et al., 1999; Lennox et al., 1999; Kompus et al., 2011), *Wernicke's area and its homologue* (Dierks et al., 1999; Lennox et al., 1999, 2000; Copolov et al., 2003; Hoffman et al., 2011; Fuentes-Claramonte et al., 2021; Kompus et al., 2011; Zmigrod et al., 2016), *Broca's area and its homologue* (Lennox et al., 1999, 2000; Copolov et al., 2003; Diederer et al., 2010; Hoffman et al., 2011; Jardri et al., 2011; Kühn

⁵ Alice in Wonderland Syndrome is characterized as “a perceptual disorder characterized by distortions of visual perception, the body schema, and the experience of time” (Blom, 2016.).

⁶ Charles Bonnet Syndrome is characterized “by the presence of complex visual hallucinations in psychologically healthy but visually impaired people” (Schwartz and Vahget, 1998).

and Gallinat, 2012; Fuentes-Claramonte et al., 2021), *superior temporal gyri* (Lennox et al., 1999, 2000; Copolov et al., 2003; Diederer et al., 2010; Jardri et al., 2011; Zmigrod et al., 2016), *middle temporal gyri* (Dierks et al., 1999; Lennox et al., 1999, 2000; Copolov et al., 2003; Hoffman et al. 2011; Kompus, et al. 2011; Jardri et al., 2011), *hippocampus* (Silbersweig et al., 1995; Dierks et al., 1999; Copolov et al., 2003; Jardri et al., 2011; Kompus and colleagues (2011), Zmigrod et al., 2016); *parahippocampus* (Silbersweig et al., 1995; Copolov et al., 2003; Diederer et al. 2010; Jardri et al., 2011; Zmigrod et al., 2016), *precentral gyrus* (Dierks et al., 1999; Diederer et al., 2010; Fuentes-Claramonte et al., 2021; Jardri et al., 2011), *postcentral gyrus* (Dierks et al., 1999; Diederer et al., 2010; Jardri et al., 2011; Kühn and Gallinat, 2012).

This variation in findings across studies may be due to a variety of reasons that mostly stem from methodology. For instance, the number of participants that have taken part in the (earlier) studies is insufficient as the number does not go over 8 in many cases (i.e. Silbersweig et al., 1995; Dierks et al., 1995; Lennox et al., 1999, 2000; Copolov et al., 2003; Hoffman et al., 2007). Such a limited number of participants has a detrimental impact on the statistical effect of the findings, and the recommendation for fMRI studies is of at least 20 subjects per group (Thirion et al., 2007; Desmond & Glover, 2002; Jardri & Sommer, 2013). In connection to this, the statistical threshold used in earlier studies (such as Silbersweig et al., 1995; Dierks et al., 1999; Lennox et al., 1999, 2000) was liberal ($p = .001$, uncorrected), and may have resulted in type I and type II errors (Somers et al., (2008). Therefore, the results of such studies should be taken with caution.

On another note, the BOLD activity found across certain studies may have been confounded by motor behavior, which is an essential element in the experimental paradigm to test AVHs, as it serves as an indication of onset and end of AVHs. In some cases, the motor activity for button press during AVHs onset/duration was not compared with the motor activity for button press without AVHs — not allowing for motor activity to be cancelled out (e.g. Fuentes-Claramonte et al., 2021). Because of this, the activation behind the button press may affect the activation during AVHs. It may be worthwhile in future experimental design to implement blocks in which patients conduct the button press during time periods of when they do not experience AVHs.

Lastly, it would be beneficial to supplement one technique, such as fMRI, with other techniques, such as EEG, that target other resolutions better in order to provide the full AVH picture.

In order to test the perceptual model thoroughly and overcome potential limitations as found across previously mentioned studies, the following experimental paradigm is suggested.

2.2.1.2. Proposal of Symptom Capture Paradigm

Three groups of participants will take part in the prospective fMRI study and all tasks involved: 25 right-handed patients diagnosed with schizophrenia or schizoaffective disorder according to DSM-5 with frequent AVHs (Group 1); 25 right-handed patients diagnosed with schizophrenia or schizoaffective disorder without AVHs for at least 6 months (Group 2); and 25 right-handed healthy controls (Group 3). The task that will be implemented is based on Fuentes-Claramonte and colleagues (2021), but with one notable modification, and is presented in *Figure 3*. Group 1 will press a button with their right index finger at the onset of the AVHs, and press a button with their left index finger at the onset of real speech. To be more precise, randomly and within a 10-minute period, 40 instances of real speech will be presented through headphones with contents individually tailored to resemble each patient's AVH. Patients will be required to press a button when they hear these examples of real speech with their left index finger. Furthermore, four 15-second blocks will be interspersed throughout the task in which participants will also be asked to randomly and alternatively press both buttons in time periods when they do not hear AVHs. This enables activations associated with experiencing AVHs to be compared with those when none are experienced, and thus overcome confounding activation for AVHs potentially leaking from motor activity. With regards to Group 2 and Group 3, as they do not experience AVHs, they will only be presented and respond to real speech, and the content of the stimuli will be based on a composite version of voice content from Group 1. Both groups will also perform the 15-second blocks to control for motor activity.

The statistical analyses will be performed at a level of $p < .05$, corrected at the cluster level using Gaussian field methods, with a voxel level threshold of $z > 3.1$ ($p < .001$, uncorrected).

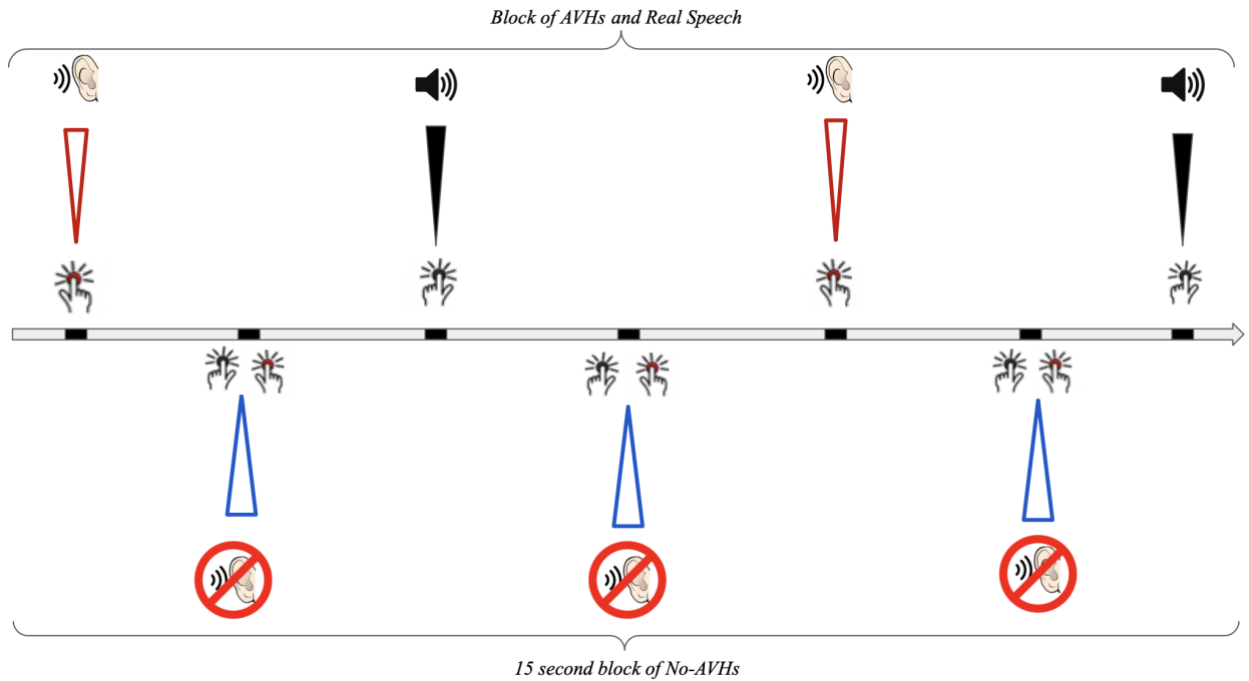


Figure 3. *Proposal of Symptom Capture Paradigm.* The top figure represents the paradigm that has been tested by Fuentes-Claramonte et al. (2021), and the bottom figure is the proposed modification, namely in the absence of AVHs, patients are to press both buttons with both index fingers.

a) Hypotheses

1. *Patients with schizophrenia who experience frequent AVH will show activation in brain cortical regions involved in sound and/or speech perception when they experience AVH, as well as when they hear real speech with similar characteristics.*
2. *Conjunction analysis of the two above networks of activation in patients with frequent AVH will show significant overlap.*
3. *Conjunction analysis will reveal significant overlap between areas activated by voices in patients with frequent AVH and areas activated by external speech in patients without AVH and healthy controls.*

Building upon previous studies, this task allows for an elaborate targeting of the perceptual model and the neural signature behind it. As this proposal of the prospective fMRI study aims at taking different approaches to paint the full picture of AVHs, however, what shall now be considered is the other side of the coin: rather than perceptual processes, cognitive processes will now be put under the microscope.

2.2.2. The Cognitive Model

The following section targets two separate theories that make up the Cognitive model, which maintain that AVHs arise from a dysfunction that causes internal, non-perceptual processes to be incorrectly interpreted as external. The first is *Intrusive Memory Theory*, which puts forth the argument that AVHs are unstable memories activated due to “a breakdown in the processes monitoring the source of memories” (Seal et al., 2004, p. 53). The second is *Inner Speech Theory*, which puts forth the argument that AVHs are due to deficits in speech monitoring. It must be kept in mind that, although both could be considered ‘cognitive’ models of AVHs, the theoretical groundwork behind them has not been fully laid out as of yet, and the associated experimental work is still in its nascent stage.

2.2.2.1. Intrusive Memory Theory

If in good condition, the mind has a peculiar gift: the ability to travel back into its past experiences - recalling the places it has seen, the smells it has processed, and most importantly, delving into the footprints left behind by other minds. As Elden Turving (2005, p. 15) once said, “There can be no travel without a traveler”, and it is the travelling self, the mind, that can wander from memory to memory recalling the pieces of the puzzle of its existence (or episodic memory).

If, on the other hand, the mind’s condition has deteriorated, a malfunction of storing and retrieving such memories takes place - a variant known as the theory of misattribution of intrusive or traumatic memories. The proposition that hallucinations are reactivated memories could be said to date back to Aristotle’s age:

“Sometimes we do not know when such stimuli occur in our soul from an earlier sensation, and we are in doubt whether it is memory or not. But sometimes it happens that we reflect and remember that we have heard or seen something before. Now, this occurs whenever we first think of it as itself, and then change and think of it as referring to something else (...) *The opposite also occurs, as happened to Antiphenon of Oreus, and other deranged people (egistamenois); for they spoke of their mental pictures (fantasmata) as if they had actually taken place, and as if they actually remembered them*” (Berrios, 1996, p. 210; Bicknell, 1981).

The theory of misattribution of intrusive or traumatic memories originates in the theory of episodic memory retrieval. Essentially, an experience embedded in one’s memory is never a reproduction of the same replica, as it undergoes error and reconstruction (Seal et al., 2004; Chalfonte & Johnson, 1993; Schacter, 1995; Schacter et al., 1998). The entire episodic memory engram of the given experience consists of a

multitude of features that represent different parts of the experience and are distributed across various areas of the neural system (Schacter et al., 1998; Damasio, 1989, Squire, 1992). Said features can encompass “sensory or perceptual information, semantic or conceptual information (...) emotional response, motor actions, and concurrent cognitive processes”, all of which form a bound or coherent representation of the past experience (Seal et al., 2004, p. 53; Schacter et al., 1998, 1989; Moscovitch, 1994). In this case, in order to retrieve the engram of the past experience, a process of pattern completion takes place in which “a subset of the features comprising a particular past experience are reactivated, and activation spreads to the rest of the constituent features of that experience” (Schacter et al., 1998, p. 291).

As a result of the complexity inherent in the memory system, there are disruptions in reconstructing the past experience that may arise from a variety of factors. For instance, if there are disruptions in binding processes, this can lead to inadequate activation and binding of certain features (Schacter et al., 1998). Conversely, even if the binding processes are intact, there may be insufficient information stored in the bound representation, or an incompleteness of encoding the given memory taking place, which ultimately leads to the representation becoming vulnerable in its priming and to abnormal activation (Schacter et al., 1998; Ćurčić-Blake et al., 2017). Ergo, the disruption in the reconstruction of memory that can take place is *source memory failure* wherein “people retrieve fragments of an episode but are unable to recollect how or when the fragments were acquired” (Schacter et al., 1998, p. 291). This, in turn, causes patients to reconsider the source of their voices, for instance, “did they say that before or did I just imagine it?” (Seal et al., 2004, p. 53). As such, AVHs are hypothesized to be “the result of a breakdown in the processes monitoring the source of memories” (Seal et al., 2004, p. 53).

On this basis, Waters and colleagues (2006, p. 65) adopt a variant of this idea and propose that AVHs are “auditory representations derived from unintentional activation of memories and other irrelevant current mental associations”, making them intrusive and unintended. The origins of AVHs, following this line of reasoning, are thought to stem from two factors. The first revolves around a basic cognitive mechanism, *inhibition*, which is defined as “a collection of processes that allows the suppression of previously activated cognitive contents and the clearing of irrelevant actions or attention from consciousness” (Waters et al., 2006, p. 67). Emphasis is placed particularly on *intentional inhibition*, in which the individual has control over which item is suppressed by deciding that it is irrelevant (Waters et al., 2006). Thus, according to Waters et al. (2006, p. 66),

there is “a fundamental deficit in intentional inhibition which leads to auditory mental representation intruding into consciousness in a manner that is beyond the control of the sufferer” (Waters et al., 2006, p. 66). The second revolves around *contextual memory*, which “provides cues that allow us to differentiate one memory from another” (Waters et al., 2006, p. 72). It follows, according to the authors (2006, p. 66), that AVHs emerge as a result of “a deficit in binding contextual cues, resulting in an inability to form a complete representation of the origins of mental events”. Combining the deficits in intentional inhibition and contextual memory, Waters and colleagues (2006, p. 66) propose a model in which AVHs in schizophrenia are the result of “mental events which are experienced as involuntary and intrusive and are not recognized because the contextual cues that allow them to be identified correctly are missing or incomplete”.

The potential significance of memory in AVHs has been somewhat reflected in the brain activity preceding AVHs as well as in their duration. As already mentioned in Section 2.2.1.1., two studies showed the involvement of the parahippocampus, the brain area responsible for spatial memory and temporal memory, and which processes context information of a past event, prior to patients hearing voices. Diederer and colleagues (2010) showed that 6 seconds *prior to* the hallucinations, 15 out of the 24 patients showed significant “deactivation in the left parahippocampal gyrus” (Kompus et al., 2013, p. 432). On the other hand, Hoffman et al. (2011) showed a decrease in activation in the right parahippocampal gyrus. What is more, brain activation throughout *the duration of* AVHs has been shown by single studies and meta-analyses to not only involve parahippocampal gyri (i.e. Silbersweig et al., 1995; Diederer et al., 2010; Jardri et al., 2011; Kompus et al., 2011; Zmigrod et al., 2016), but also the hippocampus - the brain region fundamental for the formation of long-term episodic memory, particularly context memory, and the construction of mental images. Perhaps most importantly, it binds item information and context information together, creating the detailed episodic memory (i.e. Silbersweig et al., 1995; Dierks et al., 1999; Copolov et al., 2003; Jardri et al., 2011; Kompus et al., 2011; Zmigrod et al., 2016; Bird & Burgess, 2008; Slotnick, 2017). Such findings of brain activation suggest a potential neural link between memory retrieval and AVHs which encompasses the hippocampal complex - this link may be involved in the onset and duration of voice hearing. The way this may come to be, for instance, as proposed by Diederer (2010), is that the disinhibiting state of the parahippocampus in particular may potentially “trigger the bilateral language-related areas originally involved in the perception of speech”, and it may also prepare other areas, such as the inferior

temporal gyrus or the insula “for activation in the course of hallucination” (McCarthy-Jones, 2012, p. 273). As it stands, it may be that the dysfunction in memory inhibition may allow the memory fragments (such as auditory representations) to become unintentionally and intrusively activated, making the patient relive their past experience, not being able to differentiate the source of the given memory.

Such reliving of past experience in the form of AVHs has been proposed to involve not just memories per se, but traumatic memories in particular (i.e. McCarthy-Jones et al., 2014; Steel, 2015). This goes hand in hand with the link between being diagnosed with schizophrenia and the prevalence of traumatic memories in a given patient (Steel, 2015; Grubaugh et al., 2011). What is more, 15% of patients that are diagnosed with schizophrenia will also have suffered from post-traumatic stress disorder (PTSD), a mental disorder based on “an intrusive memory of a traumatic event, most likely in the form of a visual image” (Steel, 2015, p. 1; Achim et al., 2011). Such intrusive memories have been found to be present in the phenomenology of AVHs in patients diagnosed with schizophrenia. For instance, Morrison and colleagues (2002, p. 3) interviewed 35 patients with either schizophrenia, schizoaffective disorder or schizophreniform disorder, and found that “74.3% ($n=26$) were able to identify an image in relation to their psychotic symptoms, (...) patients who were able to identify idiosyncratic images experienced in conjunction with their hallucinations or delusions, 69.2% (18 out of 26) reported that their images were recurrent, 96.2% ($n=25$) were able to link the image to the experience of a particular emotion and to a particular belief, and 70.8% ($n=17$) were able to associate the image with a memory for a particular event in their past”. For instance, Morrison et al. (2002) provides an example of a patient who was assaulted with a gun at a club, and he experienced voices that related to that traumatic event.

Hardy et al. (2005) assessed 75 patients with either schizophrenia, schizoaffective disorder or delusional disorder who experienced AVHs and found that 53.3% reported a trauma, of which the most common were bullying (30%), adult sexual abuse (20%), and child sexual abuse (17.5%). Most significantly, the authors (2005, p. 506) found that, of these 53.5% patients, “just over half of these (30.6%) had at least one type of phenomenological association between their traumas and hallucinations”. This is seen in *Example (7)* of a patient who has gone through such trauma and experiences intrusive AVHs:

Example (7) : “My mother psychologically abused me, like mental cruelty, she constantly interfered with and controlled my life” (*Experienced Trauma*).

“I hear my neighbor giving me some form of therapy. She makes comments and tells me what to do. Sometimes it is neutral but sometimes she is more critical and I feel persecuted by her” (*Experienced AVHs*) (Hardy et al., 2005, p. 505).

McCarthy-Jones et al. (2014) interviewed 199 patients with AVHs, of which 80.9% had schizophrenia, 13.6% had affective psychosis, 3% had other nonorganic psychoses, and 2.5% had borderline personality disorder. The authors (2014, p. 231) found that “12% of participants reported AVHs as like identical replays from memory, 31% reported AVHs as similar to memories”.

En masse, the collected data from the above-mentioned interviews point to an important fact, namely that only some AVHs in schizophrenia can be accounted for by trauma. This, however, does not point to a categorical description of AVHs. Furthermore, to date there is little functional neuroimaging research that has precisely and directly tested the mechanism of intrusive memories despite the fact that the brain regions involved in conscious memory recall are well known (Seal et al., 2004; Slotnick, 2017). Were the theory of intrusive memory thoroughly tested, this could lend a helping hand in understanding the associations between AVHs composed of rather negative valence and its potential link to psychological trauma.

One approach that can be taken is by considering autobiographical memory (AM), which is the active retrieval of personal past experiences. It involves highly complex “retrieval processes, semantic content, personal significance, subjective re-experience, spatiotemporal context, emotion, social interactions and varying levels of specificity, remoteness and rehearsal” (Jacques & de Brigard, 2015, p. 265). Interestingly, it activates a network of regions known as the “AM retrieval network” or “core network”, which consists of regions that consistently interact with one another, specifically “the medial and lateral prefrontal cortices, lateral and medial temporal lobes (MTL; hippocampus, parahippocampal gyrus), ventral parietal cortex and posterior cingulate cortex” (Jacques & de Brigard, 2015, p. 265).

Interestingly, the complex AM circuits largely overlap with the neural network that is activated during resting or passive states, known as the Default Mode Network (DMN), as shown in Figure 4 (Raichle et al., 2001; Buckner et al., 2008). Midline regions (medial prefrontal, posterior cingulate and precuneus cortices) are considered ‘core’

regions of the network and have been associated with self-referential processes during AM retrieval. Additionally, some authors also define an MTL sub-network within the DMN that comprises hippocampal, ventromedial prefrontal, retrosplenial and medial parietal cortices, which “has been linked to constructing a scene based on memory” (Jacques & de Brigard, 2015, p. 266). Moreover, the frontoparietal or central executive network, which includes lateral PFC, anterior cingulate, and inferior parietal cortices, also contributes to the retrieval of AM and is associated with “adaptive cognitive control processes” (Jacques & de Brigard, 2015, p. 266).

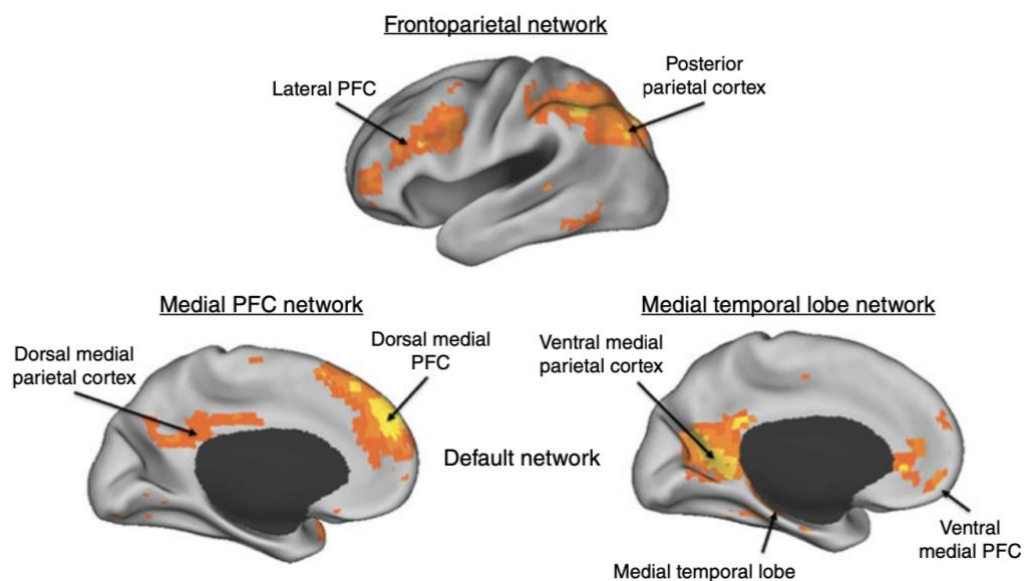


Figure 4. Brain networks that make up AM as borrowed from Jacques & de Brigard (2015, p. 266). The contribution of large-scale networks to AM that share parts of DMN: *Frontoparietal network* (top), *Medial PFC network* (bottom-left); *Medial temporal lobe network* (bottom-right).

Of particular current interest is the dysfunction of the default network in schizophrenia, as a number of studies have found evidence for the failure to activate or deactivate particular regions during attentional tasks as well as abnormality found in functional connectivity (i.e. Pomarol-Clotet et al., 2008; Salgado-Pineda et al., 2011; Guerrero-Pedraza et al., 2012; Hu et al. 2017). The link between both the AM and DMN networks lies not only in their spatial overlap, but in that autobiographical memory is one of the proposed roles for the DMN, among others, that include processing “self-relevant information, including self-reflection, making social and emotional judgements about

oneself and others, envisioning the future or performing theory of mind operations” (Fuentes-Claramonte et al., 2019, p. 2).

As of now, only a handful of studies have tested AM in schizophrenia by implementing the autobiographical recall task (which will be discussed in the next section), that targets the AM and DMN circuits. Such studies’ interests lay in either narrowing down the neural basis of AM (e.g. Cuervo-Lombard et al., 2012); analyzing the activation pattern of the DMN (e.g. Fuentes-Claramonte et al., 2019); or understanding how the DMN “behaves during a task like autobiographical memory” (Martin-Subero et al., 2021, p. 2). However, *no study* as of yet has implemented the autobiographical recall task to test the biological basis of AVHs by presenting the task to a group of schizophrenic patients who specifically experience hearing voices.

Therefore, to test one side of the Cognitive Model, the following paradigm targeting the question of whether intrusive or traumatic memories act as the main generator of AVHs shall be proposed.

2.2.2.2. Proposal of Autobiographical Recall Task

The same three groups of participants as in the perceptual paradigm will be presented with keywords that are designed to either evoke or not evoke autobiographical memories previously described by the subjects - a task that has already been validated in healthy individuals and schizophrenic patients (e.g. Fuentes-Claramonte et al., 2019; Martin-Subero et al., 2021). Prior to the fMRI session, each participant will be given the Crovitz test (Crovitz & Schiffman, 1974) and the autobiographical memory interview (AMI for short) (Kopelman et al., 1989) in order to obtain a description of a total of 20 autobiographical memories from different times in life (childhood, adolescence, adulthood and the last year) which will be of negative valence. Memories will be evaluated based on their clarity, specificity and descriptive richness according to the criteria of the AMI, and must receive the maximum score to be included. For each memory, 2 keywords will be selected that identify it, and that will be displayed during the task to indicate that that particular memory should be recalled. The control condition will be to present keywords that are not associated with any specific memory.

During the fMRI scan and the task, 10 autobiographical memory blocks will be presented, interspersed with 10 control blocks, with a duration of 20 seconds per block. Each block will contain 2 memory-evoking or non-evoking keywords. After each block, 2 questions will be presented on the screen to the participant: the first is whether they

managed to recall the memories; the second regarding whether any AVHs occurred during the block. As in the previous task, the participant must provide a manual response, indicating "yes" (right index finger) or "no" (left index finger). What is more, the hand assigned to each answer will be counterbalanced between participants. Lastly, there will be a fixation point between blocks, presented for 16 seconds, that will act as the baseline. The paradigm is presented in *Figure 5*.

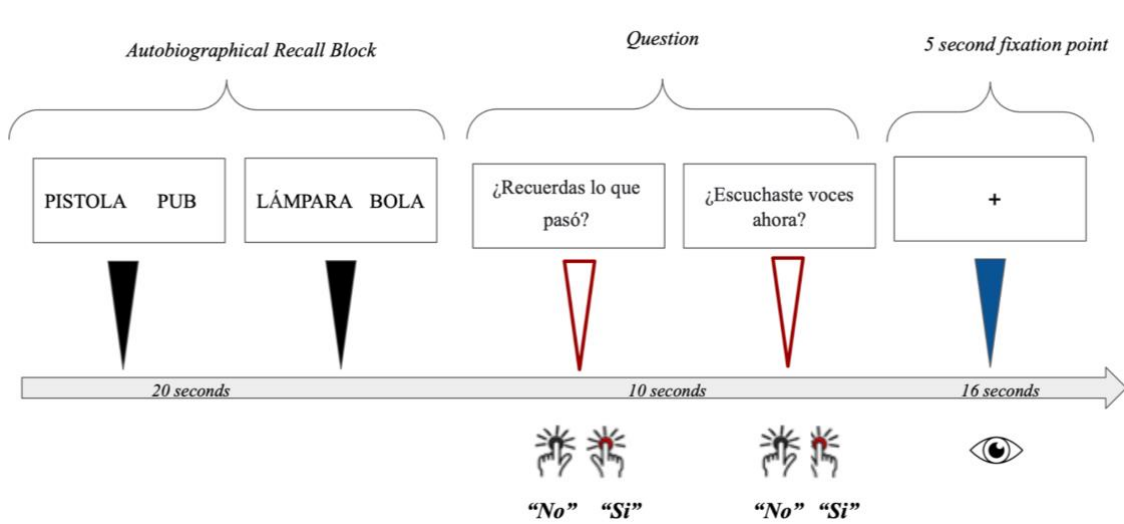


Figure 5. Proposal of *Autobiographical Recall Task* based on Fuentes-Claramonte and colleagues (2019) and validated by Martín-Subero et al. (2021).

For the statistical analysis, at the intra-subject level, the memory blocks and the control blocks will be compared, using General Linear Models (GLMs), to delimit the regions involved in the evocation of negative autobiographical memories. At the group level, mean activation maps will be generated for each group that will then be compared in order to identify differences in autobiographical memory between all three groups of participants.

In Group 1 (the patient group with AVHs), the autobiographical memory blocks with the presence of hallucinations will be compared with autobiographical memory blocks without hallucinations. This shall be done in order to assess whether hallucinations modulate the activity of the brain regions that are involved in the experience. The statistical analysis will be performed at a level of $p < 0.05$, corrected at the cluster level using Gaussian field methods, with a voxel level threshold of $z > 3.1$ ($p < 0.001$, uncorrected).

a) Hypotheses

1. Patients with AVHs will show a brain activation pattern in response to cues to evoke negative memories that will differ from that observed in patients without AVHs and healthy controls.
2. Activation differences will be located in brain regions involved in autobiographical memory, including DMN regions such as the medial prefrontal cortex, the posterior cingulate and precuneus, among others.
3. Alternatively or additionally, hallucinations will transitorily alter the activity of these regions.

Although this experimental paradigm tests the cognitive model, it only does so up to a certain extent. Thus, the other side of the coin, which heavily relies on a different cognitive mechanism, shall now be demonstrated.

2.2.2.3. Inner Speech Theory

Memory is the vehicle that permits one to travel back in time, yet it is the subjective voice inside one's head that puts forth the narration of one's reality. The discussion of inner dialogue or inner speech is illustrated in the Platonic dialogue, *The Theaetetus*, which is a question-and-answer dialogue that arises between Socrates and Theaetetus, a young and brilliant mathematician (Chappell, 2021). In essence, Socrates considers judgment (*doxa*) to be a silent statement (*logos*), and judging (*doxazein*) to be silent speaking (*legein*):

- “(Socrates): Very nice. But do you call *thinking* exactly what I call it?
(Theaetetus): What do you call it?
(Socrates): A talk which the soul carries on itself with itself about the things it examines. This I tell you in ignorance. For this is how it seems to me. *The soul, when thinking, does nothing other than discuss, asking itself questions and answering them, both affirming and denying.* Whenever it first determines something, either sluggishly or sharply, then says the same thing and does not hesitate, we posit that as its judgement. *So I, at least, call judging, speaking and judgment a state, not articulated to someone else but in silence to oneself.*” (Duncombe, 2016, p. 106).

Centuries later, the father of behaviorism, Watson (1913), recognized inner speech as subvocalized language, or more precisely as “a purely mechanical process in which speech becomes quieter and quieter until it is merely a whisper, and then silent thought” - thus designating inner speech as thinking (Alderson-Day & Fernyhough, 2015, p. 932). Vygotsky (1934, 1987) disagreed with Watson (1913) and posited that inner speech is a much more complex process than simply consisting of behavioral components of overt speech. To the contrary, Vygotsky (1934, 1987) believed that inner speech was subvocalized language, formed in the development stage, as a developmental process, and that what becomes internalized conversation with the self is based on the “linguistically mediated social exchanges such as those between the child and a caregiver” (Alderson-Day & Fernyhough, 2015, p. 932).

The early link between both inner speech and AVHs comes from a series of studies that examined patients’ own subvocal speech via a technique, the electromyogram (EMG), which records muscle potentials. Of particular interest are those movements of speech organs during overt speech, as well as the silent articulation of speech. The workings of the electrogram “represents the outcome of a succession of processes unfolding consecutively in the central nervous system, which find a correspondence in the alternate processes occurring in muscle elements” (Sokolov, 1975, p. 158). One of the very first subvocalization studies conducted by Jacobson (1931, 1932) and Max (1937) demonstrated that the participants who took part in their study had hidden muscle tensions while being fully engaged in finding solutions to various mental problems. Such findings on healthy individuals demonstrate that verbal thinking coincides with subvocalization and has been confirmed by further research (i.e. Davis, 1938; Shaw, 1940; Aserinsky & Kleitman, 1953; Woodworth & Schlosberg, 1962; Sokolov, 1975).

In this framework, AVHs were proposed to be due to the malfunction of internally generated speech, and thus should be accompanied by subvocalization that can be detected by EMG (Kandinskii, 1890). One of the very first to demonstrate this link between AVHs in schizophrenia and subvocalization was done by Gould (1948, 1949, 1950). By recording muscle potentials from both the chin and lips, Gould showed that “80% of schizophrenic patients with AVHs or with probable AVHs exhibited an increase in muscle potentials as they were hallucinating” (Ditman & Kuperberg, 2005, p. 282). Unfortunately, due to the fact that the author did not measure motor activity in nonvocal areas, there was a constraint in determining whether AVHs do increase motor activity, generally speaking (Ditman & Kuperberg, 2005). A different study by McGuigan and

colleagues (1966) chose “the chin, tongue and nondominant arm from one psychotic patient during periods of on and off hallucinations”, and found that there was increased EMG activity prior to reporting the hallucinations, and such activity was at its peak in the midst of hallucination (Ditman & Kuperberg, 2015). This was further replicated by Inouye and Shimizu (1970). Further studies have shown that disrupting, blocking (i.e. Bick & Kinsbourne, 1987; Green & Kinsbourne, 1990), or suppressing subvocalization leads to a decrease in AVHs (Slade, 1974; Margo et al., 1981; Gallagher et al., 1994). Recently, Rapin and colleagues (2013, p. 2) recorded lip muscle activity in 11 schizophrenic patients throughout the duration of their AVHs and found “an increase in EMG activity in the orbicularis oris inferior muscle, during covert AVHs relative to rest state”.

It must be pointed out that the evident link in the form of a temporal relationship between AVHs and subvocalizations or inner speech has not been found consistently across these studies, which may come from a combination of limitations (e.g. Green & Kinsbourne, 1990). This may be because when these studies were conducted, the development of the precise diagnostic definitions of schizophrenia were recently undertaken, and thus the precise establishment of patient intake may have confounded the findings (Ditman & Kuperbeg, 2005). Secondly, the patient sample was small and thus insufficient to provide statistical significance (Ditman & Kuperbeg, 2005). Adding on, because of the sensitivity of EMG, the data obtained from the already small number of patients was further reduced (Ditman & Kuperbeg, 2005). Lastly, there was potential for high inter-subject variability that may have impacted surface electrode placement and affected signal detection, such as skin thickness, facial hair, subcutaneous fat, temperature, or humidity (Rapin, 2013).

The next theory was based on auditory verbal imagery, which “refers to the process of imagining speech”, the malfunction of which could potentially be attributed to AVHs (Shergill et al., 2001, p. 241). Based on this, a patient with AVHs is thought to experience “vivid and lifelike mental imagery” and “this experience was theorized to be so convincing that the hallucinating individual would be led to believe that they actually heard a voice speaking; the vivid imagery explanation of AVHs” (Seal, 2004, p. 45). A review conducted by Seal (2004) found that a number of early studies tried their hand at investigating the link between AVHs and aberrant auditory imagery (i.e. Coren, 1938; Roman & Landis, 1945). Until now, only one study has been able “to identify the relationship between vividness of auditory mental imagery and predisposition to AVHs”

(e.g. Mintz & Alpert, 1972). Further complicating matters, some studies have found that schizophrenic patients with AVHs have decreased auditory imagery compared to those without AVHs (e.g. Seitz & Molholm, 1947; Starker & Jolin, 1982; Seal, 2004).

More recent theoretical background proposes that inner speech is reflected as AVHs because of the malfunction in verbal self-monitoring, as proposed by Frith (1987, 1992). The basis of this theory is that there is a malfunction in the brain's monitoring system which does not distinguish self-generated action from externally generated actions. This 'self-monitoring' system "misattributes self-generated actions to an external agent", and as a consequence patients with AVHs fail to monitor their own actions, in this case speech (Frith, 1992, p. 73). This may stem from a mechanism known as 'corollary discharge' or 're-afference copy', first observed by Helmholtz (1866), which "depends upon a comparison between intentions to move and actual movements" that is based on an 'internal forward model' (Frith, 1992, p. 74). In addition, it is proposed that "efference copy signals are used to make a prediction of the sensory consequences of the motor act and this prediction is then compared with the actual consequences of such an act", and that "if the prediction matches the actual sensory consequences then the sensation is likely to be self-generated" (Blakemore et al., 2000, p. 1131-1132). Thanks to the workings of this mechanism, self-produced action can be distinguished from other factors, such as the stimuli created by the environment. Any form of malfunction in the self-monitoring system thus causes given thoughts or actions to be 'detached' or isolated from the individual and their sense of will (Frith, 1992; Blakemore et al., 2000). In this manner, the voices that schizophrenic patients experience seem to be coming from 'outside' of the individual rather than from 'within' the individual. Despite having the intention to speak, the patient is unaware of having initiated speaking, and so from their perspective it seems that the sense of initiation comes from an external source.

Due to this phenomenon, only a handful of studies have attempted to test the theory of auditory verbal imagery and speech monitoring as the basis for AVHs by implementing different tasks.

One such study by McGuire and colleagues (1995) examined three groups of participants (6 schizophrenic patients with AVHs, 6 schizophrenic patients without AVHs, and 6 healthy controls). They were presented with three tasks. The control tasks consisted of the participants silently reading single words which consisted of adjectives salient to the experienced AVHs (from derogatory, complementary to neutral), such as 'stupid', 'clever', 'awake'. In the inner speech task, patients were presented with the same

stimuli as in the control task, but were also asked to “mentally recite a sentence ending with the presented words in their usual inner voice, without making articulatory movements”, such as ‘You are [stupid]’ (McGuire et al., 1995, p. 597). In the auditory verbal imagery task, subjects engaged in the inner speech task, but were asked to “imagine the sentences being spoken to them in an unknown expressionless voice that they had heard on a tape while practising the task” (McGuire et al., 1995, p. 598). Once the participant completed the two active experimental conditions, they were asked to rate “their ability to perform the task as instructed on analogues scales of 0-10” (McGuire et al., 1995, p. 598).

The authors (1995, p. 596) found that during the auditory verbal imagery task, which involves generating and monitoring of inner speech, patients with AVHs demonstrated “reduced activation in the left middle temporal gyrus (MTG) and the rostral supplementary motor area (SMA) which were activated by both normal subjects and non-hallucinators”. Such results are interesting as the left MTG is activated “by tasks which entail speech analysis including alien speech when it may be involved in the internal perception of speech” (McGuire et al., 1995, p. 599). Furthermore, the SMA “is involved in the initiation of movement, including articulation, and lesions in this area can produce the alien limb syndrome, when the limb contralateral to the lesion makes apparently purposeful movements without the patients’ intent”. The authors (1995, p. 599) conclude by stating that “a predisposition to AVHs might reflect aberrant connectivity between areas concerned with the generation and monitoring of inner speech, and hence defective communication between the mind’s voice and the mind’s ear”.

Shergill et al. (2000b) examined the internal speech model with a paradigm in which 8 schizophrenic patients experiencing AVHs were presented with four conditions in an fMRI study. In the inner speech condition, “subjects silently articulated a sentence in the form “I like...” or “I like being...” ending with the presented word” (Shergill et al., 2000, p. 1691). In the first person imagery conditions, the subjects were exposed to the same stimuli as in the previous task, but were asked to imagine “the sentence spoken in their own voice”. In the second-person imagery condition, participants were to imagine a sentence “in the form ‘You Like...’ or ‘You like being...’ ending with the presented word and spoken to them in the voice heard during screening” (Shergill et al., 2000b, p. 169). In the third person imagery condition, participants were to do the same procedure as in the second-person imagery condition, except they were to imagine a sentence “in the form ‘He likes...’ or ‘He likes being...’ ” (Shergill et al., 2000b, p. 1691). In a total of 6 (of 8)

patients with AVHs, the authors (2000b, p. 1691) found that “patients showed no differences while generating inner speech but experienced a relatively attenuated response in the posterior cerebellar cortex, hippocampi, and lenticular nuclei bilaterally and the right thalamus, middle and superior temporal cortex, and left nucleus accumbens during auditory verbal imagery”. The authors (2000b) concluded by emphasizing the implication of functional abnormalities or defects in areas responsible for verbal self-monitoring.

Fu and colleagues (2001) conducted a PET study in three groups of patients (10 patients with acute psychotic symptoms, 6 patients in remission, and 10 healthy controls). They were asked to read adjectives out loud, and “heard their voice which was either: undistorted; distorted (by a pitch change); replaced by another male (“alien”) voice; replaced by a distorted male voice” (Fu et al., 2001, p. S1052). The participants were asked to indicate the source of the heard voice as either ‘self’, ‘other’ or ‘unsure’ by pressing a button. The authors (2001, p. S1052) demonstrated that when healthy controls were exposed to their own voice in a distorted manner, “the hippocampus, cingulate and cerebellum were particularly activated”, whereas when acutely psychotic patients were exposed to the stimuli “they mis-identified their distorted voice as ‘other’ and failed to engage these areas”, and thus showed impairment in their performance. Patients in remission, however, exhibited intermediate results between the other two groups. The authors (2001, p. S1052) concluded that the verbal self-monitoring system consists of a network of brain regions “implicated in the generation and perception of speech”, and the group of patients with acute psychotic symptoms demonstrates a defect in the engagement of the brain regions found in the given network. Thus, such patients have deficits in verbal self-monitoring which may be the underlying mechanism behind AVHs.

Similarly, Sommer and colleagues (2008) attempted to capture AVHs in an fMRI study by asking 24 psychotic patients to squeeze a balloon when experiencing AVHs, and to release it when the AVHs end. Patients were to indicate their AVHs not only when in a resting state (thus testing the perceptual model in this condition), but also during a *paced letter fluency task* in which the subjects had to silently generate a word that started with a given letter of the alphabet that was displayed on a screen inside the scanner. As this task targeted language brain areas, this allowed the authors to directly compare brain activity during hallucinations and determine whether such areas responsible for language processing are responsible. Brain activation for AVHs was mostly found in the right hemisphere, specifically in “the right inferior frontal area, including the right insula, and

Broca's homologue, (...) left insula, bilateral supramarginal gyri, and the right STG" (Sommer et al., 2008, p. 4). However, no such activation was found in Broca's area or the left STG. Brain activation for the language task was found "in the Broca's area and to a lesser degree its contralateral homologue, both extending to the left insula, the STG, the MTG (...) the ACC" (Sommer et al., 2008, p. 4). In this way, activation was generally found more on the left side. With the lack of activation in the PAC, the authors (2008, p. 7) concluded by stating that "hallucinations mainly activate the right homologues of the language areas, especially the insula and the right homologue of Broca's area, while normal language production predominantly activates frontal and temporal language areas in the left hemisphere".

Such results are significant, as this particular study is one of the first functional neuroimaging studies to recruit over 20 participants, allowing for sufficient statistical power when compared to previous studies, which recruited between 1 to 8 participants (e.g. Sielbersweig et al., 1995). One potential confounding factor may be that the authors substituted the traditional button press with squeezing a balloon for the purposes of indicating the onset and end of AVHs. Such alterations in the methodology may create a difference in the specific timing of AVHs when comparing button press versus balloon squeezing, particularly as participants were to release pressure on the balloon to indicate the end of their hallucination. The limiting details of the motor task may be reflected in the peculiarities of the elicited brain activation - motor activity in particular is generally expected "in the motor cortex and SMA of the contralateral hemisphere and in the right cerebellum", whilst this study only showed significant activation in the right inferior frontal area (Sommer et al., 2008, p. 8; Cramer et al., 2002). To move forward, future research could aim at comparing the timing of both techniques in one experimental paradigm.

Waters and colleagues (2012) conducted a review of studies using a wide variety of tasks, all aimed at determining whether the perceived stimuli (such as words or the patient's own distorted voice) were self-generated or externally generated. They found that performance on these tasks was worse in schizophrenic patients with AVHs than in those without AVHs, although the number of studies was low. Yet, as demonstrated above, to date, very few functional imaging studies have examined cognitive models of AVHs.

To sum up, a number of studies have attempted to investigate inner speech via different experimental paradigms, yet not only do results remain inconclusive, but there

is also a lack of such experimentation. In addition, the theory that would underlie such experimentation is in the process of being formulated.

One way of tackling the question of whether inner speech and its malfunction results in AVHs in schizophrenia is by taking into consideration the verbal component of working memory, or *the phonological loop* (Frith, 1992, p. 72). The phonological loop is “the central component to working memory of verbal material” (Buchsbaum, 2016, p. 866). It “is used for the temporal usage of verbal material and to hold the inner speech needed for short-term memory tasks”, being “a slave system that is under the supervisory control of the central executive component” (Frith, 1992, p. 72; Buchsbaum, 2016, p. 866; Baddeley, 1986, 2000; Baddeley & Hitch, 1974). What is more, it is composed of two elements: *the phonological store*, or “passive buffer wherein verbal information can be stored for brief (approximately 2 s) periods”; and *the articulatory rehearsal process*, which “serves to refresh the contents of the store, thereby allowing the system to maintain sequences of verbal items in memory over some interval of time” (Buchsbaum, 2016, p. 866). As there is a division of labor, both components consistently interact with one another.

The idea to consider the phonological loop comes from Baddeley and colleagues (1986), who posit that “the loop and its rehearsal processes are operating at a much deeper level...apparently relying on central speech control codes which appear to be able to function in the absence of peripheral feedback... it is not surprising that attempts to study inner speech through the monitoring of the peripheral speech musculature have had only limited success”. The phonological loop is thought to be responsible for subvocal repetition (such as “remembering a string of digits for a short-time which can be achieved by repeatedly saying the digits subvocally”).

Based on these premises, to test the other side of the Cognitive Model a paradigm that generates rhyming judgements which dips into phonological encoding, should provide the answer as to whether malfunction to inner speech acts as the main generator of AVHs shall be proposed.

2.2.2.4. Proposal of Rhyming Task Experimental Paradigm

The same three groups of participants will take part in this paradigm. All subjects will perform a rhyming task during the fMRI scan. In the experimental condition, participants will be presented with 2 images of 2 different objects and will be instructed to think about the name of each of the objects and decide whether they rhyme or not. One

crucial element is that illustrations of all objects will be used instead of written words. This is because Spanish is a language in which the task of rhymes can be done based on visually comparing the sequence of letters, thus orthographically speaking, pictures will be used to avoid this. Participants will provide their answer for every pair by pressing a button. For “yes”, they will press a button with their right index finger, and for “no” they will press a button with their left index finger. The assignment of the buttons will be counterbalanced across all participants in all three groups. The rhyming task will be presented in blocks of 15s. At the end of each block, the participant will be asked if they experienced AVHs, to which they will answer with the same manual response. In the control condition, 2 distorted images will be presented in each trial, and the participant must decide if they are the same, giving the same manual response. As before, at the end of the block they will be asked if they experienced AVHs during that block. Lastly, between blocks, a fixating point will be presented for 15s that will act as a baseline. The paradigm is presented in *Figure 6*.

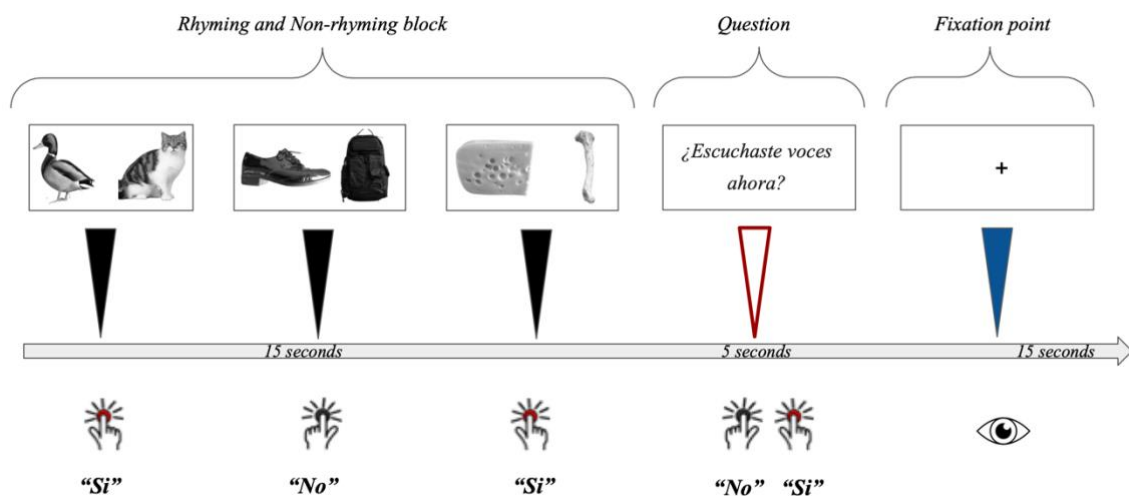


Figure 6. Proposal of the *Rhyming Task*.

The significance underlying this task is twofold. Firstly, rhyming requires processes of phonological coding that dip into internal speech and short-term verbal memory. Secondly, deciding whether the distorted images are the same or not requires only perceptual processes because, by not being able to identify the object represented, phonological and semantic processing are avoided.

Therefore, in Group 1 (the patient group with AVHs), the rhyming judgement blocks with the presence of hallucinations will be compared with the rhyming judgement

blocks without hallucinations. This shall be done for the purposes of assessing whether hallucinations modulate the activity of brain regions that are involved in the phonological encoding and short-term verbal memory. The statistical analysis will be performed at a level of $p < 0.05$, corrected at the cluster level using Gaussian field methods, with a voxel level threshold of $z > 3.1$ ($p < 0.001$, uncorrected).

a) Hypotheses

1. *It is hypothesized that verbal short-term memory mechanisms are involved in AVHs.*
2. *Patients with frequent AVHs will show a pattern of brain activation associated with short-term verbal memory different from that of patients without AVHs and healthy controls.*
3. *Activation differences will be located in regions involved in the short-term maintenance of verbal material (Broca's area, premotor regions, and supramarginal gyrus of the left hemisphere)*
4. *Alternatively or additionally, the activity of these regions will be temporarily altered when hallucinations occur.*

Of particular note here is that no previous study has provided appropriate stimuli in the Rhyming task suitable for the Spanish population.

Therefore, *the aim of the experimental part of this TFM* is to run a pilot study that attempts to design and test the stimuli in Spanish for the Rhyming Task that will be utilized in the prospective fMRI study for Spanish-speaking schizophrenic patients and healthy controls.

b) Hypotheses

1. *It is hypothesized that the rhyming and non-rhyming pairs chosen for the Rhyming task will generate enough agreement by being appropriately named by the majority of healthy participants.*
2. *The groups of rhyming and non-rhyming stimuli will be rated as emotionally positive or neutral.*
3. *There will be no differences in emotional valence ratings between rhyming and non-rhyming stimuli.*

3. METHODOLOGY

3.1. Data acquisition

All data was acquired via Psychtoolkit (Stoet, 2010, 2017), which saved all data inputs, and extracted them in an excel file.

3.2. Participants

Participants were recruited via different social media outlets by researchers from their circles of relatives and acquaintances, as well as independent sources in the community. All participants provided their consent online right before beginning the survey. This pilot study was approved by FIDMAG Hermanas Hospitalarias Research Foundation's Ethical Committee.

3.3. Stimuli

The original stimuli consisted of 21 rhyming pairs, and 19 non-rhyming pairs. The stimuli were first created by putting together Spanish nouns that are frequent in everyday use in either rhyming or non-rhyming pairs. The criteria for two words to form a rhyming pair consisted of them having *perfect rhyme*, meaning that both words were to have an identical stressed vowel sound, any following sound was identical, and the onset of the stressed syllables in both words would be completely varied. The criteria for two words to form a non-rhyming pair consisted of them not meeting the aforementioned conditions. In either case, both words ought to have had the same number of syllables. What is more, the number of categories of objects was aimed to be even across rhyming and non-rhyming pairs (i.e. people, animals, food etc.) as demonstrated in *Appendix 1*. In addition, all pairs consisted of two different categories (i.e. animals and fruit) and could not be semantically related (i.e. not *cat & dog* but *dog & pencil*).

Once the word pairlist was created, 2 image corpi representing objects were used for all rhyming and non-rhyming pairs, as demonstrated in *Appendix 2*. The first corpus was borrowed from Hebrat and colleagues (2019), and the second corpus was specifically created for this study. The images taken from the first corpus, initially colored, were first desaturated, the background was erased, and a white background was applied so that the main object was in the foreground, and then the whole image was resized to 400 x 400 pixels. The images taken from the second corpus were first created, smoothed, desaturated, the background was erased, and a white background was applied so that the main object

was in the foreground, and then the whole image was resized to 400 x 400 pixels. Next, 2 sets of the same images were made. The first set was used to put together images according to the word pair they belonged to (implemented in Task 1 and Task 2). The second set was used for each image to be separated (implemented in Task 3).

3.4. Procedure

Participants were sent a direct link to the online survey via social media outlets. When the link was opened, the survey began with the participants being exposed to a detailed account of the aim of the survey, which was followed by them providing their consent to gather data. The first 6 questions, aimed at acquiring demographic information, in which participants were asked to provide feedback on their gender, age, birthplace, place of residence, mother tongue, second language, and other potential foreign languages that they spoke. Next, the participants were provided with a detailed account of the instructions to the first task, and they were to check a box acknowledging that they understood the instructions well, allowing them to move onto the next question.

Having done all the above, the participants were then able to begin the first part of the survey, which consisted of two tasks. In the first task, *Rhyming Judgement Task*, they were presented with 2 objects and were asked whether their names rhyme (i.e. *niña* - *piña*). If the pair of objects rhymed, the participants had to tick yes (“Sí”), and if they did not rhyme (i.e. *zapato* - *mochila*), they had to tick no (“No”). Next, participants were presented with the second task, *Object Naming Task*, in which the same pair was presented again and were asked to provide the specific name for each object separately.

After the participants completed the first part of the online study, they were then presented with the second part of the survey, which consisted of the third and final task, *Rating Task*, in which they were presented with each of the pictures used in the task and were asked to rate their emotional valence on a scale from 1 to 5 (1 = *very negative*; 2 = *negative*; 3 = *neutral*; 4 = *positive*; 5 = *very positive*), using the self-assessment manikin (Bradley and Jang, 1994)

Once the participants finished the survey, they were asked whether they wanted to leave a comment for the researchers voluntarily, after which they were redirected to the end of the survey.

3.5. Data Cleaning

Once the data of the survey was collected from Psychtoolkit (Stoet, 2010, 2017), it was diligently cleaned in excel.

Firstly, data was not considered from participants who *did not* provide their consent (5 out of 84). Secondly, data was also excluded from participants who: did not understand the instructions (1 out of 84); provided responses to more than one example of either task due to closing the survey (27 out of 84); providing an answer inconsistent with the requirements (e.g. 1 participant wrote “z” for the first couple of questions) (1 out of 84). Here it must be noted that the survey was designed specifically for participants not to skip examples, yet 1 participant missed their response to one example. This must have been due to a glitch in the program, and so their data was not included in the analysis. On a different note, 2 other participants whose birthplace was not in Spain (i.e. *Veracruz*, Mexico; *Odessa*, Ukraine) were not included due to the possibility of deviation from European Spanish (2 out of 84). In addition, 1 participant conducted the study fully in Catalan rather than Spanish, so their results were omitted (1 out of 84). Thus, out of 84 participants, a total of 47 participants, having completed the survey and being born in Spain, were included in the analyses. We also excluded responses for 2 rhyming pairs due to an error in the number or structure of syllables (i.e. *delfin - calcerin*) and erroneous sound pattern (*avión - bastón*). Thus, the final set of stimuli consisted of 19 rhyming pairs, and 19 non-rhyming pairs.

All participant responses were then unified, particularly in the *Object Naming Task*, in which participants were to provide the name for every object in every pair. Firstly, all responses were transformed from upper-case to lower-case (e.g. *Archivador* to *archivador*; *LIBRETA* to *libreta*). In addition, because Psychtoolkit (Stoet, 2010, 2017) did not save the Spanish spelling appropriately, all words were accented where necessary (e.g. *JudÃ-a* to *judía*; *sueter* to *suéter*). All misspellings were then corrected for, such as missing letters (e.g. *jean* to *jeans*; *goma de borar* to *goma de borrar*; *crocil* to *crocodilo*); additive letters (*mochilla* to *mochila*; *copia* to *copa*); spelling mistakes (*aveja* to *abeja*; *tecladi* to *teclado*; *calcetij* to *calceñin*; *blobo* to *globo*). What must be mentioned is that all descriptive data, particularly *place of birth*, *place of residence*, *mother tongue* and all *foreign languages* were translated to English, whereas the participant responses for *all tasks* were left in Spanish. Lastly, some participants provided more than one name for an object, and thus, only the first noun was taken into consideration, and any informative

responses, such as descriptive adjectives, were dropped (i.e. *vaca*, *buey*, *ternera* to *vaca*; *rosa roja* to *rosa*).

3.6. Statistical Analysis

All statistical analyses were conducted by utilizing SPSS for Mac (version 2018) and Python (3.8 version). The level of statistical significance was set at 0.05 across all statistical tests. Tests were used to conduct comparison between rhyme and non-rhyme stimuli and potential effects on rating.

4. Results

4.1. Demographic information

Demographic information for all 47 participants can be found in *Table 1*.

The total number of participants in the online survey was 84. The reported results, however, come from 47 participants, after data cleaning, who successfully completed the survey and come from the territory of Spain. Out of 47 participants, 19 were male, 26 were female, and 2 identified as other, of which the youngest was aged 16 and the oldest was aged 70 (data from participants under 18 was included since no personal data was collected in this study). Their mean age was 36.12 (SD = 15.83). Such an average age of healthy participants in this study is similar to the average age of schizophrenic patients with AVHs who take part in functional neuroimaging studies (i.e. Shergill et al., 2001; Copolov et al., 2003; Diederer et al., 2010; McCarthy-Jones et al., 2014; de Boer et al., 2019).

The most common birthplaces were the Balearic Islands (10 participants), Madrid (10 participants), and Barcelona (9 participants). The most common place of residence were Barcelona (12 participants), Madrid (11 participants), and Balearic Islands (10 participants).

Education-wise, 35 participants were university educated, 8 received high school education, and 4 received vocational training. With regards to occupation, 23 participants were employed, 11 were students, 7 were students and workers, 3 were unemployed and 3 were self-employed.

The mother tongue for 30 participants was Spanish, and for 17 participants was Catalan. Next, 46 participants spoke a second language, the most common being English (22 participants), Spanish (14 participants), and Catalan (7 participants). Furthermore, 29

participants spoke a third language, the most common being English (16 participants) and French (6 participants). Moreover, 10 participants spoke a fourth language, the most common being French (3 participants) and English (2 participants). Lastly, the total time that it took all 47 participants to complete the survey is approximately 26 minutes (mean 25.78, SD 10.89).

Table 1. Demographic information of all participants.

	<i>N</i>	%
Sex		
female	26	55.3%
male	19	40.3%
other	2	4.3%
Place of Birth		
balears	10	21.3%
madrid	10	21.3%
barcelona	9	19.1%
granada	2	4.3%
zaragoza	2	4.3%
cádiz	2	4.3%
valencia	1	2.1%
zamora	1	2.1%
alicante	1	2.1%
sevilla	1	2.1%
mallorca	1	2.1%
ciudad real	1	2.1%
lleida	1	2.1%
tarragona	1	2.1%
pontevedra	1	2.1%
asturias	1	2.1%
cadiz	1	2.1%
castellón	1	2.1%
Place of Residence		
barcelona	12	25.5%
madrid	11	23.4%
balears	10	21.3%
granada	3	6.3%
alicante	3	6.3%
tarragona	1	2.1%
pontevedra	1	2.1%
araba	1	2.1%
cáceres	1	2.1%
ciudad real	1	2.1%
mallorca	1	2.1%
cádiz	1	2.1%
almería	1	2.1%
Education		
university	35	74.5%
vocational training	8	17.0%
high school	4	8.5%

Occupation		
employed	23	48.9%
student	11	23.4%
student/employed	7	14.9%
self-employed	3	6.4%
unemployed	3	6.4%
Mother Tongue		
spanish	30	63.8%
catalan	17	36.2%
Second Language 1		
english	22	46.8%
spanish	14	29.8%
catalan	7	14.9%
french	2	4.3%
galician	1	2.1%
-	1	2.1%
Second Language 2		
-	18	38.3%
english	16	34.0%
french	6	12.8%
sign language	2	4.3%
catalan	1	2.1%
italian	1	2.1%
japanese	1	2.1%
russian	1	2.1%
spanish	1	2.1%
Second Language 3		
-	37	78.7%
french	3	6.4%
english	2	4.3%
arabic	1	2.1%
basque	1	2.1%
danish	1	2.1%
german	1	2.1%
italian	1	2.1%

4.2. Stimuli Selection

Out of the total rhyming and non-rhyming pairs presented to participants, the pairs that were chosen for the prospective fMRI study were based on high agreement of object names as appropriately named by the majority of participants and positive or neutral emotional ratings as shown in. The total number of chosen pairs of both groups is 24 (12 rhyming pairs and 12 non-rhyming pairs), as the rhyming judgement condition in the prospective fMRI study consists of 24 trials.

The descriptive analysis is shown below.

4.2.1. Rhyming Judgment Task

Based on the chosen pairs for both groups, the frequency of rhyming judgements (*Table 2*) and non-rhyming judgments (*Table 3*) for every pair was calculated as presented below.

Table 2. Frequency of *rhyming judgements* for every pair.

<i>Rhyming Pairs</i>		
<i>Pair</i>	<i>"Yes" Frequency</i>	<i>"No" Frequency</i>
pato - gato	47	0
cama - rama	47	0
nariz - maiz	46	1
oreja - abeja	45	2
ventana - manzana	45	2
fresa - mesa	43	4
queso - hueso	47	0
niña - piña	46	1
globo - lobo	46	1
capa - mapa	46	1
cubo - tubo	45	2
helado - teclado	42	5

Table 3. Frequency of *non-rhyming judgements* for every pair.

<i>Non-Rhyming Pairs</i>		
<i>Pair</i>	<i>"Yes" Frequency</i>	<i>"No" Frequency</i>
gorra - dado	1	46
vaso - cuna	1	46
rosa- regla	0	47
llave - cerdo	0	47
mochila - zapato	1	46
tenedor - lechuga	0	47
falda - coche	0	47
perro - lapiz	1	46
calabaza - elefante	0	47
esqueleto - cocodrilo	0	47
tomate - cuchara	0	47
goma - jersey	0	47

4.2.2. Object Naming Task

The objective of this analysis was to determine the frequency of responses of names for every object in every pair (rhyme and non-rhyme) and in this way chose the 12 pairs of both categories with the highest agreement.

With the help of Python (version 3.8), the first step that was taken was counting the frequency of a given word for every object in the rhyme-pairs. For instance, for the object *folder*, 27 participants said *carpeta*, 14 participants said *libreta*, 4 participants said *cuaderno*, 1 participant said *clasificador*, 1 participant said *archivador*. A summary of all responses for the rhyme objects can be found in **Appendix 3**, and all responses for the non-rhyme objects can be found in **Appendix 4**. Once said frequency was counted, the percentage of participants selecting the most frequent word (percentage of agreement) was calculated. For instance, in the previously mentioned example (which consists of a rhyming pair *carpeta-galleta*) for the object *folder*, the most frequent is *carpeta* according to 27 participants (57%), and for the object *biscuit*, the most frequent is *galleta* according to 47 participants (100%). This was done for every object of every rhyming pair as. The percentage of agreement for each pair was calculated as the average of the individual percentages of agreement for the 2 objects forming the pair (e.g. 78.5% in the previous example). All pairs were then sorted in a descending fashion, and the top 12 with the highest agreement were selected (as the rhyming judgement condition in the fMRI

scanner requires 24 trials, thus 12 pairs of both groups are needed). The chosen pairs as shown in **Table 4**.

Table 4. Rhyming Pairs with highest agreement. The chosen 12 are highlighted in red.

<i>Rhyming Pairs</i>							
<i>Stimulus 1</i>	<i>Frequency 1</i>	<i>Percentage 1</i>	<i>Stimulus 2</i>	<i>Frequency 2</i>	<i>Percentage 2</i>	<i>Robust Percentage of Pair</i>	
pato	47	100%	gato	47	100%	100%	
cama	47	100%	rama	47	100%	100%	
nariz	47	100%	maiz	46	98%	99%	
oreja	47	100%	abeja	46	98%	99%	
ventana	46	98%	manzana	47	100%	99%	
fresa	46	98%	mesa	47	100%	99%	
queso	47	100%	hueso	46	98%	99%	
nina	45	96%	pina	47	100%	98%	
globo	47	100%	lobo	45	96%	98%	
capa	46	98%	mapa	46	98%	98%	
cubo	45	96%	tubo	45	96%	96%	
helado	42	89%	teclado	47	100%	95%	
foca	46	98%	boca	41	87%	93%	
ropa	36	77%	copa	47	100%	89%	
mantel	47	100%	pastel	37	79%	88%	
manta	38	80%	planta	38	81%	80%	
carpeta	27	57%	galleta	47	100%	79%	
bata	34	72%	rata	38	81%	76%	
casa	43	91%	gasa	23	49%	70%	

The same procedure was applied to the non-rhyming pairs and the results are shown in **Table 5**.

Table 5. Non-Rhyming Pairs with highest agreement. The chosen 12 are highlighted in red.

<i>Non-Rhyming Pairs</i>							
<i>Stimulus 1</i>	<i>Frequency 1</i>	<i>Percentage 1</i>	<i>Stimulus 2</i>	<i>Frequency 2</i>	<i>Percentage 2</i>	<i>Robust Percentage of Pair</i>	
gorra	47	100%	dado	47	100%	100%	
vaso	47	100%	cuna	46	98%	99%	
rosa	46	98%	regla	47	100%	99%	
llave	46	98%	cerdo	47	100%	99%	
mochila	47	100%	zapato	45	96%	98%	
tenedor	45	96%	lechuga	46	98%	97%	
falda	46	98%	coche	45	96%	97%	
perro	45	96%	lapiz	46	98%	97%	
calabaza	43	91%	elefante	47	100%	96%	
esqueleto	47	100%	cocodrilo	42	89%	95%	
tomate	46	98%	cuchara	41	87%	93%	
goma	41	98%	jersey	41	87%	87%	
reloj	47	100%	lata	35	74%	86%	
gallina	41	87%	cafe	35	74%	81%	
abrigo	32	68%	enchufe	43	91%	80%	
guisantes	27	57%	botella	47	100%	79%	
vino	30	63%	piernas	36	77%	70%	
bombilla	47	100%	pantalón	14	30%	69%	
mano	47	100%	vaca	37	79%	54%	

4.2.3. Rating Task

Since the aim of the task is to engage phonological encoding processes, the selected stimuli need to be emotionally neutral to avoid the confounding effects of emotional responses to the pictures. To ensure that this was the case, we extracted descriptive measures from the picture ratings, in terms of affective valence, and also compared the ratings of rhyming and non-rhyming pairs, to make sure no significant differences were found between the two groups of stimuli. Only the ratings of objects that are part of the 12 rhyming pairs and 12 non-rhyming pairs selected for the fMRI task were included.

Firstly, with the use of Python (version 3.8), data from outliers, or participants whose responses were extreme, were omitted. Thus, for this task, data from 45 out of 47 participants were considered.

Secondly, an independent two sample t-test between both the rhyming and non-rhyming groups was carried out (for which all assumptions were met). Firstly, to test for normality, *the Shapiro-Wilk Test of Normality* was applied which showed that $p > .05$ ($p = .71$). Thus, the sample is gaussian and the null hypothesis failed to be rejected, as both groups are approximately normally distributed. Similarly, there was homogeneity of variance of rating for rhyming and non-rhyming, as assessed by *Levene's Test for Equality of Variances* which showed $p > .05$ ($p = .48$). Lastly, the *Independent two sample t-test* showed no significant difference between both groups, $t(22) = -1.22$, $p = .23$.

5. DISCUSSION

Hearing voices, or experiencing auditory verbal hallucinations (AVHs) is a detrimental symptom of schizophrenia (among other conditions). Not having the opportunity to experience tranquility or the ability to control what is whispered in one's 'ear' affects the patient to a large extent. The complex phenomenological basis of AVHs demonstrates that they are not part of the patient's imagination, but are rather an additional feature of their perception of the world.

Despite their clinical significance, the origins of AVHs are still unknown. In order to find the key to their biological basis, an experimental design of a prospective fMRI study has been proposed that takes into consideration different perspectives that have targeted AVHs exploratorily of which two main approaches or models have been built.

The first, perceptual model, aims at understanding whether AVHs are due to the abnormal activity of the primary auditory cortex (which is part of the superior temporal gyrus), a brain area responsible for primary sound perception and processing. On the one hand, some single studies and meta-analyses have found activation in the auditory cortex during AVHs (Dierks et al., 1999, Lennox et al., 1999; Kompus et al., 2011), while others have not (Silbersweig et al., 1995; Lennox et al., 2000; Copolov et al., 2003; Diederer et al. 2010; Hoffman et al., 2011; Fuentes-Claramonte et al. 2021; Jardri et al., 2011; Kühn and Gallinat (2012); Zmigrod et al., 2016). The limitations of these studies, which range from not recruiting enough patients to not precisely controlling for motor activity, should not be understated, as they may have significantly confounded the main results. This demonstrates the conflicting nature of such studies, and does not fully provide a sufficient answer to whether aberrant activation in the PAC leads to AVHs. For this reason, the paradigm proposed to test this model is based on Fuentes-Claramonte and colleagues (2021), with a modification to control for motor activity. This is done by asking patients to press a button with both index fingers in the fMRI scanner during those time periods in which they do not experience AVHs.

The second, *the Cognitive Model*, has two sides which aim at understanding whether AVHs are due to either misattributions of intrusive or traumatic memories, or malfunction in inner speech. It must be pointed out that both the theoretical and experimental work behind both theories are still under construction, and many questions remain open.

One side of the Cognitive Model lies in the theory of episodic memory and more particularly, source memory failure, in which the retrieval of memories is fragmented. As such, the patient is confused regarding the origins of the memory. The activation of intrusive memories is theorized to come from the deficits in intentional inhibition and contextual memory, which causes auditory mental representation to intrude into consciousness - a phenomenon out of control for the patient. This goes hand in hand with the fact that some studies have shown that the parahippocampus becomes activated a few seconds *before* patients experience AVHs (e.g. Diederer et al., 2010; Hoffman et al., 2011), and that both the parahippocampus and hippocampus become activated *during* the experience of hearing voices (Silbersweig et al., 1995; Dierks et al., 199; Diederer et al., 2010; Jardri et al., 2011; Kompus et al. 2011; Zmigrod et al. 2016). One way of determining whether the intrusion of traumatic memories is the reason behind AVHs is by considering autobiographical memory - the active retrieval of personal past

experiences involving highly complex retrieval processes. This type of episodic memory activates a network of regions known which overlap with the neural network that is activated during resting or passive states, known as the DMN (which has been thought be impaired in schizophrenia, though the findings are inconclusive (e.g. Starck et al., 2005; Zhou et al., 2018; Martin-Subero et al., 2021). Although some studies have explored AM in schizophrenia, no previous study has placed enough emphasis on AVHs in schizophrenia and the potential link to AM. Because of this, the paradigm proposed to test this model, *the Autobiographical Recall Task*, relies on Fuentes-Claramonte and colleagues (2019), which has been validated by Martin-Subero and colleagues (2021). Here, patients will be presented with keywords that are designed to either evoke or inhibit autobiographical memories which the patients will share with the researchers prior to the study. In this way, the stimuli will be tailored individually to every patient taking part in the study.

The other side of the Cognitive Model lies in the malfunction of inner speech - a malfunction in the brain's monitoring system which does not recognize self-generated speech and attributes it to an external agent. Due to this, the voices that schizophrenic patients experience seem to be coming from 'outside' from the individual, rather than interpreting voices as coming from 'within' the individual. Despite having the intention to speak, the patient is unaware of having initiated speaking, and so for them it seems that the sense of initiation comes from an external source. The way in which this theory has been studied has been based on implementing a variety of tasks that target auditory verbal imagery, wherein the patient imagines speech or inner speech tasks which attempt to understand whether there is a breakdown in self-monitoring. Because of this, the paradigm proposed to test this model, the Rhyming Judgement Task, will present participants with 2 images of 2 different objects and will be instructed to think about the name of each of the objects and decide whether they rhyme or not. If the pair rhyme, they are to press a button with their right index finger, if the pair does not rhyme, they are to press a button with their left index finger.

Because of the fact that no study as of yet has tested the Spanish population with such image stimuli, a pilot study was conducted to determine the precise picture stimuli that will be used in the prospective fMRI study in the Inner Speech testing of the cognitive model. For this reason, an online survey asking participants whether the presented pairs rhymed, the names of both objects in each pair, as well as rating each object separately on the Likert scale was conducted. Based on the results, we were able to select the 12

rhyming and non-rhyming pairs with the greatest agreement in terms of rhyming (Yes/No) and the name assigned to the presented object. Furthermore, additional statistical analyses showed that there was no significant difference between rhyme and non-rhyme pairs in affective valence ratings. This will ensure that the stimuli used in the task will elicit, on average, the same verbal responses in most of the participants, and confounding factors like unclear object naming will not contaminate the observed brain activations in the fMRI study.

Only by taking a variety of approaches can the appropriate brain regions and circuits underlying AVHs be determined which may provide the appropriate clinical intervention, such as therapeutic targets for pharmacological or brain stimulation interventions which can lead to the improvement of the patient's life. With this in mind, this study has many advantages that can make this happen.

With regards to the prospective fMRI study, the major advantages are that it tests different approaches to find the biological basis of AVHs. In this way, the two major approaches (or three theories) that have been common across literature have been put together into one experimental design. Firstly, the entire prospective fMRI study aims to have 25 participants per group which will allow for statistically significant results. Gathering this number of participants per group will be doable as the FIDMAG research team cooperates with many different hospitals in Catalunya, and many of their previous studies have successfully included such a number of participants (i.e. Fuentes-Claramonte et al., 2019, 2021; Martin-Subero et al., 2021). In connection to this, apart from testing schizophrenic patients with AVHs and healthy controls, the prospective fMRI study will include schizophrenic patients *without* AVHs which will allow comparisons across a broad range of subjects, two groups having similar pathologies and divergent symptoms. With regards to the experimental design, it has been designed to last around an hour, which allows the participants to be tested in one sitting. Furthermore, the prospective fMRI study consists of paradigms that have already been tested for. For instance, the Symptom Capture Paradigm, which tests the perceptual model, and the Autobiographical Recall Task, which tests the intrusive memory theory (one side of the Cognitive Model), have both been meticulously experimented with by the research group that developed this TFM (i.e. Fuentes-Claramonte, 2019, 2021; Martin-Subero et al., 2021). What this TFM does suggest, however, are certain modifications to those paradigms that enable results overcoming previous limitations as shown in Figures 4, 5, and 6 in Section 2. In turn, the

experimental paradigm that targets inner speech theory (the other side of the Cognitive Model), has not been tested before on the Spanish population.

Similarly, the pilot study adds to the advantages of the fMRI framework. The online survey tested healthy participants who will most likely be matched to the recruited groups of schizophrenic patients with regards to age, as many studies outline that the mean age of schizophrenic patients recruited in studies targeting AVHs is around 35 (e.g. Sommer et al., 2008; Kompus et al., 2013 etc.). Furthermore, as the recruitment of patients will take place in hospitals residing in Catalunya, the majority of prospective schizophrenic patients may have a similar place of birth, place of residence, mother tongue and second language. In addition, the total number of participants whose data was considered was 47, which is a considerable sample size for a pilot study. With regards to the stimuli chosen, a sufficient number of both rhyming and non-rhyming pairs were tested to select the most appropriate ones, as the rhyming judgement condition in the prospective fMRI study will include 24 trials, hence the 12 pairs of each group.

Conversely, both the prospective fMRI study and pilot study may have some possible caveats that shall be mentioned.

With regards to the prospective fMRI study, testing schizophrenic patients in a functional neuroimaging study poses challenges because the severity of symptoms for some patients might not allow them to follow through with the entire experiment. Consequently, some patients might not be able to tolerate the conditions of fMRI experiment. Furthermore, the prospective schizophrenic patients will most likely be receiving antipsychotic drug treatment, which is a limitation in most functional imaging studies that investigate schizophrenia. On top of that, studying hallucinations is a complex procedure, as patients experience brief AVHs that are unpredictable, and thus are difficult to investigate when compared to other sensory experiences. Lastly, any potential limitations regarding each proposed paradigm will come to light only once the prospective fMRI is conducted.

With regards to the pilot study, even though the instructions of the study stated to use Spanish, what could have been more precisely mentioned is to not to use Catalan, as in some examples in the Object Naming Task, participants provided the names of objects in this language rather than Spanish (such as that 1 participant whose data was excluded as they used Catalan for the majority of responses). This may have been due to the frequency of usage of the given name of the object, and thus the most dominant word for a given object became activated, and so participants provided the first name that came to

mind. Similarly, what could also have been mentioned more explicitly is to only use *I word* for every object, in this way, participants would focus their attention on thinking of one name rather than four or five as took place in some cases. For instance, some participants added descriptive adjectives to the object (e.g. *rosa roja*). On a different note, the images that were chosen may not have been as well illustrated despite the pair being frequently used in Spanish, which caused some participants to have a difficulty with providing the names for objects as found in the pairs that were not chosen (i.e. *casagasa* or *mano-vaca*). Lastly, as the mean time of all participants is 25 minutes long, this may have been too long for the participants who were not rewarded for their participation. Taking these factors into consideration, participants' attention spans might have declined, along with their motivation, when they were conducting the pilot study - particularly the last task they were exposed to (the Rating task) - and thus some ratings may have been impacted by this.

Therefore, future research should precisely consider these implications when trying their hand at exploring AVHs, and when developing appropriate stimuli and corpi. One way to overcome these limitations would be to conduct the fMRI study itself, and test the mentioned experimental paradigms that target different perspectives of AVHs. By doing so, previous limitations found across many previous studies can be overcome.

Once conducted, our speculation is that brain activation during the symptom capture paradigm will not show significant activation in the PAC, but rather point to the significance of language areas, as they are the ones responsible for inner speech. Furthermore, although significant activation will be found in the autobiographical recall task during the evocation of negative memories, no significant difference will be found across all three groups, meaning that traumatic memories are less likely to be the cause of AVHs which will be reflected in brain activity. Therefore, the one likely premise is that malfunctions in inner speech, or self-monitoring, is the reason why schizophrenia patients experience voices. In this way, there will be activation differences in brain areas that are responsible for short-term maintenance of verbal material, such as the Broca's area and others. Taken together, our speculation is in line with Frith's (1992, p. 76) proposal: "some auditory hallucinations are based on inner speech which the patient misattributes to an external source".

6. CONCLUSIONS

In summary, this study has attempted to make two significant contributions to the fields of Cognitive Science and Psychiatry. The first attempt was to propose an experimental design of a prospective fMRI study which targets different aspects of the biological basis of AVHs: abnormal activation in the auditory cortex; the misinterpretations of intrusive or traumatic memories; the malfunction in inner speech, or speech monitoring. This was done by proposing three different experimental paradigms, created and validated by previous research, and by implementing certain modifications to overcome previous limitations. The second attempt was to develop novel stimuli (12 rhyming and 12 non-rhyming pairs) that will be implemented in the rhyming judgement condition in the fMRI study, which tackles the malfunctioning in inner speech. The chosen stimuli (12 rhyming pairs and 12 non-rhyming pairs) was based on having high agreement of object names as appropriately named by the majority of participants and having positive or neutral emotional ratings.

Solely by taking such a diverse approach to understanding the biological basis of AVHs can the most fundamental aim of research on hallucinations be addressed: pinpointing the brain regions which are responsible for the genesis of AVHs. In doing so, there can be a direct impact on this symptom of schizophrenia at hand - only then can sufficient clinical intervention be devised, such as personalized medicine in the form of pharmaceutical intervention or brain stimulation. In treating a disease as heterogeneous as schizophrenia, such knowledge is imperative in adjusting treatments to the needs of each patient so that the maximum clinical improvement is obtained minimizing the risks and the adverse effects.

Those, like Socrates, whose voices deter them from their actions and intentions, by whispering ill omens in the vacuum of tranquility, may finally achieve the silence of their “soul”.

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APPENDICES

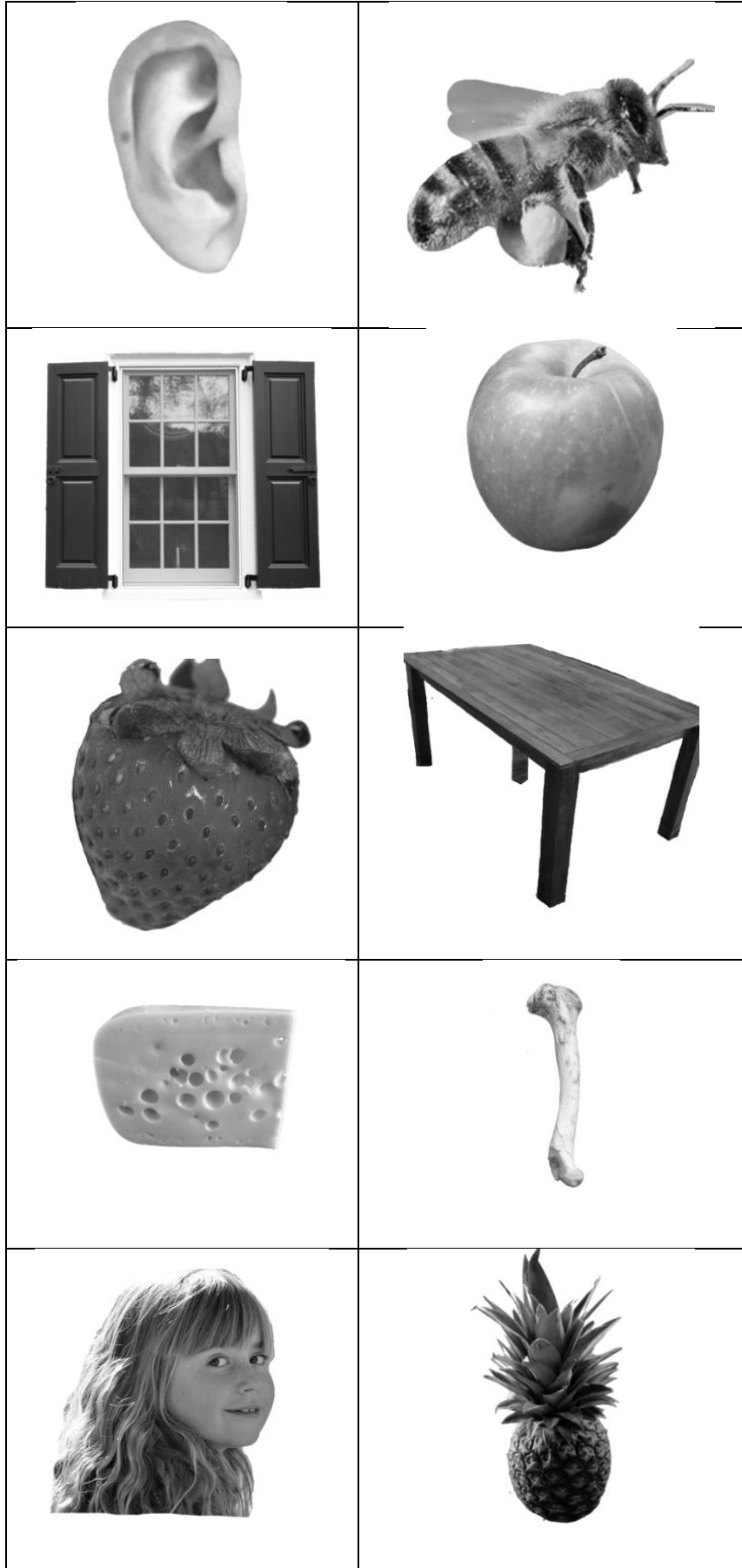
APPENDIX 1

Rhyming Pairs		
<i>Category of Stimuli</i>	<i>Object</i>	<i>Frequency</i>
Body Parts	boca	4
	nariz	
	oreja	
	hueso	
People	nina	1
Animals/Insects/Nature	foca	9
	pato	
	gato	
	rata	
	abeja	
	delfin	
	lobo	
	planta	
	rama	
Food	fresa	8
	helado	
	galleta	
	queso	
	manzana	
	pastel	
	piña	
	maiz	
Clothing/Accessories	ropa	6
	bata	
	capa	
	calcetin	
	bastón	
Transportation	avión	1
Household items	ventana	9
	copa	
	casa	
	mantel	
	cubo	
	tubo	
	manta	
	cama	
mesa		
Office items	carpeta	3
	mapa	
	teclado	
Singular	gasa	2

Non-Rhyming Pairs		
<i>Category of Stimuli</i>	<i>Object</i>	<i>Frequency</i>
Body Part	pierna esqueleto mano	3
People	-	0
Animals/Insects/Nature	pollo cocodrilo elefante cerdo vaca perro rosa	7
Food	cafe vino guisante calabaza lechuga tomate	6
Clothing/Accessories	zapato suéter vaqueros gorra mochila falda chaqueta gorra	8
Transportation	coche	1
Household Items	reloj bombilla botella cuna vaso clave tenedor	7
Office Items	goma lapiz enchufe regla	4
Singular	dado cuchara	3

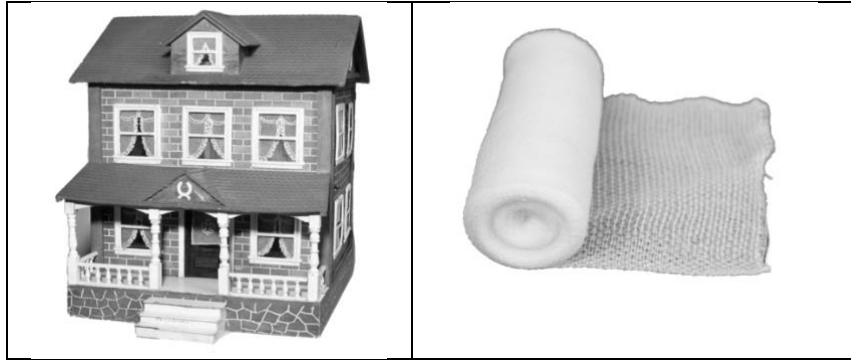
APPENDIX 2

<i>Rhyming Pairs Stimuli</i>	
	
	
	





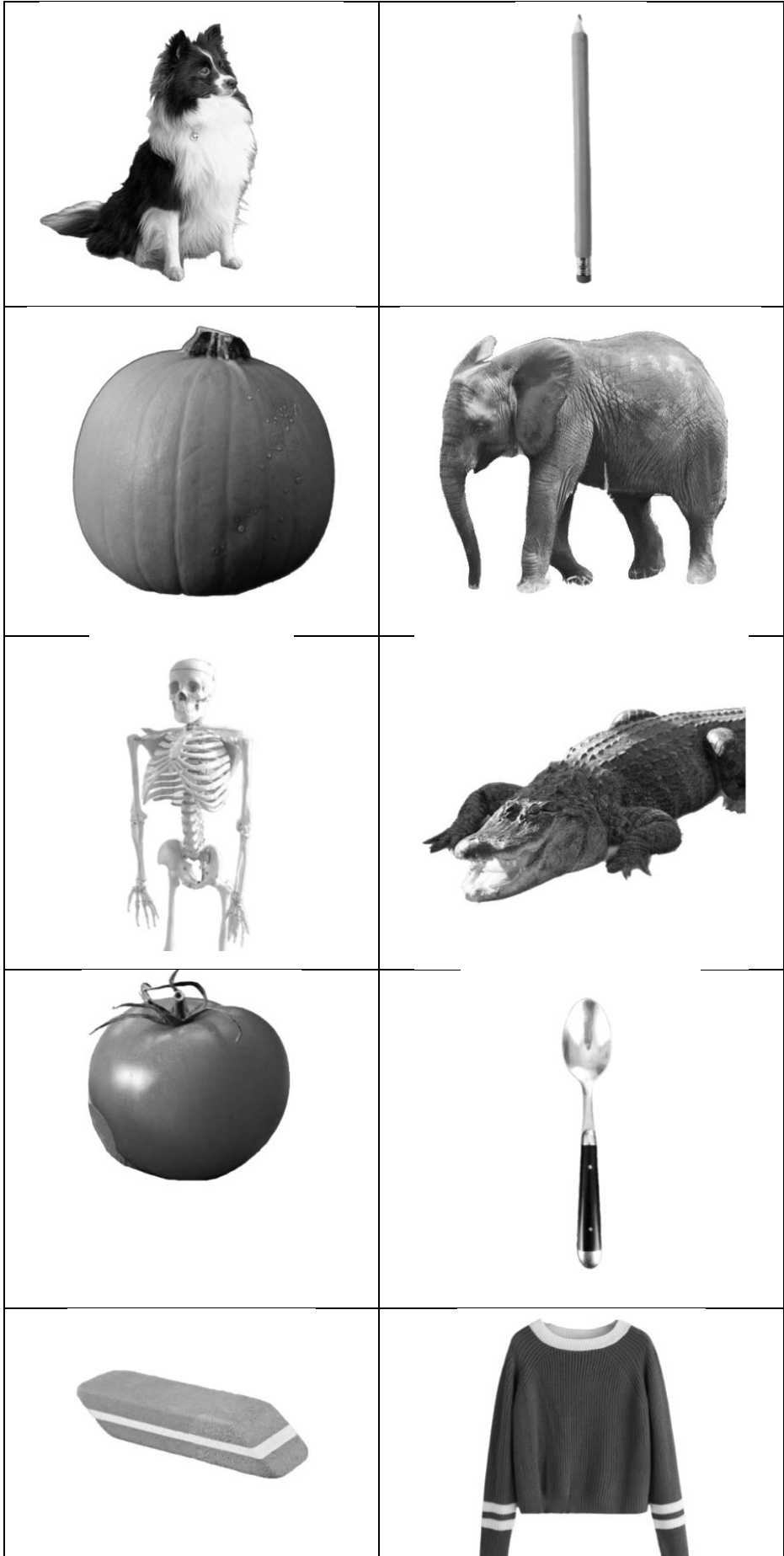




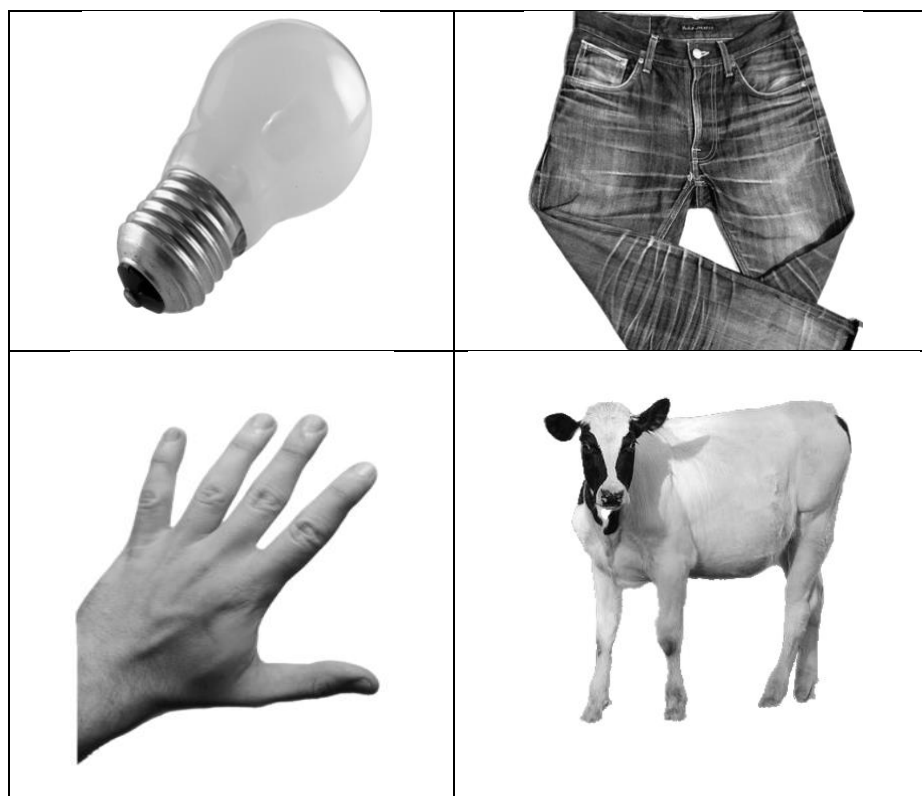
Non-Rhyming Pairs









APPENDIX 3

<i>Rhyming Pairs</i>						
<i>Pair Name</i>	<i>Stimulus 1</i>	<i>Frequency 1</i>	<i>Stimulus 2</i>	<i>Frequency 2</i>		
<i>carpets- galleta</i>	carpeta	27	galleta	47		
	libreta	14				
	cuaderno	4				
	archivador	1				
	clasificador	1				
<i>ventana-manzana</i>	ventana	46	manzana	47		
	contras	1				
<i>foca-boca</i>	foca	46	boca	41		
	leopardo					
	marino	1			labios	6
<i>manta-planta</i>	manta	38	planta	38		
	toalla	7			maceta	7
	tela	2			sábana	1
					palmera	1
<i>casa-gasa</i>	casa	43	gasa	23		
	casita	3			venda	6
	maqueta	1			toalla	5
					manta	3
					alfombra	2

			plástico de burbujas	2
			rollo	2
			pañó de cocina	1
			moqueta	1
			lana	1
			celofán	1
<i>capa-mapa</i>	capa	46	mapa	46
	mapa	1	cartografía	1
<i>bata-rata</i>	bata	34	rata	38
	albornoz	12	ratón	8
	batin	1	rima	1
<i>ropa-copa</i>	ropa	37	copa	47
	vestidos	3		
	armario	2		
	ropero	1		
	vestidor	1		
	perchero	1		
	camisetas	1		
	rack	1		
<i>oreja-abeja</i>	oreja	47	abeja	46
			avispa	1
<i>niña-piña</i>	niña	45	piña	47
	cara	2		
<i>fresa-mesa</i>	fresa	46	mesa	47
	fresas	1		
<i>cubo-tubo</i>	cubo	45	tubo	45
	cubeta	2	cono	1
			cilindro	1
<i>queso-hueso</i>	queso	47	hueso	46
			fémur	1
<i>cama-rama</i>	cama	47	rama	47
<i>helado-teclado</i>	helado	42	teclado	47
	cucurucho	5		
<i>pato-gato</i>	pato	47	gato	47
<i>naríz-maíz</i>	naríz	47	maíz	46
			mazorcas	1
<i>globo-lobo</i>	globo	47	lobo	45
			perro	2
<i>mantel-pastel</i>	mantel	47	pastel	37
			tarta	10

APPENDIX 4

<i>Non-Rhyming Pairs</i>				
<i>Pair Name</i>	<i>Stimulus 1</i>	<i>Frequency 1</i>	<i>Stimulus 2</i>	<i>Frequency 2</i>
<i>gorra-dado</i>	gorra	47	dado	47
<i>guisante-botella</i>	guisantes	27	botella	47
	vaina	8		
	guisante	8		
	judía	2		
	vaina de guisantes	1		
	habas	1		
<i>perro-lápiz</i>	perro	45	lápiz	46
	pañó de cocina	1	boli	1
	collie	1		
<i>pollo-cafe</i>	gallina	41	café	35
	gallo	4	taza	11
	pollo	2	cafeina	1
<i>zapato-mochila</i>	mochila	47	zapato	45
			zapatilla	1
			botin	1
<i>bombilla-vaqueros</i>	bombilla	46	pantalón	18
	bombeta	1	pantalones	9
			tejanos	6
			vaquero	6
			vaqueros	4
			jeans	3
			tejano	1
<i>tomate-cuchara</i>	tomate	46	cuchara	44
	mandarina	1	cucharilla	3
<i>vaso-cuna</i>	vaso	47	cuna	46
			mecedora	1
<i>goma-suéter</i>	goma	41	jersey	41
	borrador	6	suéter	5
			sudadera	1
<i>esqueleto - cocodrilo</i>	esqueleto	47	cocodrilo	42
			caimán	4
			lagarto	1
<i>vino-pierna</i>	vino	30	piernas	36
	copa	17	pierna	5
			sin ropa	1
			pies	1
			pantorrilla	1
			pie	1
			tobillo	1

			gemelo	1
<i>clave-cerdo</i>	llave	46	cerdo	47
	tapon	1		
<i>mano-vaca</i>	mano	47	vaca	37
			ternero	5
			ternera	2
			becerro	2
			oveja	1
<i>tenedor-lechuga</i>	tenedor	45	lechuga	46
	tensor	1	acelga	1
	cubierto	1		
<i>reloj-lata</i>	reloj	47	lata	35
			bote	7
			papelera	2
			conserva	1
			latón	1
			-	1
<i>rosa-regla</i>	rosa	46	regla	47
	flor	1		
<i>abrigo-enchufe</i>	abrigo	32	enchufe	43
	chaqueta	10	cable	2
	anorak	3	cabezal	1
	parka	1	aplique	1
	tabardo	1		
<i>calabaza-elefante</i>	calabaza	43	elefante	47
	melón	1		
	calabacin	1		
	nuez	1		
	fruta	1		
<i>falda-coche</i>	falda	46	coche	45
	faldilla	1	automobil	2