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EXPLORATION OF SELF-INTEGRITY IN PSYCHOTIC DISORDERS THROUGH ELECTROENCEPHALOGRAPHIC ACTIVITY ANALYSIS DURING A SPEECH PRODUCTION AND PERCEPTION TASK

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EXPLORACIÓN DE LA INTEGRIDAD DEL "*YO*" EN LOS TRASTORNOS PSICÓTICOS MEDIANTE EL ANÁLISIS DE LA ACTIVIDAD ELECTROENCEFALOGRÁFICA EN UNA TAREA DE EMISIÓN Y PERCEPCIÓN DEL HABLA

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A mi madre, mi padre y mi hermano

Las neuronas son como misteriosas mariposas del alma,
cuyo batir de alas quién sabe si esclarecerá algún día
el secreto de la vida mental.

Santiago Ramon y Cajal

I'm happy if anything I find is useful, of course.
But it's not what drives me. What drives me is curiosity.

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Abstract

Schizophrenia has been proposed as a self-disorder, and Anomalous Self-Experiences (ASEs) have been consistently identified as a relevant finding in people with psychosis, even in at-risk states and early stages, remaining stable within this syndrome. These experiences translate into an impairment or loss of the natural, preconscious evidence by which we identify our mental contents as our own, encompassing both cognitive and somatic aspects. Thus, ASEs can potentially impair the experience of ipseity, i.e., the automatic and preconscious experience of individual identity. The ipseity disturbance model suggests that diverse symptoms, including positive, negative, cognitive, and disorganized ones, may all share forms of disturbed ipseity. Given the preconscious nature of ASEs, it is likely that some neural alteration underlies them. However, current studies reveal little about the possible neural mechanisms involved.

The accurate identification of actions and thoughts originating from ourselves is fundamental for developing and maintaining an intact sense of self. Corollary discharge is a neural mechanism by which the sensory consequences of self-initiated acts are attenuated or suppressed. The integrity of this mechanism is essential for developing a sense of agency over psychomotor experiences and sensations arising from self-generated acts, as opposed to externally generated perceptions. This phenomenon contributes to self-identification and appears to be altered in people with schizophrenia. A potential link between ASEs and alterations in corollary discharge has been proposed, suggesting that early corollary discharge dysfunction could hinder the pre-reflective coordination of an individual's sensorimotor actions with their environment, gradually diminishing the sense of self-agency over one's

experiences and leading to the development of self-disorders. However, this hypothesis has not yet been tested.

The present doctoral thesis sought to explore the corollary discharge mechanism as a potential biological substrate of ASEs in psychotic disorders. To this end, the auditory N1 Event-Related Potential (ERP) during Electroencephalographic (EEG) recordings was studied as an index of corollary discharge-mediated auditory cortical suppression. First, in a sample of healthy controls, the N1 and P2 components were elicited by three task conditions: i) real-time listening to self-pronounced vowels while speaking (*talk* condition), ii) subsequent passive listening to the same previously recorded self-uttered vowels (*listen-self* condition), and iii) passive listening to vowels recorded with an external voice (*listen-other* condition). Then, the *talk* and *listen-self* conditions were also studied in a sample of people with schizophrenia. ASEs were scored alongside positive and negative symptoms using the *'Inventory of Psychotic-Like Anomalous Self-Experiences'* (IPASE), the *'Positive and Negative Syndrome Scale for Schizophrenia'* (PANSS), and the *'Brief Negative Symptom Scale'* (BNSS), respectively. Finally, the specificity of the corollary discharge alteration and its relationship with ASEs was explored by comparing the results found in schizophrenia with a group of people with bipolar disorder.

N1 ERP amplitude was lower in the *talk* condition compared to the *listen-self* and *listen-other* conditions in healthy controls. Conversely, there were no differences found between the two listening conditions, nor in the amplitude of P2 during the three task conditions. The lower N1 amplitude in the *talk* condition compared to the *listen* condition was also found in both patient groups. However, N1 suppression was significantly reduced in schizophrenia and was inversely correlated with ASEs, as well as with the severity of positive

and negative symptoms, with the same results found when first-episode and chronic patients were studied separately. People with bipolar disorder showed an intermediate attenuation between healthy controls and schizophrenia patients (i.e., not significantly different from either group), though the level of N1 suppression was not related to the severity of ASEs in this group.

These results replicate previous findings and corroborate the use of N1 auditory ERP suppression as an index of the correct functioning of the corollary discharge mechanism during vocalization. When speaking, we do not recognize our own voice based on the physical characteristics of that specific auditory stimulus. Instead, sensory identification of our own voice occurs at a pre-stimulus level, before the perception of the emitted sound, where corollary discharge takes place. Additionally, these results support previous data linking auditory N1 ERP amplitude with altered corollary discharge mechanisms in schizophrenia and suggest that corollary discharge dysfunction may underlie ASEs in this illness, which are also related to positive and negative symptoms. However, this altered mechanism is less evident in bipolar patients, and no relationship with ASEs could be found. The intermediate suppression values observed in bipolar patients might suggest that a cortical inhibitory deficit is present in a smaller subset of individuals with bipolar disorder compared to those with schizophrenia.

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Acronyms

ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance
ASEs	Anomalous Self-Experiences
AVH	Auditory Verbal Hallucinations
BACS	Brief Assessment of Cognition in Schizophrenia
BNSS	Brief Negative Symptom Scale
dB	Decibels
CD	Corollary Discharge
EASE	Examination of Anomalous Self-Experiences
EEG	Electroencephalography
ERP	Event-Related Potential
FE	First Episode
HC	Healthy Controls
Hz	Hertz
ICA	Independent Components Analysis
IPASE	Inventory of Psychotic-Like Anomalous Self-Experiences
IQ	Intelligence Quotient
LO	*Listen-Other* condition
LS	*Listen-Self* condition
M/F	Masculine/Feminine
kΩ	Kiloohms
PANSS	Positive and Negative Syndrome Scale
ROIs	Regions of Interest
rs_fMRI	Resting-state functional Magnetic Resonance Imaging
SD	Standard Deviation
SPL	Sound Pressure Level.
TK	*Talk* condition
µV	Microvolts
WAIS	Wechsler Adult Intelligence Scale
WCST	Wisconsin Card Sorting Test

Chapter 1

Introduction

This doctoral thesis focuses on exploring the corollary discharge mechanism as a potential biological substrate for Anomalous Self-Experiences (ASEs) in psychotic disorders. The relevance and originality of this work lie in the fact that the association between cortical auditory sensory suppression following our own acts (*i.e.* the corollary discharge mechanism) and the experience of ASEs has not been previously analysed.

This research work has led to the publication of three scientific articles in journals indexed by the Journal Citation Report (JCR). The first article aimed to describe the functioning of the corollary discharge mechanism in healthy controls. The second article assessed the alterations of this mechanism and its association with ASEs in schizophrenia. Finally, a sample of participants with bipolar disorder was included to evaluate the specificity of this alteration. The three articles are presented in the Chapters 3, 4 and 5, respectively, followed by a general discussion and conclusion. In this introductory chapter, the main concepts are briefly summarized, and the thematic consistency of the doctoral thesis is justified. Additionally, an extended summary in Spanish has been included in Appendix A.

Sense of self

Mental experiences constitute a subjective reality, and understanding the essential characteristics of human subjectivity can be highly useful for comprehending the substrates of normal mental activity and its alterations. Intentionality of consciousness can only be understood in relation to the external world, *i.e.* the person's relationship with other people

or situations (Molina, 2021). Therefore, the importance of developing an intact sense of self also lies in its role in fostering proper cognitive and motor functioning.

Ipseity, reflective self and narrative self

The *sense of self* refers to the experiential and subjective notion of oneself. Different levels of the sense of self have been proposed: i) *ipseity*: it is a pre-reflective and tacit level of selfhood, also referred as the minimal or core self (Parnas, 2009). It supports various aspects of conscious experiences and forms the foundational level upon which other levels of selfhood are built (Nelson et al., 2014a). It leads to the implicit awareness that my experience is articulated from a first-person perspective and involves a range of subjective experiences that create the sense of being a self-present embodied subject immersed in the world (Nelson et al., 2014a; Zahavi, 2009); ii) *reflective self*: it refers to the enduring aspect of our consciousness and the sense that I am an invariant and persistent subject of experiences and actions, remaining the same person over time (Parnas, 2009); iii) *narrative self*: it involves reflective and metacognitive processes (Nelson et al., 2014a) and encompasses elements such as social identity, personality, habits, style, personal history, self-esteem, self-image and other related factors (Nelson et al., 2014a; Parnas, 2009).

Given this, the *self* is neither an indescribable transcendental prerequisite nor merely a social construct that changes over time. Instead, it is an integral aspect of our conscious existence, possessing an immediate pre-conscious experiential reality. This reflects the relationship between the self as an experiential dimension and the self as a narrative construction; thus, the self can be seen as the constant aspect of first-person givenness amidst a multitude of changing experiences (Zahavi, 2009). Therefore, an individual with a first-

person perspective can recognize their perceptions, memories, affections, thoughts, values and aspirations as their own, and integrate and craft a narration about them.

Sense of agency and ownership

The accurate identification of actions and thoughts originating from ourselves is fundamental for developing and maintaining an intact sense of self. The experience of performing an action is determined by at least two distinct processes governed by different neurobiological mechanisms (Bühler et al., 2016; Hubl et al., 2014): i) a*gency*: refers to the sense of causality, where the subject recognizes that their action leads to a specific effect (a sensation, emotion, thought or movement) at a particular moment. This corresponds to the awareness of being the one generating the outcomes of the action; ii) *ownership*: involves the perception of the effect's characteristics, independent of who is performing the action, by comparing the features of the stimulus with memory content. Linking these two processes with the levels of selfhood described previously in this section, the tacit feeling of agency and ownership that permeates subjective experience can be included in the development of the basic core self (i.e., ipseity), whereas the emergence of reflective self-awareness encompasses the thematic aspect of both senses.

The sense of agency and ownership are the main components of the complex process of *self-monitoring,* which determines our ability to monitor and recognize as our own our speech, thoughts and self-generated movements (Feinberg, 1978). The capacity to identify our own actions relies on internal representations which replicate aspects of external transformations (Blakemore & Frith, 2009; Frith, 2019). One specific type of internal model, known as a *forward model*, captures the causal relationship between actions and their sensory

outcomes (Wolpert & Miall, 1996), allowing us to determine the source of the stimuli. The mechanism involved in this will be developed in depth in the next section of this chapter.

Self-disorders and Anomalous Self-Experiences

The psychopathological notion of *self-disorder* specially refers to a disturbed sense of the basic self, *i.e.* the ipseity. Ipseity serves as the central point of orientation for human beings, underpinning motivation and structuring our experiential world according to our desires and needs (Molina, 2021). Therefore, an alteration in this fundamental central sense can lead to a disorganization of perception and experience, potentially resulting in the assignment of aberrant meanings to external or subjective events (Molina, 2021).

From a phenomenological perspective, disruptions in the core sense of self can result in various experiences such as depersonalization, a loss of common sense, distortions in the flow of consciousness, and a diminished understanding of perceptual and situational meanings, along with disturbances in identity and embodiment (Sestito et al., 2015). These experiences are known as ASEs, and involve a wide array of subtle, nonpsychotic experiential deviations affecting the core experience of being an embodied, self-present individual engaged with the surrounding world (Raballo & Parnas, 2012; Sass & Parnas, 2003).

Despite their differences in thematic content, ASEs all share a fundamental distortion at the ipseity level of selfhood. To reflect the different phenomenological aspects of a global change in the structure of experiences and awareness, some distortions have been described across different domains (Raballo & Parnas, 2012): i) s*tream of consciousness*: a shift in the implicit sense of the naturalness of mental processes results in modified thinking experiences. For instance, thoughts may appear anonymous, spatialized, or take on a quasi-sensory

concreteness instead of being perceived as abstract and intangible. This could lead to intensified introspective self-monitoring due to the experiential gap between the self and mental content; ii) *sense of presence*: experiences normally appear to us in a first-person mode. Instead, disturbance in this domain can interfere with this first-person perspective, modifying the usual smooth immersion in daily activities and social interactions and changing how the person engages pragmatically. People might report experiencing different types of depersonalisation or derealisation, a feeling of inner emptiness, and a diminished capacity to be affected or influenced by events or others; iii) *sense of corporeality:* involves an increasing experiential separation between the self and bodily sensations, leading to scrutiny of the body as an object rather than being lived through; iv) *self-demarcation*: refers to transitivity experiences and a loss of permeability in self-world boundaries. Distortions in this domain lead to difficulties in distinguishing the self from others, resulting in a loss of the ability to determine whether thoughts or feelings originated from oneself or another person, as well as a sense of passivity toward the world and others; v) *existential reorientation*: entails a unique preoccupation with supernatural, metaphysical and philosophical themes, often accompanied by solipsistic feelings of centrality and uniqueness. The person is trying to explain or justify the rupture in their self-experience.

Assessment instruments

Clinically, ASEs can be widely explored through symptom checklists. The gold standard instrument is the *'Examination of Anomalous Self-Experiences'* (EASE) (Parnas et al., 2005). The EASE is a semi-structured phenomenological interview, created from self-reports gathered from people with schizophrenia spectrum disorders. Additionally, there is a self-reported inventory, the *'Inventory of Psychotic-Type Anomalous Self-Experiences'* (IPASE)

(Cicero et al., 2017), the scores of which show a high correlation with those of the EASE (Cicero et al., 2017; Nelson et al., 2019). The IPASE will be described in more detail as a shorter, more pragmatic, accessible and well-stablished alternative to the EASE or as an initial screening option.

The IPASE has 57 self-report items with a 5-factor structure. Patients, in presence of the evaluator, rate their agreement with statements on a Likert scale from 1 (Strongly Disagree) to 5 (Strongly Agree). The factors include (Cicero et al., 2017): i) *Cognition*: refers to unusual experiences related to one's own thoughts or cognitive processes, such as thought interference or hearing one's thoughts being echoed externally; ii) *Self-Awareness and Presence*: includes items related to a loss of basic identity and disconnection from the world, encompassing aspects such as hyper-reflexivity (*i.e.* an intense self-focus on automatic aspects) that obscure the first-person experience of existence; iii) *Consciousness*: reflects disruptions in the conscious experience of reality, the perception of time, alterations in intentionality, and difficulty distinguishing between imagination and reality; iv) *Somatization*: includes items associated with distortions in bodily sensations, such as experiencing electric sensations, perceiving changes in the shapes of the limbs, feeling that the body is difficult to control, and thoughts of not feeling physically or psychically present in one's own body; v) *Demarcation/Transitivism*: showcases an existential sense of nonexistence, blurring the boundaries between the self and the world.

Neurocognitive correlates

Several neurocognitive correlates may be involved in the basic self-experience. Broadly speaking, there seems to be two areas that have been associated with the phenomenological

disturbances mentioned above (Nelson et al., 2014b): i) *source monitoring deficits*, and ii) *aberrant salience.*

Source monitoring deficits are the difficulty in distinguishing between the origins of endogenous and exogenous stimuli (*i.e.,* internally or self-generated vs externally or other-generated, respectively). These deficits may result from failures in neural mechanisms, particularly the efference copy (Crapse & Sommer, 2008) and the corollary discharge (Poulet & Hedwig, 2007), which will be examine further in the next section, along with reduced functional connectivity (Ford et al., 2013) and an elevated resting state brain activity (Northoff & Qin, 2011). From a cognitive and behavioural perspective, these source monitoring deficits may lead to endogenous-exogenous confusion and prediction errors, which could result in diminished ownership of mental content, self-other boundary confusion and hyper-reflexivity as a compensation for the lack of automatic identification of experiences such as thoughts or sensations (Nelson et al., 2014b).

On the other hand, aberrant salience is the excessive attention paid to information that is irrelevant or highly familiar, and the resultant effect on goal-directed behaviour (Nelson et al., 2014c). Normally, perceptual processes go beyond merely reproducing stimuli; they involve matching fragmented sensory inputs with working models of the world, which are shaped by the consistent and recurring aspects of our environment (Nelson et al., 2014c). This model helps us fill the gaps in sensory information, enabling us to interact efficiently with a complex and ever-changing external world. A brain-based disruption in memory and attention, and the related issue of aberrant salience, can lead to idiosyncratic behaviour and social disconnection (Nelson et al., 2014c). Inaccurate perceptions may result in incorrect beliefs and distorted interpretations of events, which distances an individual from common

sense and shared reality, potentially leading to delusions and hallucinations (Sass, 2014). These neurocognitive disturbances can also be related to various disruptions in subjective experience, such as hyper-reflexivity, rigidity and perplexity in interactions with the external world, a lack of common sense to distinguish between what is relevant and irrelevant, a disturbed grip or hold on the conceptual and perceptual fields, diminished perspectival abridgement and a reduced affordance value of objects (Sass, 2014; Nelson et al., 2014c).

Corollary discharge

As previously pointed out, pre-consciously and reliably distinguishing sensations caused by our actions from those of external origin constitute a basic element to develop an intact sense of self and, therefore, an adequate and adaptive cognitive and motor functioning.

Corollary discharge is a neural mechanism by which the sensory consequences of self-initiated acts are attenuated or suppressed (Sperry, 1950). The integrity of this mechanism is essential for developing a sense of agency over psychomotor experiences and sensations arising from self-generated acts, but not externally generated perceptions, prioritizing the processing of the latter (Crapse & Sommer, 2008; Frith, 2019) and ensuring coherence in our interactions with the external world (Poletti et al., 2019).

The synchronization of neural activity before self-generated actions may reflect the functioning of the forward model, which aims to reduce sensations caused by those actions (Chen et al., 2011; Ford et al., 2002, 2005, 2007). The forward model identifies the causal relationship between actions and sensory outcomes (Wolpert & Miall, 1996) and uses the corollary discharge (Sperry, 1950) to predict the sensory consequences of self-generated motor commands based on the efference copy sent from motor to sensory regions (Von Holst

& Mittelstaedt, 1950). The predicted sensory consequences are then compared to the actual sensory feedback received from the movement (Ford & Mathalon, 2019; Frith, 2019). This internal prediction is then used to cancel the sensory effect of the self-generated motor act. On the contrary, externally generated sensations lack an efference copy and thus cannot be predicted by the model, leading to a greater sensory discrepancy (Blakemore & Frith, 2009).

This sensory-motor integration is evident across all sensory modalities. Neural phase synchrony between Broca's area and auditory cortex preceding speech onset is greater during vocalizing than listening to a playback of the same spoken sounds when the expected auditory consequence of speech does match the auditory experience (Chen et al., 2011; Ford et al., 2002, 2005, 2007). Motor-related signals influence auditory processing at the cortical level through a feed-forward inhibitory process, where motor neurons directly excite auditory pyramidal cells and exert indirect inhibition mediated by excitatory connections with parvalbumin interneurons. Despite this, the motor-auditory connectivity targets more inhibitory interneurons than pyramidal cells resulting in motor-induced hyperpolarization of these cells (Eliades & Wang, 2008; Nelson et al., 2013; Reznik & Mukamel, 2019; Schneider et al., 2014). As a result, cortical responses to self-generated speech are suppressed.

When external sounds are processed, two Event-Related Potentials (ERPs) emerge in the primary and secondary auditory cortex (Ford et al., 2016): i) N1, and ii) P2. N1 component reaches its maximum negative peak around 100 milliseconds (ms) after the onset of the auditory stimulus and is followed by the positive P2 component at approximately 200 ms. Both ERPs represent different stages of auditory perception and are linked to attention processing. However, when self-generated sounds are processed, the N1 component is largely attenuated as a consequence of the corollary discharge mechanism.

Therefore, the auditory N1 ERP has been studied as an index of corollary discharge-mediated auditory cortical suppression. N1 is suppressed during self-generated speech, whereas it is preserved when people passively listen to their voice (Hubl et al., 2014; Wang et al., 2014; Whitford, 2019), so that self-generated spoken sounds are not consciously processed in the same way as external stimuli. Thus, corollary discharge could enable a preconscious recognition of the source of sensory stimulation, determining whether it originates internally or externally, which helps distinguish between self-generated sounds, thoughts, memories and external stimuli and so likely contributes to self-identification. Corollary discharge mechanism might also play a role in internal representations unrelated to external stimuli (Buzsáki, 2018), thereby contributing to the natural, preconscious experience of the self and the external world, whose disturbances manifest in ASEs.

Source monitoring deficits

Difficulty distinguishing between the origins of endogenous and exogenous stimuli may arise from failures in the corollary discharge mechanism. A disruption in the connectivity between regions activated during speech production and those involved in auditory processing (*i.e.* the frontal and temporal region, respectively) leads to a mismatch between the predicted auditory consequences of the motor act and the real auditory experiences of speaking (Ford et al., 2002, 2005, 2007).

In normal experience, we accurately anticipate outcomes based on the sensory inputs we have learned to associate with specific events (Nelson et al., 2014b). Consequently, a crucial distinction between stimuli generated by oneself and those generated by others is that

self-generated stimuli are predictable and controllable, whereas other-generated stimuli are not (Nelson et al., 2014b).

A malfunction in the corollary discharge mechanism might hinder the recognition of self-generated actions, leading to their misattribution to external sources (Feinberg, 1978) and a diminished sense of agency over one's experiences, and in turn contributing to the development of self-disorders (Poletti et al., 2019). Notably, disruptions in corollary discharge have been consistently observed in some disorders, where a hampered source monitoring is likely, such as those within the psychotic spectrum, with patients exhibiting significantly less reduction in the N1 ERP during speech (for a review see Whitford, 2019). This phenomenon occurs even when the association between action and sensation is not direct and results from other motor acts like pressing a button (Baess et al., 2008, 2011; Hazemann et al., 1975; Horváth, 2013; Jo et al., 2019; Klaffehn et al., 2019; Martikainen et al., 2005; Sowman et al., 2012) or blowing (Mifsud & Whitford, 2017).

A potential link between ASEs and alterations in corollary discharge has been proposed, suggesting that an early corollary discharge dysfunction could gradually diminish the sense of self-agency over one's experiences (Poletti et al., 2019). This reduction in self-agency might lead to ASEs and possibly positive symptoms like delusions of passivity or verbal hallucinations. Moreover, the strong link between the integrity of the corollary discharge and an harmonious motor development suggests that disruptions in the corollary discharge mechanism might occur early in neurodevelopment, heightening the risk of later psychotic conditions (Poletti et al., 2019). An early disruption in the corollary discharge mechanism could hinder the initial, pre-reflective implicit coordination of an individual's sensorimotor actions

with their environment, potentially leading to the development of self-disorders (Poletti et al., 2019). However, this hypothesis has not yet been tested.

Assessment instruments

One of the most effective and non-invasive methods to assess the function of the corollary discharge mechanism is to record the cortical electrical activity with an Electroencephalogram (EEG) during the performance of an action.

The electrical activity recorded by the electrodes is generated by the postsynaptic potentials of pyramidal neurons, caused by ionic currents. ERPs are typically defined in the time domain, representing the brain's electrical response to the occurrence of events or stimuli. As mentioned in the first part of this section, the auditory N1 ERP has been studied as an index of corollary discharge-mediated auditory cortical suppression. To evaluate this component, a voice emission and listening task has been described to assess cortical activity in response to these events (Ford et al., 2010): i) *Talk* condition: Participants are instructed to vocalize the phoneme [a:]. Concurrently, a microphone captures the vocalizations, which are then amplified and relayed to the participant in real-time through headphones, allowing them to hear their own pronounced vowels; ii) *listen* condition: participants are instructed to listen passively to the same previously self-uttered vowels. Additionally, to assess the importance of stimulus predictability in facilitating sequential processing, variations of this paradigm have been applied, such as presenting an alien voice (Heinks-Maldonado et al., 2005), shifting the pitch (Behroozmand & Larson, 2011; Mathalon, 2005; Heinks-Maldonado et al., 2005; Sitek et al., 2013) or delaying or changing the real-time feedback in other tasks, such as listening to a sound after pressing a button (Klaffehn et al., 2019) or producing inner speech (Chung et al., 2023).

Psychosis spectrum

The psychosis spectrum includes several disorders that exhibit a wide range of psychotic symptoms. These disorders are defined by abnormalities in one or more of the following five domains: delusions, hallucinations, disorganized thinking and speech, disorganized or abnormal motor behaviour, and negative symptoms (American Psychiatric Association, 2022).

Core symptoms are significantly shared with other mental disorders. Consequently, the delimitation between diagnoses becomes unclear, complicating the diagnostic process. Different categories of psychotic disorders have been identified, including non-affective psychotic disorders, affective psychoses, substance-induced psychotic disorder, and psychotic disorder due to a general medical condition (American Psychiatric Association, 2022). In this section, schizophrenia and bipolar disorder will primarily be described.

Schizophrenia

Schizophrenia is considered one of the most severe psychiatric disorders. It affects 1% of the world's population and does not differ between men and women (American Psychiatric Association, 2022). However, the incidence significantly varies across different locations and migrant groups, with symptoms, treatment response, and the course of the illness differing among individuals (Van Os & Kapur, 2009). It is a heterogeneous clinical syndrome, involving a range of cognitive, behavioural, emotional and motor dysfunctions (American Psychiatric Association, 2022). Currently, no biological measurements are used in diagnosing schizophrenia; the diagnosis relies on signs and symptoms gathered from self-reported experiences, clinical interviews and observations.

Psychotic features for diagnosing schizophrenia typically emerge between the late teens and mid-30s, with the peak onset occurring in the early to mid-20s for men and late 20s for women. The onset may be abrupt or gradual, but most individuals gradually develop a range of clinically significant signs and symptoms. These often include social withdrawal, emotional changes, and cognitive impairments, which contribute to a decline in role functioning (American Psychiatric Association, 2022).

The diverse set of signs and symptoms that characterize schizophrenic disorders are usually classified into different domains (American Psychiatric Association, 2022): i) *positive symptoms*: including hallucinations (that may occur in any sensory modality, thought auditory hallucinations are the most common), delusions and formal thought disorder; ii) *negative symptoms*: characterized by the absence or diminishment of normal activity or expression, consisting of anhedonia, apathy, flattening of affect, lack of volition and poverty of speech; iii) *disorganized symptoms*: encompassing a range of irregularities in thought, speech, and attention, such as tangentiality and derailment, incoherence and pressured speech, speech content deficiency as well as grossly disorganized and catatonic behaviour; iv) *cognitive impairments*: involving decrements in attention, declarative memory, working memory, language function, and slower processing speed, along with alterations in sensory processing and inhibitory capacity, and other executive functions, as well as social cognition deficits.

Bipolar disorder

Like in schizophrenia, bipolar disorder is considered a spectrum of disorders with some common characteristics. It has blurred boundaries with unipolar depressions on one side and schizophrenia on the other, in terms of symptomatology, family history and genetics (Akiskal,

2006; American Psychiatric Association, 2022) and a shared psychotic core (Sorella et al., 2019).

Bipolar disorder affects approximately 1,5% of the population and does not differ between men and women. Symptoms typically appear in late adolescence or early adulthood, around early 20s, and are a major cause of disability in young individuals (American Psychiatric Association, 2022).

Bipolar I disorder reflects the contemporary understanding of the classic manic-depressive disorder or affective psychosis. Individuals with this disorder experience manic episodes, which may or may not be accompanied by depressive episodes and are combined with periods of euthymia. On the other hand, individuals with bipolar II disorder experience at least one major depressive episode and one hypomanic episode, without any history of mania (American Psychiatric Association, 2022).

During a manic episode, the mood is euphoric, excessively cheerful and high. It is easily recognized as excessive and may be characterized by boundless and erratic enthusiasm for interpersonal, sexual, or occupational interactions. This mood is often accompanied by inflated self-esteem, uncritical self-confidence, and grandiose delusions. Speech can be rapid, pressured, loud, and difficult to interrupt, and there is a decreased need for sleep. These manic episodes frequently include severe psychotic symptoms and result in marked impairment in social or occupational functioning (American Psychiatric Association, 2022; Saunders & Goodwin, 2010).

Ipseity disturbance model

ASEs are an important psychopathological domain for the characterization of schizophrenia spectrum disorders. ASEs might serve as an early indicator for the future onset of schizophrenia (Brent et al., 2014) and have been found to predict the transition to psychosis in high-risk individuals, beyond other clinical symptoms (Nelson et al., 2012). Moreover, ASEs are associated with both positive and negative symptoms (Nordgaard & Parnas, 2014).

From a phenomenological approach, the *ipseity disturbance model* (Sass, 2014) is a theoretical framework proposed to understand the experience of ASEs in schizophrenia. The disturbance of the self, or ipseity, in this disorder is thought to involve two primary interdependent aspects (Sass, 2014): i) *hyper-reflexivity*: an excessive self-consciousness where focal attention is directed toward processes that are typically experienced tacitly as part of oneself, making something usually implicit become explicit; ii) *diminished self-affection*: a reduction in the intensity of one's subjective self-presence, leading to a diminished sense of being a subject of awareness and an agent of action. Normal self-affection encompasses appetite, vital energy, and orientation, driving human actions and structuring our experiential world based on needs and desires. This process gives objects their significance as obstacles, tools, or objects of desire.

There are patients and phases of illness where one facet becomes more pronounced than the other (Sass, 2009, 2014). However, both facets are interdependent, equally important, and play an equally fundamental pathogenetic role (Sass, 2009). There exists a continuum between explicit, objectified awareness and the more implicit, tacit dimension of knowing (Polanyi, 1964). This can be illustrated by differentiating between the *body image* (*i.e.* an objectified representation of one's body) and the *bodily subject* (*i.e.* the body as a

sensorimotor agent that not only experiences but also constitutes the world and our basic sense of self) (Gallagher & Meltzoff, 1996; Sass, 2009). Object-directedness and subjective self-affection are interdependent aspects of the intentional arc, which can be seen as a gradient from tacit or implicit knowledge to focal or explicit awareness (Sass, 2009). Ipseity, is partly based on proprioceptive and kinesthetic awareness, which usually remain outside the objectifying focus of attention, serving instead as subjective correlates of object-directed intentionality (Sass, 2009). The tacit dimension, or pre-reflective self-awareness, is essential for all intentional activity. Focusing explicit attention on something previously experienced tacitly leads to its objectification or alienation, making it feel distant or removed. Thus, disruptions in this tacit-focal structure can destabilize the balance, affecting both self and world (Sass, 2009).

In addition to the two main aspects discussed, a third interconnected aspect is a simultaneous disruption in the field of awareness, often referred to as a *disturbed hold* or *grip* on the world. This involves a loss of clarity or stability in distinguishing objects within an organized field of awareness (Sass & Parnas, 2003). It pertains to disturbances in how the world is structured in space and time, as well as in key experiential distinctions, such as those between perception, memory, and imagination (Sass, 2014).

The ipseity disturbance model suggests that diverse symptoms such as positive, negative, cognitive and disorganized, may all share forms of disturbed ipseity (Sass & Parnas, 2003). Many positive symptoms in schizophrenia are characterized by diminished self-affection, manifesting as a loss of the sense of inhabiting one's actions, thoughts, feelings, impulses, bodily sensations, or perceptions (Sass, 2009; Sass & Parnas, 2003). This

diminishment can blur the distinction between self and other and lead to symptoms such as auditory verbal hallucinations or hearing one's thoughts echoed outside of one's head.

Negative symptoms, like apathy, avolition or anhedonia, are often accompanied by experiential disturbances affecting cognition, perception, bodily experience, action, and emotion (Sass & Parnas, 2003). People with schizophrenia often rely on analytical, sequential, conscious, and quasi-voluntary cognitive processes in situations that typically require more automatic or spontaneous holistic processing (Frith, 1992). When the tacit dimension becomes explicit, it can no longer provide the grounding, orienting function that only background processes can offer (Sass, 2009; Sass & Parnas, 2003). This hyperawareness hinders spontaneity, contributing to a diminished sense of vitality, motivation, or legitimacy as a perspective on the world. Thoughts seem to disappear or appear as objects of introspective awareness and emotions can seem unnatural, absent, or unsatisfying (Sass, 2009; Sass & Parnas, 2003).

In addition, other symptoms, such as cenesthesias, are frequently accompanied by feelings of declining vital energy and physical awkwardness, and also seem to involve a hyper-reflexive awareness of bodily sensations that no longer serve as a medium of self-affection (Klosterkotter, 1992; Sass & Parnas, 2003). Finally, disorganization in schizophrenia can be seen as a hyper-reflexive cascade, with a proliferation of metaperspectives and a tendency to view one's own mind from an external standpoint, considering all possible viewpoints and forms. This leads to a vast juxtaposition of concepts, each appearing equally necessary and dubious (Sass, 2009; Sass & Parnas, 2003).

Biological substrates of psychosis

Schizophrenia has been associated with altered brain structure and function, but its aetiology is largely unknown, and heterogeneity is widely accepted in terms of clinical manifestations, biological findings, and response to treatment or outcome. Additionally, the biological mechanisms likely involved in schizophrenia are also common to other psychiatric conditions.

Neuroimaging studies have shown anatomical alterations such as grey matter deficits particularly affecting the frontal lobe and hippocampus, as well as the anterior cingulate, thalamus, and temporal regions. In addition, focal alterations in white matter tracts and lateral ventricular enlargement have been found (Ellison-Wright & Bullmore, 2009; Glahn et al., 2008; Haijma et al., 2013).

Neurochemical studies have been demonstrated heightened dopamine synthesis and release, along with elevated resting-state dopamine levels (Guillin et al., 2007; McCutcheon et al., 2018). Consequently, the dopamine hypothesis has been one of the most enduring theories. Schizophrenia is characterized by frontal hypodopaminergia, resulting in striatal hyperdopaminergia, which leads to negative and positive symptoms respectively (Davis et al., 1991). Nowadays, it has been proposed that interactions between gene variants, including those affecting dopaminergic function, and environmental risk factors represent another potential pathway to dopaminergic dysfunction. Thus, multiple factor such as genes, stress, drugs or a fronto-temporal dysfunction, interact to cause striatal dopamine dysregulation, altering the appraisal of stimuli and resulting in psychosis (Howes & Kapur, 2009). In addition, interactions with other neurotransmitter systems, such as the effects of NMDA receptor blockade or other potential causes of glutamatergic dysfunction, are modulatory, with GABA

interneurons also involved in regulating subcortical dopamine function (Howes & Kapur, 2009).

Microglial cells, which are found throughout the central nervous system and are activated in response to neuronal injury and inflammation, have been proposed to contribute to the development of schizophrenia through their dysfunction (Munn, 2000). In fact, post-mortem studies have shown higher levels of activated microglia in patients with schizophrenia compared to controls (Bayer et al., 1999). The synaptic hypothesis of schizophrenia (Howes & Onwordi, 2023) has tried to integrate the different information exposed before with a multi-hit model where genetic variants heighten synaptic vulnerability to elimination. Subsequent environmental risk factors, such as stress, trigger abnormal glial-mediated pruning. This aberrant pruning can impact glutamatergic synapses, including dendritic spines and collaterals that synapse onto inhibitory interneurons, as well as the inhibitory synapses onto pyramidal neurons. The result is an imbalance between cortical excitation and inhibition, leading to cognitive impairment, negative symptoms, and dysregulated projections to the striatum and the midbrain. This imbalance causes disinhibition of dopaminergic neurons, impairments in predictive learning, and disruptions in the processing of sensory stimuli, which result in psychotic symptoms. Besides this, the stress associated with living with psychosis exacerbates this system, leading to further abnormal pruning (Howes & Onwordi, 2023).

It has also been reported that people with schizophrenia show a deficit in modulating brain electrical activity during cognitive tasks compared to healthy controls, which is related to both cognitive and clinical symptoms (Bachiller et al., 2014; Gomez-Pilar et al., 2018; Molina et al., 2018; 2020). Additionally, these patients exhibit increased resting-state cortical activity (Cea-Cañas et al., 2020; Díez et al., 2013), which has also been linked to deficits in modulation

during a P300 oddball task (Iglesias-Tejedor et al., 2022). Moreover, increased baseline functional connectivity in the whole brain network but decreased connectivity modulation during a cognitive task have been shown in these patients (Cea-Cañas et al., 2020; Á. Díez et al., 2024; Gomez-Pilar, de Luis-García, et al., 2018). There is also higher cortical reactivity following transcranial magnetic stimulation single pulses over the left dorsolateral prefrontal cortex compared to healthy controls, which is associated with EEG modulation (Fernández-Linsenbarth et al., 2024). Inhibitory transmission plays a crucial role in cognitive activity, as it allows for the proper selection of underlying synaptic assemblies (Buzsáki, 2009). Consequently, an inhibitory deficit could lead to disorganized activity, resulting in a hyperactive and hypomodulatory network that contributes to symptoms and cognitive deficits. This may occur through a process of aberrant salience and monitoring deficits, where the corollary discharge mechanism could also be altered.

Justification of the research

In many cases, the basic elements of mental disorders are alterations in the subject's relationship with other people or situations, which can be conceptualized as altered intentionality of consciousness (Molina, 2021). These external objects can, especially in early stages, condition the properties of the brain when facing new situations. If consciousness can only be understood in relation to the external world, understanding the modes of interaction between brain activity and the world is crucial for comprehending both normal consciousness and its psychiatric alterations.

ASEs represent a significant psychopathological feature for characterizing schizophrenia spectrum disorders and may serve as an early marker for the potential

development of schizophrenia (Brent et al., 2014), predicting the transition to psychosis in high-risk individuals beyond other clinical symptoms (Nelson et al., 2012). Considering the preconscious nature of ASEs, it is probable that some neural alterations underlie them. Furthermore, alterations in the corollary discharge mechanism have been consistently reported in schizophrenia, characterized by a notable decrease in the auditory ERP N1 suppression (for a review see Whitford, 2019), and corollary discharge has been proposed as a transdiagnostic mechanism of psychosis (Ford et al., 2013; Yao et al., 2024).

A potential link between ASEs and alterations in corollary discharge has been proposed, suggesting that an early dysfunction in corollary discharge could gradually diminish the sense of self-agency over one's experiences (Poletti et al., 2019). This reduction in self-agency might lead to ASEs and possibly positive and negative symptoms, such as delusions of passivity, verbal hallucinations or a diminished sense of existing. However, this hypothesis has not yet been tested, and it remains unclear whether these deficits in the expression of corollary discharge and their relationship to ASEs are specific to schizophrenia or are also seen in other psychotic disorders.

Chapter 2

Aims and hypotheses

Aims

General aims

The primary aim of this doctoral thesis is to explore the corollary discharge mechanism as a potential biological substrate of ASEs in schizophrenia, and to evaluate its specificity compared to other disorders within the psychotic spectrum.

Specific aims

The following specific aims were derived from the general one:

1. To assess the sense of agency and ownership in healthy controls by exploring the corollary discharge mechanism through the measure of N1 ERP suppression during a *Talk-Listen* paradigm using EEG.
2. To investigate whether the identification of the self-generated speech is due to motor or sensory processes by adding an extra listening condition (i.e., listen to an other's voice).
3. To confirm the previously reported alterations in the corollary discharge mechanism in people with schizophrenia in a larger sample.
4. To assess the relationship between ASEs and alterations in corollary discharge in people with schizophrenia.
5. To assess the relationship between positive and negative symptoms and alterations in corollary discharge in people with schizophrenia.

6. To explore differences in the functioning of the corollary discharge mechanism and its relation to ASEs, as well as positive and negative symptoms, between patients with schizophrenia in their first psychotic episode and chronic patients.
7. To explore the specificity of corollary discharge alteration and its relationship with ASEs in people with schizophrenia compared to those with bipolar disorder.

Hypotheses

In order to achieve the objectives proposed above, and based on current evidence, the following hypotheses are established:

1. The cortical response will be the same whether the person hears their own voice or someone else's, but it will be suppressed when they hear their own voice simultaneously with their speech in healthy controls.
2. There will be less suppression of cortical activity in people with schizophrenia when they are talking, due to impaired functioning of the corollary discharge mechanism.
3. The level of suppression of cortical activity during speech will be inversely related to the severity of ASEs in people with schizophrenia.
4. The level of suppression of cortical activity during speech will be inversely related to the severity of positive and negative symptoms in people with schizophrenia.
5. There will be no differences in cortical activity and its relationship with ASEs, positive and negative symptoms, between first-episode and chronic schizophrenia.
6. People with bipolar disorder will also show alterations in the corollary discharge mechanism, but these alterations will not be as pronounced as in schizophrenia.

Chapter 3

Corollary discharge function in healthy controls: evidence about self-speech and external speech processing

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Chapter 4

Corollary discharge dysfunction as a possible substrate of Anomalous Self-Experiences in schizophrenia

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Chapter 5

Corollary discharge and Anomalous Self-Experiences in schizophrenia and bipolar disorder: A specificity analysis

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Chapter 6

Discussion

This doctoral thesis has focused on assessing the suppression of cortical auditory activity caused by the sensory consequences of self-generated motor acts as a measure of the functioning of the corollary discharge mechanism, using the well-established *Talk-Listen* paradigm (Ford et al., 2010), which is described in Chapters 3, 4 and 5. The findings of these studies have provided a more direct approach to understanding a possible neural mechanism underlying the development of an intact sense of self and the experience of ASEs in psychotic disorders.

The first study aimed to differentiate between agency and ownership processes in healthy controls and to evaluate whether the identification of self-generated speech is due to motor or sensory processes associated with the recognition of physical characteristics by introducing the novel *Listen-other* condition. Our results align with the idea that the sensory identification of our own voice while speaking occurs at a pre-stimulus level.

The second article intended to examine the suppression of speech-related potentials as a possible altered substrate of the corollary discharge mechanism in people with schizophrenia and its association with ASEs, which had not been previously tested. As expected, a dysfunction in corollary discharge was found, indicated by lower attenuation of the N1 ERP during speech. The lack of N1 suppression was associated with the severity of ASEs as well as with positive and negative symptoms, with no differences found between first-episode or chronic patients.

Finally, the third study allowed us to determine the specificity of this alteration by including a sample of people with bipolar disorder who had shown psychotic symptoms. The results showed that bipolar disorder patients exhibited intermediate sensory suppression between the schizophrenia and healthy control groups, demonstrating a continuum in attenuation between the three groups. Additionally, N1 ERP suppression inversely correlated with the severity of ASEs in schizophrenia, but not in bipolar disorder. In this paper we renamed the two task conditions as *listen/talk* (i.e., *talk* condition) and *listen/no talk* (i.e., *listen* condition) to emphasize that in both conditions N1 is an auditory ERP. Thus, in the *talk* condition, the ERP is not generated by the act of speaking but by the perception of the sound of our own voice while speaking.

In the following sections, the findings of the studies included in this doctoral thesis are discussed in depth and integrated considering previous literature in the field.

Corollary discharge function and pre-stimulus sensory identification in healthy controls

Corollary discharge mechanism is one of the several neurocognitive correlates that may be involved in the basic self-experience (Nelson et al., 2014b). It enables the pre-conscious attribution of agency to sensations that result from self-generated actions, rather than external perceptions (Crapse & Sommer, 2008; Frith, 2019). As exposed in the first chapter of this thesis, agency, on the one hand, refers to causality and how the action of the subject is followed by and effect at a specific moment and ownership, on the other hand, focuses on the features of the effect regardless of the action being performed by the subject (Hubl et al., 2014). With this paradigm, the *talk* condition may refer to the agency experience

reflected in the processing of one's speech, while the *listen-self* condition assessed the ownership experience by playing one's recorded voice from an external source.

Our findings align with the idea that corollary discharge is involved in the auditory N1 suppression during self-generated speech, which serves to inform other brain regions that these actions are self-generated, thereby facilitating the processing of external stimuli. During the *talk* condition a P2 wave was elicited, confirming sensory detection of their own voice while speaking. Therefore, the N1 suppression observed during speech is unlikely to be due to a problem in sound perception during this task condition, but rather to the involvement of the corollary discharge mechanism and the efference copy of the motor command sent to sensory regions just before speech takes place (Von Holst & Mittelstaedt, 1950).

Before speech onset, gamma synchrony is more pronounced during vocalization than when listening passively to auditory stimuli, particularly between the inferior frontal gyrus and the auditory cortex (Chen et al., 2011; Ford et al., 2005). This indicates its role in the corollary discharge mechanism and how the recognition of our own voice starts at a pre-stimulus level, when the consequences of our motor acts are predicted before the voice is produced. Speaking enhances coherence between frontal and temporal regions across all frequency bands, in contrast to listening (Ford et al., 2002). This is also consistent with the communication between motor and sensory regions involved in speech production, which is crucial for the correct functioning of the corollary discharge mechanism. Particularly, Theta-band activity plays a vital role in long-range communication between motor and sensory areas during vocalization (Wang et al., 2014), with Theta Intertrial Phase Coherence serving as another sensitive marker for cortical suppression due to the corollary discharge (Roach et al., 2020).

These results highlight the importance of a forward model that manages motor control, sensory processing, and cognition, functioning as an internal feedback loop between motor commands and sensory experiences (Crapse & Sommer, 2008). Motor-related signals impact auditory processing at the cortical level through a feed-forward inhibitory mechanism. Activity in motor regions directly stimulates auditory pyramidal cells and indirectly inhibits them through excitatory connections with parvalbumin interneurons, defining a circuit capable of modulating auditory cortical activity. Motor-auditory connectivity targets more inhibitory interneurons than pyramidal cells. Thus, during vocalization, activity in the motor cortex predominantly inhibits auditory pyramidal cells indirectly, resulting in a suppressed cortical response to self-generated speech (Eliades & Wang, 2008; Nelson et al., 2013; Reznik & Mukamel, 2019; Schneider et al., 2014)..

In contrast to the *talk* condition and in line with the previous literature, an N1 ERP was observed during both listening conditions in response to the auditory stimulus (Heinks-Maldonado et al., 2005; Hubl et al., 2014; Wang et al., 2014). This differentiation in the auditory cortical response between self-generated and external stimuli allows for accurate source monitoring. When a sensation occurs, its source can be identified by using the efference copy of the motor command to predict the sensory outcomes of self-generated movements. During vocalization, there is minimal sensory discrepancy between the predicted and actual feedback, which results in the suppression of perception. On the other hand, when we passively listening to externally generated sensations, these stimuli do not have an associate efference copy, making them unpredictable. Consequently, no suppression is made by the corollary discharge mechanism, resulting in a higher cortical activity. In fact, studies altering real-time auditory feedback during speech (Heinks-Maldonado et al., 2005)

demonstrate that N1 suppression decreases when the predicted sensory feedback from an efference copy does not align with the actual sensory feedback.

The fact that no differences in ERP amplitude and latency were found between the *listen-self* and the *listen-other* conditions, indicates that the auditory N1 and P2 responses are similar, regardless of whether the voice is recognized as one's own based on the physical characteristics of the stimulus. However, there was a notable decrease in N1 amplitude during the *talk* condition, accompanied by the preservation of P2. This once again supports the interpretation of the importance of the motor act and the role of the corollary discharge mechanism in recognizing when we are the agents producing our own voice. The brain does not passively perceive stimuli; perception is an action-driven process in which the brain actively explores the environment and records the outcomes of its actions (Buzsáki, 2018). This effect is likely due to central rather than peripheral mechanisms, underscoring the role of motor-related signals in auditory processing at the cortical level (Eliades & Wang, 2008; Horváth & Burgyán, 2013; Nelson et al., 2013; Reznik & Mukamel, 2019; Schneider et al., 2014). Sensory regions receive inputs both from external stimuli and from motor neurons that produce sensory feedback from our own actions, establishing a closed-loop system in which external and internal computations are compared (Buzsáki, 2018).

Finally, different paradigms underscore the role of predictive modelling in perception and advanced cognitive functions (for a review see Bendixen et al., 2012). The suppression of the auditory N1 ERP when concurrent listening to self-produced sounds (*talk* condition) is consistent with findings from other motor activities, such as pressing a button (Baess et al., 2008, 2011; Hazemann et al., 1975; Horváth & Burgyán, 2013; Jo et al., 2019; Klaffehn et al., 2019; Martikainen et al., 2005; Sowman et al., 2012) or blowing (Mifsud & Whitford, 2017)

(Mifsud & Whitford, 2017). Not only does the brain engages with the environment through physical actions but also through cognitive process and, in this line, similar results are reported for imagined movements and inner speech (Brumberg & Pitt, 2019; Jack et al., 2019; Pinheiro, et al., 2020b; Whitford et al., 2017). The prefrontal cortex sends efferent signals to the limbic system to formulate action plans before actual movement, comparing possible actions and their anticipated outcomes with stored information. This interaction with the external world enables the corollary discharge mechanism to simulate real actions without sending signals to the muscles, thereby activating the same target circuits (Buzsáki, 2018).

Corollary discharge dysfunction as a potential underlying mechanism for Anomalous Self-Experiences and its association with clinical symptoms in schizophrenia

Understanding the correct functioning of the corollary discharge mechanism and the distinction between agency/motor acts and ownership/perception in healthy controls, paves the way for exploring disorders with disrupted self-experience, such as psychotic disorders.

As we have explained in the previous section of this chapter, the auditory N1 ERP during speech is suppressed compared to the passive listening to one's own voice, due to the functioning of the corollary discharge mechanism. As expected, our results showed that N1 was also suppressed in people with schizophrenia, but this attenuation was significantly lower compared to healthy controls (for a review see Whitford, 2019). Although N1 suppression was altered during the *talk* condition, schizophrenia patients exhibited a normal N1 ERP while listening to their own pre-recorded voice (*listen* condition), suggesting that the sensory recognition of their own voice remains intact. Thus, the diminished attenuation observed in

people with schizophrenia when listening to themselves while uttering their own speech is likely secondary to the effects of the corollary discharge (Feinberg, 1978). This suggests that the preconscious identification of the origin of sensory stimulation (whether it comes from within or outside oneself) may be altered. Their neural processing of mental content related to their actions resembles the processing of stimuli from an external source, making it harder to distinguish the origin. This aligns with the characteristics of ASEs and may contribute to the diminished sense of self and altered ipseity reported in schizophrenia due to the altered preconscious experience of the self and the outside world.

As mentioned in the introductory chapter of this thesis, disruptions in the core sense of self can result in the experimentation of ASEs. Given their preconscious nature, it is likely that some neural alteration underlies these experiences. This possibility is supported by findings that neurocognition is significantly related to ASEs (Hernández-García et al., 2021; Nelson et al., 2020), as well as by evidence of functional connectivity between the parahippocampal and cingulate cortices (Roig-Herrero et al., 2022) and aberrant functional interactions of the right ventral premotor cortex and bilateral posterior insula with posterior cingulate cortex (Ebisch et al., 2014), which are directly related to ASEs. Given also the automatic, early and preconscious nature of the corollary discharge, ASEs are likely linked to a deficit in this neural mechanism, which is crucial for recognizing actions as self-initiated. This process is important for self-identification, and its dysfunction could serve as a neural indicator of altered self-experience. Moreover, the strong link between the integrity of corollary discharge and sensorimotor integration, which is crucial for motor skills during early childhood (Burton et al., 2016; Hirjak et al., 2018; Poletti et al., 2019), suggests that early disruptions in the corollary discharge mechanism could occur during neurodevelopment, potentially increasing the risk of future psychotic disorders (Poletti et al., 2019). An early

disturbance in this mechanism might impair the initial, automatic alignment of an individual's sensorimotor actions with their environment, which could lead to the manifestation of self-disorders (Poletti et al., 2019). The connection between the deficit in sensorimotor attenuation and the severity of ASEs in our patients with schizophrenia aligns with the broader functions attributed to corollary discharge, such as the brain's ability to disengage from its environment and to represent current and past experiences, thereby contributing to memory and planning (Buzsáki, 2018). Thus, ASEs may be influenced by difficulties in situating oneself in the world (whether in the past or present), projecting oneself into the future, and consolidating and integrating memories, among other factors.

In addition, the auditory N1 ERP suppression was inversely associated with positive and negative symptoms in people with schizophrenia. As has been described in the introductory chapter, the ipseity disturbance model suggests that the diverse symptoms found in the psychotic disorders may all share forms of disturbed ipseity (Sass, 2014; Sass & Parnas, 2003), with ASEs potentially related to these symptoms (Poletti et al., 2019). On the one hand, the loss of subjective self-agency could lead to experiencing one's own thoughts as external stimuli, manifesting as positive symptoms such as auditory verbal hallucinations or delusions of passivity. On the other hand, hyperawareness may contribute to thoughts seeming like objects and emotions feeling unnatural or unsatisfying. Coupled with a diminished self-affection, this could lead to a reduced sense of vitality or motivation that may be related to negative symptoms. The potential relationship between psychotic symptoms and corollary discharge has yielded mixed results, with some studies supporting it (Ford et al., 2002, 2007; Heinks-maldonado et al., 2007) and others justifying the opposite (Bühler et al., 2016; Ford et al., 2001, 2007, 2013; Ford & Mathalon, 2005; Kort et al., 2017; Mathalon et al., 2019; Perez et al., 2012). The absence of a link between corollary discharge mechanisms and

symptoms in some studies might be due to the heterogeneity substrates of these symptoms, with corollary discharge alterations being just one potential factor.

The level of N1 suppression has been linked to the structural integrity of the arcuate fasciculus in these patients (Whitford et al., 2017) and, as previously discussed, corollary discharge may be related to synchronization mediated by inhibitory transmission between motor and sensory regions (Chen et al., 2011; Ford et al., 2002, 2005). In this context, the expected deficit in the corollary discharge mechanism in our patients is consistent with the effects of an overactive cortex, which aligns with reported GABA deficits in the cortex of individuals with schizophrenia (Lewis et al., 2005). Consequently, a deficit in inhibitory function could result in disorganized neural activity, leading to a hyperactive and poorly modulated network that contributes to aberrant salience and monitoring deficits. The reduced N1 suppression observed in schizophrenia patients, potentially related to GABA hypofunction, may impair their ability to discern the source of mental experiences. The spatiotemporal model of psychopathology (Northoff, 2016) suggests a connection between the brain's functional characteristics at rest and self-experience, proposing that self-experience may be rooted in spontaneous functional brain networks. If these networks are hypomodulated, the neural processes involved in distinguishing the origin of experiences could be compromised.

The specificity of corollary discharge dysfunction: A comparison between schizophrenia and bipolar disorder

Dysfunction in the corollary discharge mechanism has been proposed as a transdiagnostic factor underlying psychosis (Ford et al., 2013; Yao et al., 2024). As introduced

in the first chapter of this thesis, the psychotic spectrum includes various disorders with blurred boundaries due to the wide heterogeneity of symptoms individuals may manifest, reporting a shared psychotic core between bipolar disorder and schizophrenia (Sorella et al., 2019), with psychotic symptoms primarily manifesting during the manic phase in the former.

The speech-related suppression of the N1 auditory ERP when talking (*talk* condition) was also observed in our group of people with bipolar disorder, with no significant differences when compared to healthy controls or to the schizophrenia group. However, N1 suppression values in people with schizophrenia were less pronounced, while those with bipolar disorder showed intermediate values between the schizophrenia patients and the control group. Furthermore, as observed in the schizophrenia group, people with bipolar disorder display a normal N1 ERP when listening to their pre-recorded voice (*listen* condition), suggesting again that the sensory recognition of their own voice is preserved. Consequently, the variation in the N1 attenuation observed among the three groups (schizophrenia, bipolar disorder, and healthy controls) during vocalization is likely due to differences in the functioning of the corollary discharge mechanism. Although the impairment in N1 suppression is more pronounced in the schizophrenia group, the lack of significant differences between the two patient groups, coupled with the fact that all bipolar patients were in a euthymic state, with psychotic features typically occurring during manic and depressive or mixed phases, supports the hypothesis of a connection between corollary discharge mechanism alterations and psychotic features, which may appear in a smaller subset of bipolar patients compared to those with schizophrenia.

Considering that our data support a clear dysfunction of the corollary discharge mechanism in schizophrenia but not in bipolar disorder, and that N1 suppression was

significantly related to the severity of ASEs in schizophrenia but not in the bipolar disorder group, this suggests that when ASEs are present in bipolar disorder, they are either unrelated to corollary discharge alterations or that only a minority of patients with bipolar disorder exhibit ASEs related to the corollary discharge mechanism. This makes the examination of the ASEs and the corollary discharge mechanism less clear, and the reduction in the auditory cortical suppression during speech less evident in this group. As discussed in the previous section, the corollary discharge mechanism serves a crucial role in recognizing the source of actions as self-generated. Therefore, its dysfunction likely represents a neural marker of altered self-experience, which is more pronounced or significant in schizophrenia than in bipolar disorder. Thus, this dysfunction might pose a greater challenge for individuals with schizophrenia compared to those with bipolar disorder in distinguishing the origin of mental content.

It has been suggested that malfunctions in corollary discharge are linked to abnormal frontal white-matter myelination in schizophrenia (Whitford et al., 2012). While reduced intracortical myelin has been observed in both schizophrenia and bipolar disorder (Jørgensen et al., 2016), the myelination patterns may differ between these syndromes (Hercher et al., 2014). Consequently, the more pronounced myelination alterations in schizophrenia compared to those in bipolar disorder (Hercher et al., 2014) could account for the intermediate N1 suppression observed in the bipolar group. Additionally, GABA deficits have been reported in the cortex in people with schizophrenia (Lewis et al., 2005), whereas a smaller proportion of bipolar patients show inhibitory deficits (Volk et al., 2016). This may be coherent with the smaller speech-related suppression in the latter group. Taking this into account, if the corollary discharge mechanism relies on cortical inhibition, the intermediate suppression levels observed in bipolar patients -falling between those of schizophrenia

patients and healthy controls- might tentatively indicate that a cortical inhibitory deficit is present in a smaller subset of bipolar patients compared to those with schizophrenia.

The continuum observed in the speech-related suppression values among the three groups, along with the inverse association found between N1 suppression ASES in people with schizophrenia, is consistent with the possibility of multiple biotypes coexisting within the schizophrenic syndrome. This suggests that corollary discharge might be preserved in a subset of schizophrenia patients without ASEs, while alterations in the corollary discharge mechanism and their connection to ASEs may be present in a smaller subset of bipolar patients with psychotic features. In this context, a biotype based on EEG network properties have been defined (Fernández-Linsenbarth et al., 2021b), as well as a biotype based on cognitive deficit, which shows hyperactive cortical activity associated with hypomodulation during an oddball task (Clementz et al., 2016; Fernández-Linsenbarth et al., 2021a). All identified biotypes included individuals diagnosed with both schizophrenia (first-episode and chronic) and bipolar disorder, which may support the idea that corollary discharge is an altered mechanism related to ASEs in a subset of patients with psychosis.

Limitations

Among the limitations of the studies included in this doctoral thesis, a treatment-naïve sample has not been included and consequently, the effect of treatment cannot be entirely excluded. Although no significant relationship was found between N1 suppression and pharmacological dosage (measured in equivalent doses of chlorpromazine, mg/day), the different action mechanism of the wide variety of antipsychotic could not be controlled.

Additionally, larger sample sizes would have been preferable, especially for first episode of schizophrenia and bipolar disorder, to enhance the statistical power of the results and validate the findings. Nevertheless, the relationship between auditory corollary discharge and ASEs had not been previously explored in these groups of patients.

The IPASE was used to assess the severity of ASEs instead of the gold-standard EASE. The main advantage of the EASE is that ASEs are evaluated through an expert-guided interview rather than self-reporting. Despite this, scores from both instruments are highly correlated (Cicero et al., 2017; Nelson et al., 2019), and a researcher was present to assist participants with any misunderstandings of item phrasing.

Although corollary discharge likely underlies the ipseity experience, we cannot establish a causal relationship because our results show a correlation between ASEs and N1 auditory ERP suppression. Additionally, this suppression effect may represent just one of many potential measures regarding the corollary discharge mechanism.

The temporal order effect in the administration of the paradigm cannot be completely ruled out, as the *talk* condition must appear always in the first place. However, no significant differences were found in healthy controls when comparing the N1 ERP from passively listening to their own recorded voice versus listening to another person's voice. Therefore, the potential confound of stimulus novelty in the *listen* condition should not explain the observed results.

Chapter 7

Conclusions

Main conclusions of the study

Distinguishing the source of sensory stimulation and determining whether stimuli originate internally or externally helps differentiate between self-generated sounds, thoughts, and memories versus external stimuli. This likely contributes to self-identification and to appropriate and adaptive functioning. The corollary discharge mechanism has been described as playing a role in accurate source monitoring of stimuli by attenuating or suppressing the sensory consequences of self-initiated acts. Our results replicate previous data and corroborate the use of N1 auditory ERP suppression as an index of the correct functioning of the corollary discharge mechanism during vocalization.

While we are talking, we do not recognize our own voice based on the physical characteristics of that specific auditory stimulus. Instead, sensory identification of our own voice occurs at a pre-stimulus level, before the perception of the emitted sound. This is because our brain does not passively perceive stimuli; it examines and predicts the consequences of our actions before they occur, thanks to the efference copy of the motor commands sent to sensory regions. Sensory regions receive inputs both from external stimuli and motor neurons that provide sensory feedback from our own actions, establishing a closed-loop system in which external and internal signals are compared. Thus, cortical auditory activity does not differ when we listen passively to our own voice compared to another external voice, because there is no motor command that allows us to predict any sensory consequences.

People with schizophrenia show alterations in the functioning of the corollary discharge mechanism, as measured by diminished auditory N1 suppression when they are actively speaking. A malfunction in the corollary discharge mechanism may hinder the recognition of self-generated actions, leading to their misattribution to external sources and underpinning ASEs, which may be related to the experience of positive and negative symptoms in people with schizophrenia. This occurs independently of the duration of the illness, being observed both in people with a first psychotic episode and in a chronic state.

This altered mechanism is less evident in people with bipolar disorder, where a continuum in auditory-related N1 suppression is found between the schizophrenia group and healthy controls, and no relationship with the severity of ASEs is observed. The intermediate suppression values observed in bipolar patients, might suggest that a cortical inhibitory deficit is present in a smaller subset of individuals with bipolar disorder compared to those with schizophrenia.

The results of this doctoral thesis show that dysfunction in the corollary discharge mechanism may be associated with psychosis and could be a potential underlying mechanism for ASEs. However, this dysfunction appears to be more pronounced in people with schizophrenia compared to those with bipolar disorder.

Future research lines

Continuing to explore the potential mechanisms underlying ASEs would provide a better understanding of the development of the ipseity and its alterations in psychotic disorders. There are several potential covariates that could be assessed for their influence on the functioning of the corollary discharge mechanism and the experimentation of ASEs, as well

as positive and negative symptoms. More specific experimental designs and relationship that could be explored are as follows:

~ Including a treatment-naïve group of patients could help to completely discard the effect of treatment.

~ Testing bipolar participants during their manic phase, when they are more likely to exhibit psychotic features, would help determine whether N1 suppression is related to the psychotic state or if it is specific to schizophrenia.

~ Including other disorders within the psychosis spectrum, such as schizoaffective disorder, could help confirm whether there is a continuum or distinct differences between the various types of psychosis described.

~ Implementing a third condition where both groups of patients passively listen to an unfamiliar voice (i.e., *listen-other* condition) could be beneficial for evaluating possible differences compared to healthy controls and completely ruling out potential cofounds related to stimulus novelty in these groups.

~ Studying possible differences between groups of participants using time-frequence approaches before the auditory stimulus onset could further explore the implication of corollary discharge and perception at a pre-stimulus level, as well as the synchrony between frontal and temporal areas.

~ Performing diffusion tensor imaging studies to examine connectivity between brain areas and its association with the functioning of the corollary discharge mechanism.

~ Exploring possible associations between the corollary discharge mechanism and N1 auditory suppression with other variables such as cognitive performance.

~ Studying the association between the corollary discharge mechanism and the function of the inhibitory system by assessing its relationship with other EEG parameters, such as resting-state cortical activity, task-related modulation, and cortical reactivity following TMS-EEG single pulses.

~ Performing a cluster analysis to explore the possibility of identifying different subgroups of patients based on alterations in the corollary discharge mechanism could aid in developing a better conceptualization of the syndrome and more specific therapeutic targets.

Appendix A

Resumen extendido en español/Extended Spanish summary

Introducción

La identificación precisa de las acciones y pensamientos que generamos es fundamental para desarrollar un funcionamiento cognitivo y motor adecuado y adaptativo. Poder diferenciar entre las sensaciones causadas por nuestras propias acciones y las que provienen de una fuente externa desempeña un papel clave en el desarrollo y mantenimiento de un sentido del "yo" intacto.

El *sentido de "yo"* o *autoexperiencia* se refiere a la noción experiencial y subjetiva de uno mismo e incluye diferentes niveles: i) *ipseidad*: es un nivel prereflexivo y tácito de la identidad (Parnas, 2009). Conduce a la conciencia implícita de que mi experiencia se articula desde una perspectiva en primera persona y constituye la base sobre la que se sustentan otros niveles de identidad (Nelson et al., 2014a; Zahavi, 2009); ii) *yo reflexivo*: se refiere al aspecto duradero de nuestra conciencia y la sensación de ser un sujeto invariable y persistente a lo largo del tiempo (Parnas, 2009); iii) *yo narrativo*: implica procesos reflexivos y metacognitivos donde el "yo" se convierte en un objeto de conciencia, abarcando elementos como la identidad social, la personalidad, los hábitos, la historia personal, la autoestima y la autoimagen (Nelson et al., 2014a; Parnas, 2009). Teniendo en cuenta los diferentes niveles descritos, un individuo, desde una perspectiva en primera persona, puede reconocer sus percepciones, recuerdos, afectos, pensamientos, valores y aspiraciones como propios, aunque se encuentre en medio de una multitud de experiencias cambiantes, y puede integrar y elaborar una narración sobre ellos (Zahavi, 2009).

La identificación precisa de nuestras propias acciones y pensamientos está determinada por al menos dos procesos gobernados por diferentes mecanismos neurobiológicos (Bühler et al., 2016; Hubl et al., 2014): i) *sentido de agencia*: la persona reconoce que su acción conduce a un efecto específico (una sensación, una emoción, un pensamiento o un movimiento) en un momento particular; ii) *sentido de propiedad*: se refiere a la percepción de las características del efecto, independientemente de quién realice la acción, comparando dichas características con el contenido de la memoria. Vinculando estos dos procesos con los niveles de identidad descritos previamente, la sensación tácita de agencia y propiedad que impregna la experiencia subjetiva puede considerarse parte del desarrollo del "yo" básico (es decir, la ipseidad), mientras que la emergencia de la autoconciencia reflexiva abarca el aspecto temático de ambos sentidos.

Se han descrito varios correlatos neurocognitivos que pueden estar involucrados en la capacidad de monitorear y reconocer como propios nuestro discurso, pensamientos y movimientos y, por ende, participan en la autoexperiencia (Nelson et al., 2014b; 2014c). Déficits en el proceso de monitoreo de la fuente pueden dar lugar a problemas para distinguir entre los orígenes de los estímulos endógenos y exógenos (es decir, generados internamente o por uno mismo, versus generados externamente o por otros) y pueden resultar de fallos en mecanismos neuronales como la copia eferente (Crapse & Sommer, 2008) y la descarga corolaria o consecuente (Poulet & Hedwig, 2007). Estos déficits en el monitoreo de la fuente pueden llevar a una confusión entre lo endógeno y lo exógeno, así como a errores de predicción, lo que puede resultar en un sentido de propiedad disminuido sobre el contenido mental, una confusión de límites entre uno mismo y los demás, y una hiperreflexividad como compensación a la falta de identificación automática de algunas experiencias (Nelson et al., 2014b).

La capacidad de identificar nuestras propias acciones se basa en modelos de representaciones internas que capturan la relación causal entre las acciones que realizamos y sus resultados sensoriales (Blakemore & Frith, 2009; Wolpert & Miall, 1996), permitiéndonos determinar la fuente del estímulo. Un tipo específico de modelo interno es el conocido como modelo causal (o *forward model* en inglés). Este modelo utiliza la descarga corolaria para suprimir las consecuencias sensoriales que van a tener lugar tras las acciones motoras realizadas por la propia persona (Sperry, 1950). Para esto, las consecuencias sensoriales de los comandos motores autogenerados son predichas basándose en la copia eferente enviada desde regiones motoras a regiones sensoriales justo antes de que la acción tenga lugar (Von Holst & Mittelstaedt, 1950). Esta predicción se compara con la retroalimentación sensorial real recibida tras el movimiento (Ford & Mathalon, 2019; Frith, 2019), lo que cancela el efecto sensorial producido por el acto motor que la propia persona ha realizado. Por el contrario, las sensaciones que provienen de alguna fuente externa no pueden ser predichas por el modelo, ya que carecen de una copia eferente del acto motor que las originó. Esto lleva a una mayor discrepancia sensorial entre las consecuencias predichas y las reales, y, por tanto, no se produce una supresión de la percepción de estas (Blakemore & Frith, 2009). La integridad del mecanismo de descarga corolaria es esencial para desarrollar un sentido de agencia sobre las experiencias psicomotoras y las sensaciones que surgen de los actos generados por la propia persona, pero no sobre las percepciones de los estímulos exógenos (Crapse & Sommer, 2008; Frith, 2019), asegurando así la coherencia en nuestras interacciones con el mundo externo (Poletti et al., 2019).

Esta integración sensoriomotora es evidente en todas las modalidades sensoriales. Durante el habla, las señales motoras influyen en el procesamiento auditivo de nuestra propia voz a nivel cortical a través de un proceso inhibitorio en el que, desde regiones motoras, tiene

lugar una inhibición indirecta sobre las neuronas piramidales auditivas mediada por las conexiones excitadoras con las interneuronas parvalbúmina (Eliades & Wang, 2008; Nelson et al., 2013; Reznik & Mukamel, 2019; Schneider et al., 2014), suprimiendo las respuestas corticales generadas por la escucha de nuestra voz mientras hablamos.

Cuando se perciben estímulos sonoros, se generan principalmente los Potenciales Evocados (ERPs por sus siglas en inglés) N1 y P2 en la corteza auditiva primaria y secundaria. N1 ha sido estudiado como un índice de la supresión cortical auditiva mediada por la descarga corolaria. Al escuchar nuestra propia voz mientras hablamos, N1 se suprime o atenúa, mientras que se mantiene cuando las personas escuchan su voz de manera pasiva (Hubl et al., 2014; Wang et al., 2014; Whitford, 2019). No obstante, se han reportado de manera consistente alteraciones en el mecanismo de descarga corolaria en personas con esquizofrenia, quienes muestran una atenuación significativamente menor del ERP N1 al escuchar su propia voz mientras hablan. Puesto que el mecanismo de descarga corolaria contribuye a la identificación preconsciente de los contenidos mentales como propios, su correcto funcionamiento podría contribuir a la experiencia natural y preconsciente del "yo" y del mundo exterior. Un mal funcionamiento en el mecanismo de descarga corolaria podría dificultar el reconocimiento de las acciones y los estímulos autogenerados, llevando a atribuirlos de forma errónea a fuentes externas (Feinberg, 1978), así como a una disminución del sentido de agencia sobre las propias experiencias, contribuyendo a la perturbación de las autoexperiencias más básicas, es decir, la ipseidad, cuya alteración puede observarse en la manifestación de las llamadas Autoexperiencias Anómalas o Experiencias Anómalas del Yo (ASEs por sus siglas en inglés) (Poletti et al., 2019).

Las ASEs implican una alteración o pérdida de la evidencia preconsciente natural que nos permite identificar nuestros contenidos mentales como propios, abarcando tanto

aspectos cognitivos como somáticos. También se reflejan en la relación del sujeto con el mundo circundante, afectando dimensiones como la implicación personal o el tiempo. Estas desviaciones sutiles y no psicóticas en los dominios del afecto, la percepción, la cognición, la acción y los aspectos somáticos, se reconocen como fenotipos tempranos y relevantes de la esquizofrenia, afectando a la experiencia fundamental de ser un individuo encarnado y presente en el entorno (Raballo & Parnas, 2012; Sass & Parnas, 2003). Por lo tanto, las ASEs pueden alterar la experiencia de la ipseidad, es decir, la vivencia automática y preconsciente de la identidad individual, la cual puede verse afectada en estados psicóticos. Estas experiencias han sido consistentemente identificadas como un hallazgo relevante en personas con psicosis (Raballo et al., 2011), llevando a proponer que la esquizofrenia es, en esencia, un trastorno del "yo" (Sass et al., 2003).

El espectro psicótico incluye varios trastornos que presentan una amplia gama de síntomas psicóticos. Estos trastornos se definen por anormalidades en uno o más de los siguientes cinco dominios: delirios, alucinaciones, pensamiento y discurso desorganizado, comportamiento motor desorganizado o anormal, y síntomas negativos como abulia o apatía (American Psychiatric Association, 2022). Dentro de este espectro, encontramos la esquizofrenia, considerada una de las enfermedades mentales más graves. Afecta al 1% de la población mundial, sin diferencias significativas entre hombres y mujeres (American Psychiatric Association, 2022). Las características psicóticas para diagnosticar la esquizofrenia generalmente emergen entre la adolescencia tardía y los 30 años, ocurriendo a principios o mediados de los 20 años en los hombres y a finales de los 20 años en las mujeres. Los síntomas centrales se comparten con otros trastornos mentales, lo que hace que la delimitación entre diagnósticos sea poco clara y complica el proceso diagnóstico. Se ha descrito que el trastorno bipolar comparte un núcleo psicótico con la esquizofrenia (Sorella et al., 2019), mostrando

fronteras difusas con esta, por un lado, y con la depresión unipolar, por otro, en términos de sintomatología, antecedentes familiares y genética (Akiskal, 2006; American Psychiatric Association, 2022). El trastorno bipolar afecta aproximadamente al 1,5% de la población, sin diferencias significativas entre hombres y mujeres. Su inicio suele darse en la adolescencia tardía o principios de la edad adulta, alrededor de los 20 años, y es una de las causas de discapacidad entre los jóvenes (American Psychiatric Association, 2022).

Desde un enfoque fenomenológico, se ha propuesto el *modelo de alteración de la ipseidad* (Sass, 2014) para entender la experimentación de las ASEs en esquizofrenia, involucrando principalmente dos aspectos (Sass, 2014): i) *hiperreflexividad:* una autoconciencia excesiva, en la que la atención se centra en procesos que típicamente se perciben de forma tácita, haciendo que algo generalmente implícito se vuelva focal, explícito y se experimente de forma similar a un objeto externo; ii) *disminución de la autoimplicación*: una reducción en la intensidad de la presencia subjetiva de uno mismo, lo que conlleva una disminución del sentido de ser un sujeto de conciencia y un agente de acción. Ambos aspectos están interrelacionados, ya que la dimensión tácita o autoconciencia prereflexiva es esencial para toda actividad intencional. Enfocar la atención explícita en algo previamente experimentado tácitamente lleva a su objetivación o alienación, haciendo que se sienta distante o separado, impidiendo que proporcione el anclaje y la orientación necesarios para el resto de las experiencias (Sass, 2009; Sass & Parnas, 2003).

Además, este modelo sugiere que los diversos síntomas encontrados en los trastornos psicóticos pueden compartir formas de alteración de la ipseidad (Sass y Parnas, 2003) y, por ende, estar relacionados con las ASEs. Muchos síntomas positivos de la esquizofrenia (como alucinaciones, delirios o alteraciones del pensamiento) se manifiestan como una pérdida del sentido de habitar en las propias acciones, pensamientos, sentimientos, impulsos,

sensaciones corporales o percepciones (Sass, 2009; Sass y Parnas, 2003), lo que puede desdibujar la distinción entre el "yo" y los demás, dando lugar a síntomas como las alucinaciones auditivas o el eco del pensamiento. Por otro lado, los síntomas negativos (como la apatía, la abulia o la anhedonia) surgen cuando la dimensión tácita se vuelve explícita debido a la hiperreflexividad, haciendo que los pensamientos y las emociones aparezcan como objetos de conciencia o se perciban como antinaturales, lo que dificulta la espontaneidad y conduce a una disminución de la vitalidad y la motivación.

Justificación de la investigación

En muchos casos, los elementos básicos de los trastornos mentales son alteraciones en la relación del sujeto con otras personas o situaciones, que pueden conceptualizarse como una alteración de la intencionalidad de la conciencia (Molina, 2021). Si la conciencia solo puede entenderse en relación con el mundo externo, comprender los modos de interacción entre la actividad cerebral y el mundo es crucial para comprender tanto la conciencia normal como sus alteraciones.

Las ASEs constituyen un dominio psicopatológico importante para la caracterización de los trastornos psicóticos, pudiendo servir como un indicador temprano de inicio (Brent et al., 2014), prediciendo la transición a la psicosis en individuos de alto riesgo más allá de otros síntomas clínicos (Nelson et al., 2012). Considerando la naturaleza preconsciente de las ASEs, es probable que haya algunas alteraciones neuronales subyacentes a ellas. Por otro lado, las alteraciones en el mecanismo de descarga corolaria han sido reportadas de manera consistente en personas con esquizofrenia, caracterizadas por una notable disminución en la supresión del ERP N1 (para una revisión ver Whitford, 2019) y proponiendo la descarga corolaria como un mecanismo transdiagnóstico de la psicosis (Ford et al., 2013; Yao et al.,

2024). Se ha planteado un potencial vínculo entre las ASEs y las alteraciones en la descarga corolaria, sugiriendo que una disfunción temprana de la descarga corolaria podría dificultar la coordinación de las acciones sensoriomotoras de la persona con su entorno, disminuyendo gradualmente el sentido de agencia sobre las propias experiencias (Poletti et al., 2019). Esta reducción en la agencia podría llevar a la experimentación de ASEs y posiblemente a síntomas positivos y negativos, como delirios de pasividad, alucinaciones verbales o un sentido disminuido de existencia. Sin embargo, esta hipótesis aún no ha sido probada y sigue sin estar claro si estos déficits en el funcionamiento del mecanismo de descarga corolaria y su relación con las ASEs son específicos de la esquizofrenia o si también se observan en otros trastornos psicóticos.

Objetivos e hipótesis

Objetivos

Objetivos generales

El objetivo principal de esta tesis doctoral es explorar el mecanismo de la descarga corolaria como un posible sustrato biológico de las ASEs en esquizofrenia y evaluar su especificidad en comparación con otros trastornos dentro del espectro de la psicosis.

Objetivos específicos

Del objetivo general, se derivan los siguientes objetivos específicos:

1. Evaluar el sentido de agencia y propiedad en controles sanos explorando el mecanismo de descarga corolaria mediante EEG, utilizando como medida la supresión del ERP auditivo N1 durante el paradigma *Talk-Listen* (Hablar-Escuchar en español).

2. Explorar si la identificación de nuestra propia voz mientras hablamos se debe a procesos motores o sensoriales, añadiendo una condición adicional de escucha pasiva de una voz ajena.
3. Confirmar en una muestra más grande las alteraciones previamente reportadas en el mecanismo de la descarga corolaria en personas con esquizofrenia.
4. Evaluar la relación entre las ASEs y las alteraciones en el mecanismo de descarga corolaria en personas con esquizofrenia.
5. Evaluar la relación entre los síntomas positivos y negativos y las alteraciones en el mecanismo de descarga corolaria en personas con esquizofrenia.
6. Explorar las diferencias en el funcionamiento del mecanismo de descarga corolaria y su relación con las ASEs, así como con los síntomas positivos y negativos, entre pacientes con esquizofrenia en su primer episodio psicótico y pacientes crónicos.
7. Explorar la especificidad de la alteración del mecanismo de descarga corolaria y su relación con los ASEs en personas con esquizofrenia en comparación con aquellas con trastorno bipolar.

Hipótesis

Para alcanzar los objetivos propuestos anteriormente, y basándonos en la literatura actual, se establecen las siguientes hipótesis:

1. La respuesta cortical cerebral será la misma si la persona escucha de forma pasiva su propia voz o la voz de otra persona, pero se suprimirá al escuchar su propia voz simultáneamente al habla en controles sanos.

2. La supresión de la actividad cortical auditiva durante el habla será menor en personas con esquizofrenia, debido a un deterioro en el funcionamiento del mecanismo de descarga corolaria.
3. El nivel de supresión de la actividad cortical durante el habla estará inversamente relacionado con la gravedad de las ASEs en personas con esquizofrenia.
4. El nivel de supresión de la actividad cortical durante el habla estará inversamente relacionado con la gravedad de los síntomas positivos y negativos en personas con esquizofrenia.
5. No habrá diferencias en la supresión de la actividad cortical auditiva ni en su relación con la presencia de ASEs y síntomas positivos y negativos entre los participantes con primer episodio psicótico y aquellos con esquizofrenia crónica.
6. Las personas con trastorno bipolar también mostrarán alteraciones en el mecanismo de descarga corolaria, pero estas no serán tan pronunciadas como en esquizofrenia.

Materiales y métodos

Este trabajo de investigación ha llevado a la publicación de tres artículos científicos en revistas indexadas por el Journal Citation Report (JCR). El primer artículo tuvo como objetivo describir el funcionamiento del mecanismo de descarga corolaria en controles sanos. El segundo evaluó las alteraciones de este mecanismo y su asociación con las ASEs en las personas con esquizofrenia. Finalmente, se incluyó una muestra de participantes con trastorno bipolar para evaluar la especificidad de esta alteración.

El tamaño muestral de cada grupo varió ligeramente dependiendo del estudio. Los pacientes fueron diagnosticados por un psiquiatra experto siguiendo los criterios de la quinta edición del Manual Diagnóstico y Estadístico de los Trastornos Mentales (DSM-5) (American Psychiatric Association, 2022). Respecto a los participantes con trastorno bipolar, todos fueron diagnosticados con trastorno bipolar tipo I con antecedentes de síntomas psicóticos. Los datos de EEG se adquirieron durante la fase eutímica después de una hospitalización debido a su último episodio maníaco.

Los criterios de exclusión fueron: i) presencia de alguna enfermedad neurológica, ii) antecedentes de traumatismo craneoencefálico con pérdida de conciencia, iii) abuso de sustancias actual (excepto nicotina o cafeína), iv) Cociente Intelectual (CI) inferior a 70, y v) cualquier tratamiento psiquiátrico (para los controles) o vi) diagnóstico actual distinto de esquizofrenia o trastorno bipolar (para los pacientes). El comité de ética del hospital participante aprobó el estudio de acuerdo con el Código Internacional de Ética de la Asociación Médica Mundial (Declaración de Helsinki) y todos los participantes dieron su consentimiento informado por escrito después de recibir información completa impresa.

La metodología seguida en los tres estudios fue similar, pasando todos los participantes por una evaluación clínica, neuropsicológica y neurofisiológica.

Evaluación clínica y cognitiva

Los síntomas positivos y negativos de los pacientes fueron evaluados respectivamente utilizando la subescala de síntomas positivos de la "*Escala del Síndrome Positivo y Negativo"* (PANSS) (Kay et al., 1987) y la puntuación total de la *"Escala Breve de Síntomas Negativos"* (BNSS) (Kirkpatrick et al., 2011). El rendimiento cognitivo se evaluó utilizando la versión española de la "*Evaluación Breve de la Cognición en Esquizofrenia*" (BACS) (Keefe et al., 2008;

Segarra et al., 2011) y el "*Test de Clasificación de Tarjetas de Wisconsin"* (WCST: porcentaje de errores perseverativos) (Grant & Berg, 1948). El CI se estimó mediante la versión reducida de la "*Escala de Inteligencia para Adultos de Wechsler-III*" (WAIS-III) (Durá et al., 2010; Wechsler, 1997). La evaluación cognitiva se realizó únicamente con fines descriptivos.

Evaluación de las Autoexperiencias Anómalas

La presencia de ASEs se evaluó utilizando el *"Inventario de Experiencias Anómalas del Yo de Tipo Psicótico"* (IPASE) (Cicero et al., 2017), un autoinforme de 57 ítems con una estructura de 5 factores. Los participantes, en presencia del investigador, calificaron su grado de acuerdo con las afirmaciones presentadas en una escala tipo Likert de 1 (Totalmente en desacuerdo) a 5 (Totalmente de acuerdo). Los factores incluidos son: i) *Cognición:* hace referencia a las experiencias inusuales relacionadas con los propios pensamientos u otros procesos cognitivos, describiendo fenómenos como la interferencia del pensamiento o escuchar los propios pensamientos como provenientes del exterior; ii) *Autoconciencia y presencia:* contiene ítems relacionados con la pérdida de la identidad básica y la desconexión con mundo, incluyendo aspectos como la hiperreflexividad, que oscurece la experiencia de existencia en primera persona; iii) *Conciencia:* refleja interrupciones en la experiencia consciente de la realidad, la experiencia del tiempo, alteraciones en la intencionalidad y la dificultad para distinguir entre si algo ha sido imaginado o ha ocurrido realmente; iv) *Somatización*: incluye ítems asociados con distorsiones en las sensaciones corporales, como experimentar sensaciones eléctricas, percibir cambios en las formas de las extremidades, sentir que el cuerpo es difícil de controlar o no sentirse física o psíquicamente presente en el propio cuerpo; v) *Demarcación/Transitivismo:* refleja la disolución de los límites entre el "yo" y el mundo o una sensación de inexistencia.

Evaluación neurofisiológica del mecanismo de descarga corolaria

Para evaluar el funcionamiento del mecanismo de descarga corolaria ante estímulos auditivos, se siguió el ya establecido paradigma conocido como *Talk-Listen* en inglés (Hablar-Escuchar en español) (Ford et al., 2010). Esta tarea está compuesta por dos condiciones:

~ Condición *talk*: Se instruyó a los participantes a vocalizar el fonema [a:] a intervalos de aproximadamente 1-2 segundos durante 4 minutos, con un descanso de 30 segundos después de los primeros 2 minutos. Las vocalizaciones se amplificaron y trasmitieron en tiempo real a los participantes a través de unos auriculares.

~ Condición *listen-self*: Los participantes escucharon de forma pasiva, a través de auriculares, la grabación de su propia voz realizada en la condición anterior.

Además, en el estudio realizado con controles sanos se incorporó una tercera condición para evaluar si la identificación del habla autogenerada se debe a procesos motores o si en cambio están implicados procesos sensoriales asociados al reconocimiento de las características físicas del estímulo auditivo:

~ Condición *listen-other:* La única diferencia con la condición *listen-self* es que la voz que se escucha de forma pasiva ha sido grabada previamente por uno de los investigadores y no por la persona participante.

El mecanismo de descarga corolaria fue medido como la diferencia entre la amplitud del ERP N1 correspondiente a la condición *talk* y la amplitud de N1 en la condición *listen*. De esta forma, se obtuvo una medida de la supresión de la percepción de las consecuencias sensoriales que tiene lugar tras la realización de una acción autogenerada, en comparación con la estimulación que tiene lugar cuando percibimos de forma pasiva un estímulo procedente del exterior.

Antes de realizar la grabación de la condición *talk*, los participantes recibieron instrucciones detalladas sobre cómo mantener una distancia constante de 15 cm del micrófono, realizar una breve vocalización (<300 ms) del fonema [a:] y mantener un volumen entre 65 y 75 decibelios (dB) de Nivel de Presión Sonora (SPL por sus siglas en inglés). Durante esta fase de entrenamiento, se les proporcionó retroalimentación inmediata sobre el rendimiento. Se instruyó a los participantes a minimizar el movimiento, permanecer quietos, abrir la boca antes de vocalizar, mantener la mirada en la cruz de fijación durante toda la grabación y mantener un volumen vocal constante. Utilizar una vocal en lugar de un sonido más complejo tiene la ventaja de introducir menos ruido muscular en las grabaciones de EEG y, al no transmitir ninguna información semántica, requiere un procesamiento cognitivo más bajo.

La intensidad del volumen se monitoreó continuamente utilizando un medidor de nivel de sonido calibrado (modelo PCE-353N-ICA) colocado a 6 cm de la boca y se estandarizó el volumen de la salida de audio en todas las condiciones (Ford et al., 2010). Durante las tres condiciones de la tarea, un interfaz de audio (Focusrite®) y un software de procesamiento de sonido (Audacity®) fueron conectados para transmitir la señal correspondiente a cada vocalización a un rastreador de estimulación (StimTrak: Brain vision), que transforma esta señal en un marcador y lo envía al preamplificador de EEG (actiCHamp), integrándolo en las grabaciones de EEG. El nivel de sensibilidad del amplificador se configuró para que los marcadores fueran generados solo cuando el volumen de la voz del participante alcanzaba un mínimo de 65 dB, excluyendo del análisis las vocalizaciones que caían fuera del rango de 65-75 dB. Para mitigar la influencia de la conducción ósea durante la vocalización, el SPL se elevó en 15 dB por encima del SPL medio del habla de cada participante en todas las condiciones de la tarea (Ford et al., 2007; Heinks-Maldonado et al., 2007).

Adquisición y análisis del EEG

En los tres estudios se utilizó un sistema de EEG de 64 canales para registrar la actividad cortical (BrainVision, Brain Products GmbH). Se colocaron electrodos activos utilizando el sistema internacional 10-10 (FP1, FP2, F7, F8, F3, F4, Fz, FC5, FC6, FC1, FC2, T7, T8, C3, Cz, C4, CP5, CP6, CP1, CP2, TP9, TP10, P7, P8, P3, P4, Pz, O1, O2, Oz, AF7, AF3, AFz, F1, F5, FT7, FC3, FCz, C1, C5, TP7, CP3, P1, P5, PO7, PO3, POz, PO4, PO8, P6, P2, CPz, CP4, TP8, C6, C2, FC4, FT8, F6, F2, AF4, AF8). La impedancia no superó los 5 kiloohmios (kΩ), la frecuencia de muestreo fue de 500 hercios (Hz) y la referencia en línea fue la media de los mastoides ((TP9 + TP10)/2). El preprocesamiento de los datos se realizó con EEGLAB v13.6.5b (Delorme & Makeig, 2004) y Matlab R2022b (MathWorks Inc., MA, USA), aplicándose un filtro de paso bajo de 30 Hz, un filtro paso alto de 1 Hz y un filtro notch de 50 Hz. Durante la condición de habla (*talk*), cada registro continuo de EEG se monitoreó visualmente ensayo por ensayo para detectar artefactos musculares excesivos al inicio del habla, excluyendo aquellos que involucraban algunos picos de actividad anómala (Ford et al., 2010). Posteriormente, los movimientos oculares, parpadeos y cualquier artefacto relacionado con la actividad muscular facial (especialmente durante la condición *talk*) fueron identificados con un Análisis de Componentes Independientes (ICA) (Delorme et al., 2007) y rechazados manualmente. Las ventanas temporales se establecieron desde 100 ms antes del inicio del estímulo auditivo (utilizado para la corrección de la línea base) hasta 350 ms después. Los ensayos que, a pesar de la limpieza con ICA, aún contenían artefactos (voltajes superiores a ±90 microvoltios (μV)) fueron rechazados. Durante este proceso, el comando de rechazo de artefactos indicó el porcentaje de ensayos eliminados en cada participante. Consideramos que, si un participante perdía más del 70% de los ensayos, la grabación probablemente no era lo suficientemente limpia; por lo tanto, los participantes con menos del 30% de ensayos utilizables en promedio

fueron excluidos del análisis, sin encontrarse diferencias significativas en el número de ensayos utilizables para cada grupo.

El ERP N1 se identificó como el pico negativo fronto-central entre 60 y 120 ms después del inicio del fonema [a:] (Ford et al., 2010, 2014; Mathias et al., 2020), alcanzando su amplitud máxima en los electrodos de la línea media (Ford et al., 2007) y P2 se identificó como el pico positivo fronto-central subsiguiente entre 150 y 200 ms.

Análisis estadístico

Los análisis estadísticos realizados variaron ligeramente en cada uno de los estudios, dependiendo de los grupos de participantes incluidos (controles sanos, personas con esquizofrenia y personas con trastorno bipolar) y de las condiciones de la tarea llevadas a cabo (*Talk*, *Listen-self* y *Listen-other*). Las diferencias sociodemográficas y cognitivas entre grupos de pacientes y controles sanos se examinaron utilizando pruebas Chi-cuadrado o pruebas t de Student para muestras independientes, dependiendo del tipo de variable a comparar. Los tamaños del efecto se evaluaron utilizando el valor de eta cuadrado parcial (ηp^2), y para los análisis post-hoc se empleó la prueba t de Student con corrección de Bonferroni.

En el primer estudio, se evaluó el funcionamiento del mecanismo de descarga corolaria en un grupo de participantes controles sanos. Para ello, se analizó la amplitud y la latencia de los picos de los ERPs N1 y P2 mediante Análisis de Varianza (ANOVA) de medidas repetidas sobre los promedios de los ensayos. El factor intra-sujeto fue la condición de la tarea (*talk*, *listen-self* o *listen-other*). Además, para evaluar la fuerza de la evidencia a favor de la hipótesis nula, se emplearon pruebas t bayesiana para muestras relacionadas sobre los valores de amplitud de las componentes N1 y P2 entre las tres condiciones de la tarea (SPSS Statistics para Windows, Versión 23.0. Chicago: SPSS Inc.).

El segundo estudio incluyó un grupo de participantes con diagnóstico de esquizofrenia para comparar su funcionamiento con el grupo control sano. Para evaluar la ocurrencia del mecanismo de descarga corolaria, se realizó un análisis intragrupo utilizando la prueba t para medidas repetidas, con el fin de analizar las diferencias en la amplitud de N1 y P2 entre las dos condiciones de la tarea (*talk* vs *listen-self*) en cada grupo de participantes por separado. En segundo lugar, se realizó una segunda prueba t de Student, en este caso para medidas independientes, para evaluar las diferencias entre grupos, utilizando el valor de la diferencia de amplitud de los ERPs en cada una de las condiciones de la tarea (amplitud en N1 o P2 en *talk* menos amplitud de N1 o P2 en *listen-self*) como reflejo de la supresión sensorial generada por el mecanismo de descarga. Finalmente, mediante un análisis de regresión lineal, se estudió la relación entre la medida de supresión sensorial (amplitud en *talk* menos amplitud en *listen-self*) y la intensidad de las ASEs (puntuaciones IPASE) y los síntomas positivos y negativos (puntuaciones PANSS y BNSS respectivamente). Los análisis estadísticos se realizaron primero para todas las personas con esquizofrenia y, posteriormente, para los pacientes con primer episodio psicótico y crónicos por separado.

Por último, el tercer estudio incluyó un grupo de personas con trastorno bipolar. Debido al menor tamaño muestral de este grupo, se realizaron pruebas de normalidad de Shapiro-Wilk para verificar si los datos cumplían con este requisito. Una vez verificado que todas las variables se distribuían normalmente, se utilizaron pruebas paramétricas para el análisis posterior. Para evaluar las diferencias en la amplitud de N1 entre condiciones, y estudiar el funcionamiento del mecanismo de descarga corolaria en cada grupo, se realizó un ANCOVA de medidas repetidas 3x2 con “grupo” como factor entre-sujetos (esquizofrenia, bipolar y control sano) y “condición de tarea” como factor intra-sujeto (*talk* y *listen-self*). Segundo, para evaluar las diferencias entre grupos, se calcularon y compararon los valores de

supresión de N1 (*talk* menos *listen-self*) mediante un ANCOVA de un factor. En ambos conjuntos de análisis, el efecto del tratamiento (medido mediante el cálculo de equivalentes de clorpromazina en mg/día) se incluyó como covariable. Finalmente, se realizaron análisis de regresión lineal por separado para ambos grupos de pacientes, con el fin de evaluar la relación entre la supresión de N1 (amplitud en *talk* menos amplitud en *listen-self*) y la intensidad de las ASEs (puntuaciones IPASE).

Resultados

Se encontraron diferencias significativas al comparar la amplitud del ERP N1 en las diferentes condiciones de la tarea en el grupo de participantes controles sanos. Los resultados fueron debidos a una menor amplitud en la condición *talk* comparado con *listen other* y *listen self*. En cambio, no se encontraron diferencias significativas entre las dos condiciones de escucha (*listen-self* y *listen-other*) ni tampoco en la amplitud de P2. Además, no se encontraron diferencias en la latencia de N1 o P2 relacionadas con la condición de la tarea.

En cuanto a los pacientes, tanto el grupo de personas con esquizofrenia como con trastorno bipolar, mostraron una menor amplitud en N1 durante la condición *talk* al compararla con la condición *listen-self*. No obstante, la supresión de la actividad cortical como medida del funcionamiento del mecanismo de descarga corolaria, fue menor en el grupo de personas con esquizofrenia en comparación con los controles sanos, sin encontrar diferencias estadísticamente significativas al comparar personas con trastorno bipolar y controles sanos, ni entre ambos grupos de pacientes. Al estudiar a los pacientes con esquizofrenia por separado, se encontraron los mismos resultados en pacientes crónicos en comparación con los controles sanos, y una tendencia a la significancia estadística en los pacientes con primer episodio al compararlos con los controles sanos. No se encontró ningún efecto significativo de

interacción entre la condición de la tarea y tratamiento recibido por los pacientes medido en términos de equivalentes de clorpromacina (mg/día).

Las personas con esquizofrenia fueron las que mostraron menor supresión del potencial N1 durante el habla. En cambio, no se encontraron diferencias significativas en P2 en comparación con controles sanos, por lo que el resto de los análisis estadísticos se limitaron a N1. Los análisis de regresión en pacientes con esquizofrenia mostraron una correlación inversa estadísticamente significativa entre la supresión de N1 y la experimentación de ASEs y síntomas clínicos, de manera que a menor supresión de la amplitud de N1 durante el habla, mayor gravedad de las ASEs, así como de los síntomas positivos y negativos. En las personas con primer episodio psicótico, se observó la misma relación entre la supresión de N1 y los síntomas negativos, y una tendencia hacia la significancia estadística en la relación entre la supresión de N1 y la gravedad de las ASEs y síntomas positivos. En las personas con esquizofrenia crónica se obtuvieron los mismos resultados que al analizar de forma global a este grupo de pacientes.

Por último, respecto a las personas con trastorno bipolar, estas mostraron una supresión de N1 intermedia entre el grupo de esquizofrenia y controles sanos sin encontrarse ninguna relación estadísticamente significativa con la experimentación de ASEs.

Discusión

La presente tesis doctoral se ha centrado en evaluar la supresión de la actividad cortical auditiva provocada por las consecuencias sensoriales derivadas de los actos motores autogenerados, como medida del funcionamiento del mecanismo de descarga corolaria, utilizando el bien establecido paradigma *Talk-Listen* (Ford et al., 2010). Los hallazgos de los estudios incluidos, descritos en profundidad en los capítulos 3, 4 y 5, han proporcionado un

enfoque más directo hacia el estudio de un posible mecanismo neural subyacente en el desarrollo de un sentido de sí mismo intacto y la experimentación de ASEs en los trastornos psicóticos.

En el primer estudio, diferenciamos entre los sentidos de agencia y propiedad en controles sanos, a través de las condiciones *talk* y *listen-self* respectivamente, y evaluamos si la identificación del habla autogenerada se debe a procesos motores o sensoriales asociados con el reconocimiento de las características físicas del estímulo, introduciendo la novedosa condición *listen-other*. Nuestros resultados coinciden con la idea de que la identificación sensorial de nuestra propia voz mientras hablamos ocurre a nivel preestimular. El hecho de que no se encontraran diferencias en la amplitud y latencia de N1 y P2 entre las condiciones de *listen-self* y *listen-other* indica que la respuesta cortical a nivel auditivo es similar, independientemente de si la voz que se escucha de forma pasiva es reconocida como propia, basándose en las características físicas del estímulo, o no. Sin embargo, en línea con la literatura previa (Heinks-Maldonado et al., 2005; Hubl et al., 2014; Wang et al., 2014), se observó una disminución notable en la amplitud de N1 cuando la persona escucha su propia su voz mientras habla, acompañada de la preservación de P2, en comparación con la actividad cortical observada en ambas condiciones de escucha pasiva. Estos hallazgos van en línea con la idea de que la descarga corolaria está involucrada en la supresión del ERP auditivo N1 durante el habla autogenerada, lo que sirve para informar a otras regiones del cerebro que estos estímulos provienen de una acción realizada por la propia persona. El hecho de que el ERP P2 aparezca conservado en la condición *talk* confirma que la persona detecta su propia voz mientras habla. Por lo tanto, la supresión de N1 observada en esta condición es poco probable que se deba a un problema en la percepción del sonido, sino al funcionamiento del mecanismo de descarga corolaria y la copia eferente del comando motor enviado a las

regiones sensoriales justo antes de que tenga lugar el habla (Sperry, 1950; Von Holst & Mittelstaedt, 1950).

La percepción es un proceso impulsado por la acción en el que el cerebro explora activamente el entorno y registra los resultados de sus acciones. Las regiones sensoriales reciben información tanto de estímulos externos como de las neuronas motoras que producen retroalimentación sensorial de nuestras propias acciones justo antes de que estas ocurran (Buzsáki, 2018). Para determinar si un estímulo ha sido generado por una acción realizada por la propia persona o si proviene de una fuente externa, se utiliza la copia eferente del comando motor con el fin de predecir los resultados sensoriales de los movimientos autogenerados. Durante la vocalización, hay una mínima discrepancia sensorial entre la retroalimentación predicha y la real, por lo que, al compararlas, se suprime o reduce la percepción (Ford & Mathalon, 2019; Frith, 2019). En cambio, cuando escuchamos pasivamente estímulos generados externamente, estos no tienen una copia eferente asociada, ya que no han ido precedidos por un acto motor realizado por la persona. Esto los hace impredecibles y, en consecuencia, no se produce ninguna supresión por parte del mecanismo de descarga corolaria, resultando en una mayor actividad cortical (Blakemore & Frith, 2009).

En el segundo artículo, examinamos la falta de supresión de N1 durante el habla como un posible sustrato alterado del mecanismo de descarga corolaria en personas con esquizofrenia y su asociación con las ASEs, lo cual no había sido estudiado previamente. Como se esperaba según la literatura previa (para una revisión ver Whitford, 2019), encontramos una disfunción en la descarga corolaria, indicada por una menor atenuación del ERP N1 durante el habla en personas con esquizofrenia, al compararlo con la actividad cortical que tiene lugar cuando escuchan pasivamente su voz. El nivel de supresión de N1 se ha asociado con la integridad estructural del fascículo arqueado en estos pacientes (Whitford et al., 2017)

y, como se discutió anteriormente, el mecanismo de descarga corolaria podría estar vinculado a la sincronización mediada por la transmisión inhibitoria entre el área motora y la región sensorial que recibe la señal correspondiente (Chen et al., 2011; Ford et al., 2002, 2005). En este contexto, el déficit esperado en los mecanismos de descarga corolaria en nuestros pacientes es consistente con los efectos de una corteza cerebral hiperactivada y una hipomodulación de las redes (Bachiller et al., 2014; Cea-Cañas et al., 2020; de Luis-García, et al., 2018; Díez et al., 2013; 2024; Gomez-Pilar et al., 2018; Iglesias-Tejedor et al., 2022; Molina et al., 2018; 2020), lo que coincide con los déficits de GABA reportados en la corteza de personas con esquizofrenia (Lewis et al., 2005). En consecuencia, un déficit en la función inhibitoria podría resultar en una actividad neural desorganizada, llevando a una red hiperactivada y mal modulada que contribuye a la saliencia aberrante (dificultad para dirigir la atención solo hacia los estímulos que son relevantes) y a déficits de monitoreo de la fuente (dificultad para distinguir el origen de los estímulos).

La falta de supresión de N1 observada en las personas con esquizofrenia, se asoció con la gravedad de las ASEs, así como con los síntomas positivos y negativos, sin encontrarse diferencias entre pacientes con primer episodio o crónicos. Esta asociación sugiere que la identificación preconsciente del origen de las fuentes de estimulación sensorial, es decir, si el estímulo proviene de uno mismo o del exterior, probablemente está alterada en estos pacientes y, por tanto, será más difícil discernir el origen de los estímulos. Tal alteración coincide con las características de las ASEs y puede contribuir a la disminución del sentido del sí mismo y a la alteración de la ipseidad reportada en esquizofrenia, al haber problemas para diferenciar entre el “yo” y el mundo exterior (Poletti et al., 2019). Además, como se expuso en el capítulo introductorio, el modelo de perturbación de la ipseidad sugiere que los diversos síntomas encontrados en los trastornos psicóticos pueden compartir formas de ipseidad

alterada (Sass, 2014; Sass & Parnas, 2003), considerando una posible relación entre las ASEs y los síntomas psicóticos (Poletti et al., 2019). La pérdida del sentido de agencia podría llevar a experimentar los propios pensamientos como estímulos externos, manifestándose en síntomas positivos como alucinaciones verbales auditivas o delirios de pasividad. Por otro lado, la hiperreflexividad podría contribuir a que los pensamientos parezcan objetos y las emociones se perciban antinaturales o insatisfactorias, pudiendo dar lugar a una reducida sensación de vitalidad o motivación que podría estar relacionada con los síntomas negativos.

Finalmente, el tercer estudio nos permitió determinar la especificidad de la alteración del mecanismo de descarga corolaria, al incluir una muestra de personas con trastorno bipolar que habían mostrado síntomas psicóticos. La disfunción en el mecanismo de descarga corolaria se ha propuesto como un factor transdiagnóstico subyacente a la psicosis (Ford et al., 2013; Yao et al., 2024) y, como se comentó en la introducción, el espectro psicótico incluye varios trastornos con límites difusos debido a la amplia heterogeneidad de los síntomas, encontrándose un núcleo psicótico compartido entre el trastorno bipolar y la esquizofrenia (Sorella et al., 2019). Los resultados de nuestro estudio mostraron que los pacientes con trastorno bipolar exhibían una atenuación sensorial intermedia entre el grupo de esquizofrenia y el grupo de controles sanos, demostrando un continuo en la atenuación de la actividad cortical durante el habla entre los tres grupos. Además, ambos grupos de pacientes mostraron un potencial N1 normal al escuchar su propia voz pregrabada, lo que sugiere nuevamente que el reconocimiento sensorial de su propia voz se mantiene intacto. Por lo tanto, la variación en la atenuación de N1 durante la vocalización observada entre los tres grupos de participantes probablemente se deba a diferencias en el funcionamiento del mecanismo de descarga corolaria.

Aunque la alteración en la supresión del N1 es más pronunciada en el grupo de esquizofrenia, la ausencia de diferencias significativas entre los dos grupos de pacientes, sumada al hecho de que todos los pacientes bipolares estaban en un estado eutímico y que los síntomas psicóticos suelen ocurrir durante las fases maníaca, depresiva o mixta, refuerza la hipótesis de una conexión entre las alteraciones en el mecanismo de descargar corolaria y las características psicóticas. Además, la supresión de N1 estaba significativamente relacionada con la gravedad de los ASEs en el grupo de pacientes con esquizofrenia, pero no en aquellos con trastorno bipolar. Esto sugiere que estas alteraciones podrían estar presentes en un subconjunto más pequeño de pacientes bipolares en comparación con aquellos con esquizofrenia, lo que hace menos clara la relación entre los ASEs y el mecanismo de descarga corolaria, y menos evidente la reducción en la supresión cortical auditiva durante el habla en este grupo. Por lo tanto, la disfunción del mecanismo de descarga corolaria probablemente representa un marcador neural de una experiencia alterada del "yo", que es más pronunciada y significativa en esquizofrenia.

Se ha sugerido que las alteraciones en el funcionamiento de la descarga corolaria están vinculados a una mielinización anormal de la materia blanca frontal en esquizofrenia (Whitford et al., 2012). Aunque también se ha observado una reducción en la mielina intracortical en el trastorno bipolar (Jørgensen et al., 2016), los patrones de mielinización pueden diferir entre estos síndromes (Hercher et al., 2014). En consecuencia, las alteraciones en la mielinización, que son más pronunciadas en esquizofrenia, en comparación con las del trastorno bipolar (Hercher et al., 2014), podrían explicar la supresión intermedia de N1 observada en el grupo bipolar. Además, se han informado déficits de GABA en la corteza de personas con esquizofrenia (Lewis et al., 2005), mientras que solo una proporción menor de pacientes bipolares muestra déficits inhibitorios (Volk et al., 2016). Teniendo esto en cuenta,

si el mecanismo de descarga corolaria depende de la inhibición cortical, los niveles de supresión intermedios observados en pacientes bipolares -situándose entre aquellos con esquizofrenia y los controles sanos- podrían sugerir que un déficit inhibitorio cortical está presente en un subconjunto más pequeño de pacientes bipolares en comparación con aquellos con esquizofrenia.

Para finalizar, entre las limitaciones de los tres estudios incluidos en esta tesis doctoral destacan las siguientes: i) no se puede excluir completamente el efecto del tratamiento sobre los resultados obtenidos, aunque no se encontró una relación significativa entre la supresión del N1 y la dosis farmacológica (medida en dosis equivalentes de clorpromazina, mg/día); ii) es necesario confirmar los resultados en una muestra más grande de participantes, si bien la relación entre la descarga corolaria auditiva y las ASEs no había sido explorada previamente en ningún otro estudio; iii) para la evaluación de las ASEs se utilizó el autoinforme IPASE, en vez de la *gold standard* EASE. No obstante, las puntuaciones de ambos instrumentos han mostrado estar altamente correlacionadas (Nelson et al., 2019), y un investigador estuvo presente para asistir a los participantes en caso de duda con alguno de los ítems; iv) aunque la descarga corolaria probablemente subyace a la experiencia de la ipseidad, no podemos establecer una relación causal sino una correlación entre la gravedad de las ASEs y la supresión del ERP auditivo N1. Además, este efecto de supresión puede representar solo una de las muchas medidas potenciales del mecanismo de descarga corolaria; v) por último, el efecto del orden temporal en la administración del paradigma no puede descartarse por completo, ya que la condición de habla siempre debe aparecer en primer lugar. Sin embargo, no se encontraron diferencias significativas en los controles sanos al comparar el ERP N1 generado al escuchar pasivamente su propia voz grabada frente a la escucha pasiva de la voz de otra persona.

Conclusiones

Distinguir la fuente de la estimulación sensorial y determinar si los estímulos se originan interna o externamente ayuda a diferenciar entre los sonidos generados por nosotros mismos, nuestros pensamientos y recuerdos de los estímulos externos. Se ha descrito que el mecanismo de descarga corolaria está implicado en la correcta monitorización de la fuente de los estímulos al atenuar o suprimir las consecuencias sensoriales de los actos autoiniciados. Nuestros resultados replican datos previos y corroboran el uso de la supresión del ERP auditivo N1 como un índice del correcto funcionamiento del mecanismo de descarga corolaria durante el habla.

Mientras hablamos, no reconocemos la voz que emitimos como nuestra basándonos en las características físicas de ese estímulo auditivo específico. En su lugar, la identificación sensorial de nuestra propia voz ocurre a nivel preestimular, antes de la percepción del sonido emitido. Esto se debe a que nuestro cerebro no percibe pasivamente los estímulos; los examina y predice las consecuencias de nuestras acciones antes de que estas que ocurran, gracias a la copia eferente de los comandos motores enviados a las regiones sensoriales. Las regiones sensoriales reciben entradas tanto de estímulos externos como de neuronas motoras que producen retroalimentación sensorial de nuestras propias acciones. Así, la actividad auditiva cortical no difiere cuando escuchamos pasivamente nuestra propia voz en comparación con otra voz externa, ya que no hay un comando motor que nos permita predecir las consecuencias sensoriales.

Las personas con esquizofrenia muestran alteraciones en el funcionamiento del mecanismo de descarga corolaria, evidenciadas por una disminución en la supresión auditiva del ERP N1 durante la vocalización. Un mal funcionamiento de este mecanismo podría dificultar el reconocimiento de las acciones autogeneradas, lo que llevaría a atribuir

erróneamente dichas acciones a fuentes externas y contribuiría a la experimentación de ASEs, y a la manifestación de síntomas positivos y negativos.

La alteración de este mecanismo es menos evidente en personas con trastorno bipolar, donde se observa un continuo en la supresión del ERP auditivo N1 entre personas con esquizofrenia y controles sanos, sin encontrar una relación con la gravedad de las ASEs. Los valores intermedios de supresión observados en pacientes bipolares podrían sugerir que un déficit inhibitorio cortical está presente en un subconjunto más pequeño de individuos con trastorno bipolar en comparación con aquellos con esquizofrenia.

Los resultados de esta tesis doctoral muestran que la disfunción en el mecanismo de descarga corolaria puede estar asociada con la psicosis y representar un posible mecanismo subyacente a las ASEs. No obstante, esta disfunción parece ser más notoria en personas con esquizofrenia en comparación con aquellas con trastorno bipolar.

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