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Abstract

The psychosis spectrum comprises heterogeneous disorders characterized by both world-related and self-related symptoms. How these symptoms may arise with similar features in spite of the different aetiologies is yet an unsolved question. In this narrative review, we compare three conditions characterized by psychotic experiences (schizophrenia, substance-use disorder and sensory-deprivation) searching for links between their phenomenological features and the mechanisms underlying their onset. Clinically, psychotic experiences are characterized by the reciprocal contamination of world- and self-related contents, termed 'world/self ambivalence'. Neuroimaging evidence suggests that the imbalance between stimuli-, self-, and attention-related functional networks (visual/auditory, default-mode, and salience network respectively) assumes central relevance in all the conditions considered. Phenomenology and neurobiology were thus interrelated in light of the reviewed literature, identifying two key neuronal mechanisms which may lead to world/self ambivalence. First, psychotic experiences are associated with the relative dominance of one network over the other (default-mode over auditory/visual networks, or vice-versa), prompting an excess of internal or external pressure to the experienced ambivalence between world and self. Second, an altered salience network resting-state functional connectivity could generate a dysregulation of the attentive fluctuations from self- to world-related activity, thus blurring the boundary between the environment and oneself, labelled the 'world/self boundary'.

Main text

Schizophrenia, the use of psychotropic substances, and sensory-deprivation are a wide cluster of conditions that may induce similar psychotic presentations (Arciniegas, 2015; Guloksuz and van Os, 2018; Rosenzweig, 1959; Yao et al., 2018; Ziskind, 1964). By definition, all these conditions are characterized by an altered contact with reality, although the underlying aetiologies are different. The altered contact with reality is specifically defined by disturbances in two apparently complementary activities: 1) self-related processes comprising alterations in subjective mental and physical identity, distorted autobiographical and social image and impaired sense of agency; 2) world-related processes that include alterations in visual, auditory, tactile, olfactory or bodily perceptions, hallucinations, and multisensory integration deficits (van der Weiden et al., 2015).

These two activities are not markedly separated, but share significant functional overlaps (see for instance how perceptual incoherence may evoke incoherent self-experiences in Postmes et al., [2014]). We will henceforth refer to the mutual influence between world-related and self-related processes as the 'world/self relationship' (Blanke, 2012). Disturbances in the ability to distinguish self-generated processes from stimuli generated by other individuals (termed the 'self-other relationship' Ebisch and Gallese, 2015) have been extensively described in schizophrenia. However, the term world/self relationship comprises not only the ability to discriminate between oneself and others, but also the ability of the individual to experience himself as separate from the surrounding environment. This feature is altered in several types of psychotic experiences (Boydell et al., 2010), but remains a relatively unexplored issue.

1. Study aim

The aim of the present work is to explore how the theoretical background of the world/self relationship may be mirrored by specific neurobiological findings, identifying a dimension which we will later term 'world/self ambivalence'. The present work is subsequently divided

in two main sections: first, we will selectively review the literature concerning the world/self relationship, focusing specifically on the psychosis spectrum which is characterized by alterations in the world/self relationship. Second, we will describe how the identified imbalance between world and self underpins core psychotic symptoms such as hallucinations and self-disturbances, despite heterogeneous aetiologies. As such, we will define the neurobiological grounds which may characterize different psychotic experiences; substance-induced psychosis was juxtaposed with schizophrenia-related psychosis in order to compare two different psychiatric categories (A.P.A., 2013). As a third condition, we included sensory-deprivation (i.e. the elimination of environmental sounds or lights to deprive the individual of meaningful sensory stimuli) for its propensity to quickly induce psychotic-like symptoms in healthy individuals without the necessity of administering psychotropic substances (Mason and Brady, 2009; Verdoux and van Os, 2002).

2. Hallucinations and self-disorders in psychotic experiences

Hallucinations are conceptualised as perceptions which occur in the absence of a corresponding external stimulus, and in which the individual has conviction in its reality. In addition to being a key symptom of schizophrenia-related and substance-induced psychotic experiences, they may also be experienced by healthy individuals (Johns et al., 2014), especially when elicited by specific conditions such as sensory-deprivation (Daniel et al., 2014) or by individuals at clinical high risk for psychosis (Fusar-Poli et al., 2013). Although hallucinations were initially conceived as pure perceptual disorders, they may equally derive from an altered relationship between the individual (i.e. self) and reality (i.e. world) (Bentall, 1990). A fundamental link between hallucinations and self-disorders can thus be observed in the ambivalence between self- and world-related contents; when the world/self boundary becomes blurred, the individual loses the possibility to understand whether the mental content originates from the world or from oneself (Lerner et al., 1985). For instance, hallucination proneness is related to

disturbances in sense of agency, i.e. the explicit distinction between self and other as the cause of behavior (Asai, 2016; Pienkos et al., 2019; van der Weiden et al., 2015) and self-focused attention (Perona-Garcelan et al., 2013). In schizophrenia, self-agency deficits have been related to 1) the ambiguity between self and other (Asai, 2016; de Bezenac et al., 2015) and 2) the tendency to attribute the agency of self-related processes to others rather than to oneself or vice-versa (van der Weiden et al., 2015). In parallel, the very concept of self-focused attention can be defined only through the relationship between self- and world-related contents, more precisely as *''an awareness of self-referent, internally generated information that stands in contrast with an awareness of externally generated information derived through sensory receptors''* (Ingram, 1990). An increase in world/self ambivalence, i.e. a reciprocal contamination of world- and self-related contents, may thus impair the fundamental ability to discriminate what is 'internally' and what is 'externally' generated. Further evidence suggesting the centrality of world/self ambivalence is seen in the spatial self-alterations observed in patients with schizophrenia who experience more flexible bodily boundaries between oneself and the world. Compared with controls, patients with schizophrenia demonstrate greater disturbances in body ownership and a more shallow 'peri-personal space', indicating a weakened sense of self (Noel et al., 2017; Thakkar et al., 2011). Conceiving the body as the physical barrier between oneself and the world, perceptual disturbances related to the world/self boundary may impact deeply upon ones' sense of self. In fact, abnormal bodily experiences such as cenesthopathies (Stanghellini et al., 2012) relate to an early 'splitting' or fragmentation of self-related processes in schizophrenia (Sass, 2001; Scharfetter, 2019). But what does constitute the world/self boundary, and how could fragilities in this boundary connect hallucinations and self-disorders?

To address this question, one can obtain fundamental insights by analysing transient psychotic experiences. Deep alterations of the world/self relationship are in fact reported in substance-

induced psychosis, with very similar (but not identical) features to the ones characterizing schizophrenia. In such a condition, the individual experiences both hallucinations and what has been defined as 'ego-dissolution'; a diminished or even absent sense of being distinct to the world (Letheby and Gerrans, 2017). Here, the world/self relationship is characterized by a fusion of the subjective '*I*' with the world by way of a weakened world/self boundary and increased ambivalence between world- and self-related activities. While remaining different nosological entities, both self-fragmentation and self-dissolution suggest a scarce differentiation between world and self (see first-person reports of ego-dissolution in *Table 1*). Accordingly, world-related (hallucinations) and self-related symptoms (ego-dissolution/fragmentation) are reported in both schizophrenia-related and substance-induced psychosis (Liechti et al., 2017). The interrelated nature of world- and self-related activities is further highlighted by accounts of psychotic experiences induced by sensory-deprivation. In these scenarios, self-disorders and hallucinations systematically arise from the mere absence of adequate sensory stimuli (Daniel et al., 2014). In the absence of sensory stimuli, self-experience becomes prominently altered, with the alterations positively correlating with the instability of the peri-personal space (Noel et al., 2018); similarly, simple and complex auditory/visual hallucinations start to be perceived after a relatively short amount of time (10-20 minutes). The outcome is therefore comparable to the one observed in schizophrenia-related and substance-induced psychotic states: a stimulus is perceived where there is none (Kometer et al., 2013). Symptoms relating to the concept of world/self ambivalence across schizophrenia-related, substance-induced, and sensory-deprivation psychoses are further compared in *Table 1*.

3. World or Self: what comes first?

We have seen how often world-related symptoms (such as hallucinations) and self-related symptoms (such as body ownership disturbances) tend to occur simultaneously during psychotic states, thus hindering our ability to clinically determine the causal role of one phenomenon over the other. Both domains are also related to deep alterations of the world/self relationship. The altered world/self relationship as a common substrate in psychotic experiences has been described by several theories such as aberrant salience, influence of experience, and passivity (Mishara et al., 2016), but this concept is usually addressed implicitly or derived as a secondary factor. Whilst several studies have focused on core self-disturbances as primary alterations (Beck et al., 2019; Parnas and Handest, 2003), other approaches addressed the importance of sensory areas involved in early sensory processing in the emergence of the psychotic symptoms (Doniger et al., 2001; Javitt, 2009). In fact, deficits in early-stage sensory processing are reported in visual, (Butler et al., 2001; Martínez et al., 2008), auditory (Lee et al., 2017) and somatosensory (Waberski et al., 2004) modalities in schizophrenia. In light of this evidence, the adoption of a more simplistic explanation in which the primary cause of psychosis stems from *either* spontaneous, core self processes or stimuli-oriented sensory pathways would be conflicting with the large body of research supporting both of these theories. Thus, strong efforts should be directed towards attempts to elucidate how these apparently disparate hypotheses may coexist.

4. World/self ambivalence

Here, we propose a conceptual representation of the world/self relationship as a two-way interaction, in contrast with the dualistic approach in which either the self- or world-oriented activity is regarded as having a causative role over the other in the genesis of psychotic experiences. We argue that the qualitative aspects of psychotic experiences may in fact be

explained by the presence of an excessive, reciprocal influence of world-oriented and self-oriented activity (i.e. world/self ambivalence), regardless of which activity is primarily altered. Neuroimaging findings offer a deeper understanding of the concept of ambivalence in the world/self relationship from a neurobiological perspective, which we will demonstrate to be in accordance with our clinical considerations.

5. Neurofunctional insights into the world/self relationship

Functional magnetic resonance imaging (fMRI) techniques facilitate the measurement of brain activity (as fluctuations in the blood oxygenation level dependent [BOLD] signals) in deep regions which are not normally explorable by other techniques. Recent advances in the neuroimaging field suggest that the world/self relationship is at the centre of subjective experience (Northoff, 2018a). The world/self relationship has been conceptualised as the interaction of world- and self-related dynamics (Huang et al., 2017; Northoff, 2018b; Northoff et al., 2010; Scalabrini et al., 2019), which are in turn generated by the interaction of the brain's spontaneous activity with either external or internal processes respectively (see **Fig. 1**). Well-established findings suggest the relationship between self- and world-related activity is finely regulated at several levels (Di Plinio et al., 2020; Raichle, 2015). On a network level, all regions show an intrinsic activity (resting-state or default activity) and are modulated by the influence of the extrinsic activity (Ebisch and Aleman, 2016). However, self- and world-oriented activities tend to show different topologies.

The metabolic activity within specific clusters of regions such as the Default Mode Network (DMN) is increased when the individual is at rest or meditating (Fox and Raichle, 2007; Jang et al., 2011; Raichle et al., 2001) and thus focuses on self-oriented processes. In addition, the sense of self has been related to several DMN regions, all of which share an increased activation at rest when the stimulus-independent activity is predominant, i.e., rest-self overlap (Northoff,

2016; Whitfield-Gabrieli et al., 2011). On the other hand, the activity in these areas is suppressed when the attention of the individual is focused on the interaction with external stimuli (Dixon et al., 2016). Conversely, the activity of sensory networks, such as the visual or auditory networks, is instead more task-related, i.e. activity increases during specific tasks, or under specific stimuli. Other networks serve as mediators between the DMN and sensory networks. Among them, the Salience Network (SN) is one of the most studied for its active role in regulating the attentive fluctuations from self- to world-related activity, thus calibrating the impact of the stimulus on the individual (Damiani et al., 2019; Menon and Uddin, 2010). Therefore, it is not surprising that the SN has been related to both self- and world-oriented activity in psychosis (Bonoldi et al., 2019; Craig, 2011; Yao et al., 2018), given its crucial role in altering the signal-to-noise ratio in favor of the conscious perception of noise (Looijestijn et al., 2015).

It is important though to remember that all brain networks show a persistent activity independently of the state of the individual; for instance, regions responsible for the processing of world-related activity will be functional even in the absence of external triggers. Thus, on a global level, subjective experience is determined by the constant, dynamic interplay between self- and world-related activities mutually influencing one-another. The balance between the DMN and sensory networks (mediated by the SN) will therefore influence the phenomenological level of self-other integration and distinction (Scalabrini et al., 2019), to the point of not always being able to delineate the two processes (van der Weiden et al., 2015).

Currently, measures of neural activity do not enable the direct quantification of the balance between world- and self- related activities. This is not surprising if we consider the complexity of the brain dynamics and the multiple mechanisms involved in producing the global subjective experience. Nevertheless, measures such as functional connectivity and level-of-activation (see

Section 6) may give useful, albeit indirect, information relevant to the phenomenological findings.

In an attempt to better understand the clinical meaning of neural dynamics, we will define 'external pressure' as the impact exerted by the stimulus-related activity on the global experience, and 'internal pressure' as the impact exerted by the self-related activity on the global experience (**Fig. 1**). We use the term 'pressure' to 1) underline the persistency, dynamicity and ubiquity of the intrinsic brain activity, and thus the impact that self-related networks may have during world-related activity and vice-versa; 2) avoid the temptation of assimilating the complex concept of subjective experience to a single neuronal measure such as level of activation or connectivity.

6.   Imaging in psychoses: how to measure the world/self imbalance?

In resting state fMRI, the BOLD signal measures the neural activity of brain regions in individuals who are not engaged in any particular task. Resting-state functional connectivity (rsFC) indicates the level of correlation between the activity of multiple brain regions, and thus the extent of the functional integration between these areas (Friston, 1994). In other words, rsFC does not measure neural activity within a single region, but rather indicates the flow of information between brain areas. rsFC is widely used to analyse the interaction between brain networks' activities. For example, a high rsFC between the DMN and SN indicates that the activities of these two networks are highly correlated. Here, we will show how the rsFC patterns observed in the networks previously described (DMN, SN, and sensory networks) can be dysregulated in different subsets of the psychosis spectrum.

6.1 Review methodology

Due to the heterogeneity of the experimental conditions, the presence of both clinical and fMRI studies, and the different terminologies used throughout the different studies investigating the

world/self relationship, it was not possible to structure the present paper as a systematic review. For this reason, in our narrative review we preferentially selected and discussed the findings supported by replications in one or more studies, choosing systematic reviews or meta-analyses where possible. For schizophrenia, fMRI findings related to acute psychotic states were considered separately from the ones obtained at more chronic phases. This is because these two groups of patients present stage-dependent alterations in the fMRI signal (Li et al., 2017). For substance-induced psychoses, it is important to note this effect was elicited in healthy individuals, enabling the consideration of brain dynamics not only in psychiatric patients but also in healthy controls. Recent reviews were preferred due to their greater inclusiveness. fMRI studies published in the last 5 years were preferred, due to the more reliable results they provide thanks to the recent methodological advances in signal analyses. As the aim was to investigate BOLD fluctuations on a network level, we preferentially reported studies specifically investigating dynamics concerning the whole network (visual, auditory, DMN, and SN) rather than findings concerning single regions, even if they pertained to one of the listed networks. Given the cross-disciplinary nature of this work, the expert neurobiologist will provide a simplification in the networks selected and in the rsFC reports. This choice was made with the intention of making the manuscript accessible to clinicians who may be interested in the fMRI topic. Similarly, the expert clinician may find limitations in how the symptoms are presented. Here, we focused on the similarities between psychotic experiences and their common underlying substrates. Nevertheless, the three conditions described present different expressions of the symptoms when they are considered on a finer level. For instance, auditory hallucinations are more prominent in schizophrenia-related psychosis, whereas intense, complex visual hallucinations and synesthesia are more dominant in substance-induced psychosis. In sensory-deprivation, the individual typically experiences visual hallucinations,

but their complexity tends to be proportional to the duration of time exposed to a stimuli-free environment (Blom, 2009).

6.2 fMRI findings

Findings concerning fMRI rsFC and its relation to symptom dimensions in schizophrenia, substance use and sensory deprivation are presented in *Table 2*.

6.2.1 Schizophrenia-related psychotic experiences

Among the few replicated findings in schizophrenia fMRI, it has been shown that DMN rsFC tends to be elevated in schizophrenia compared with controls, independent of the type of study conducted (Hu et al., 2017; Mwansisya et al., 2017). Although, whilst this is true when the whole DMN is considered as a single seed, the rsFC showed mixed patterns when the chosen seed was not the DMN but one of its subregions (Hu et al., 2017; Sheffield and Barch, 2016). A recent meta-analysis compared patients with first-episode psychosis and chronic but not necessarily active schizophrenia. The study found increased rsFC in the DMN and executive areas, which are self-related networks. Interestingly, the increase in these areas was especially evident in patients with a first episode of psychosis, whereas in the chronic stage the main rsFC alterations were located in thalamus and basal ganglia (Li et al., 2017). However, it is important to consider the potentially confounding factors, such as age and medication status, in the interpretation of these findings. The constant presence of altered activity in DMN regions such as the posterior cingulate suggests that schizophrenia-related psychosis is characterized by an increased rsFC or internal pressure. The increased rsFC patterns of the DMN in schizophrenia correspond with previous theories suggesting that the elevated self-related activity produces psychotic symptoms in schizophrenia (Northoff and Qin, 2011). Taken together, this evidence suggests that self-related activity may have a greater impact on global brain activity in schizophrenia-related psychosis. However, findings are less concordant for auditory and visual

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networks, with studies reporting normal, reduced or, in a minority of cases, increased rsFC (Alderson-Day et al., 2016; Alderson-Day et al., 2015; Li et al., 2015). Altogether, these findings show how the balance between world- and self-related networks tends to be tilted towards the latter, with an increase in internal pressure which often corresponds to a decrease in external pressure. However, to date, no study has measured whether the strength of such an imbalance is correlated with the strength of the psychotic symptoms. We argue that this could be a fascinating topic of research for future studies.

Another strong set of findings identifies a second dynamic characterized by alterations in the SN; Krishnadas et al, (2014) found that higher rsFC in both the SN and DMN was related to clinical symptoms, but the SN rsFC was the best discriminator between patients and controls. The observation of increased SN rsFC in schizophrenia, and its correlation with the intensity of positive symptoms, has been reproduced by several studies (Hare et al., 2019; Lee et al., 2018; Palaniyappan and Liddle, 2012). An alteration in the SN, the hub connecting self- and world-related attentional processes, may thus heavily influence the ability of the individual to effectively separate internal and external contents, leading to a semantic confusion between the processes originating from the individual and the surrounding environment. Neuronally, this phenomenon may be partially mirrored by the SN rsFC, which has been found to mediate rsFC between the DMN other networks (Wang et al., 2016).

6.2.2 Substance-induced psychotic experiences

Unlike the vast amount of literature available for schizophrenia-related psychosis, few fMRI studies have been conducted in individuals under the effect of hallucinogenic substances such as lysergic acid diethylamide (LSD), 3,4-Methylenedioxymethamphetamine (MDMA), ayahuasca or psilocybin. Interestingly, the rsFC patterns observed in these studies differ substantially from those of schizophrenia-related psychosis: in fact, one of the main findings presented within the literature is that world-related networks are more active and

overconnected (Carhart-Harris et al., 2015; Carhart-Harris et al., 2016; de Araujo et al., 2012; Preller et al., 2018). More importantly, the increased impact of the visual network was highly correlated with the presence of hallucinations (Carhart-Harris et al., 2016). In the case of ayahuasca, it has been hypothesized that visual hallucinations may be related not to DMN increased rsFC, as in schizophrenia, but to the visual cortex behaving *"'as if' there is external input when there is none"* (Kometer et al., 2013). One may rephrase this concept defining it as the presence of an increased world-related activity in the absence of stimuli. In parallel, self-related networks such as the DMN show decreased rsFC (Carhart-Harris et al., 2015; Carhart-Harris et al., 2016; Preller et al., 2018). Thus, in substance-induced psychotic experiences, we observe an increased external pressure, identifiable as increased sensory versus reduced DMN rsFC. This trend is in contrast to the one which is usually observed in schizophrenia.

But what about the self? The SN has a crucial role in maintaining the world/self boundary by regulating the integration of world- and self-related activities; further, three studies report reduced SN rsFC after either LSD (Preller et al., 2018) or psilocybin administration (Carhart-Harris et al., 2012; Lebedev et al., 2015). Both the DMN (Carhart-Harris et al., 2012) and SN (Lebedev et al., 2015) rsFC have been associated with ego-dissolution, hence suggesting the possibility of separate mechanisms contributing to a similar loss of the world/self boundaries, that is, world/self ambivalence.

6.2.3 Sensory-deprivation psychotic experiences

In contrast with the clear trigger identifiable for sensory-deprivation psychotic experiences, as no fMRI research feasibly allows a stimuli-free environment and no fMRI studies have been specifically conducted on sensory-deprived individuals, only indirect data are available regarding this condition. Nevertheless, intriguing inferences can be made through the observation of fMRI activity for healthy individuals with eyes-open (EO) vs eyes-closed (EC). According to Xu et al, (2014) *"there are two mental states at opposite extremes of one another,*

an 'exteroceptive' state characterized by attention and oculomotor system activity under the EO [eyes-open] state, and an 'interoceptive' state characterized by imagination and multisensory integration under the EC [eyes-closed] state". This statement only considers the visual system, neglecting the other sensory pathways. However, it conceptualizes the presence of two inversely correlated states, one being world-related (EO) and the other self-related (EC). One may intuitively predict a reduced external pressure in the latter group: this prediction is seemingly demonstrated in the form a reduced BOLD signal in the EC condition (Zou et al., 2015). Also, a reduced visual cortex rsFC was characteristic of the EC state (Agcaoglu et al., 2019). Generalizing the observations of Xu and colleagues to other sensory systems, it would be reasonable to expect similar, but more extreme patterns in the stimuli-free settings leading to the hallucinations and self-disturbances described in Section 2. However, in this case the internal pressure would be higher than the external one, and not because of an increased self-related activity as seen in schizophrenia. Rather, the determinant would be the reduced world-related activity. The world/self boundary would hence be tilted in favor of the self-related activity due to a dramatically reduced external pressure.

7. Discussion

7.1 Mechanisms preserving and undermining the world/self boundary

In the present paper, we have observed how psychotic symptoms may be related to a loss of the boundary between the objective world and the subjective self. Hallucinations, disturbances of self, and conceptual disorganization are in fact interdependent and related to a decreased ability to discriminate the mental contents as self-related or world-related, which we called increased world/self ambivalence. This clinical concept shows two main neurofunctional correlates. A first proposed mechanism identifies world/self ambivalence from the dominance of internal over external pressure or vice-versa; in the case of schizophrenia, the increased

internal pressure (DMN rsFC or self-related activity) may lead to the superimposition of internal mental contents over the external ones, even when the patient is undertaking active tasks and DMN activity should be consequently suppressed (**Fig. 2A**). Conversely, in substance-induced psychosis, an increased rsFC is registered in sensory regions such as the visual network, whereas the DMN shows reduced rsFC. Normally, the neural activity of sensory regions is reduced during resting state, thus minimally contributing to subjective experience. Their excessive impact on the global experience would instead generate specific hallucinations. For instance, the complex and abstract visual patterns experienced after LSD intake may be caused by the combined excess of external pressure and the insufficiency of internal pressure. The world-related activity will hence overwhelm the self-related activity (**Fig. 2B**).

Finally, the individual under sensory deprivation is exposed, by definition, to the complete absence of meaningful environmental, visual or auditory stimuli. The world-related activity would hence be irrelevant, thus subjective experience is mainly determined by the self-related activity of the brain. This may explain the very short time span needed for psychotic-like symptoms to manifest under these extreme conditions in almost all individuals (**Fig. 2C**). The common paradigm would hence be a shift in the world/self boundary, whether it is tilted towards world-related or stimuli-related activity.

A second proposed mechanism is the blurring of the world/self boundary. Dysregulated SN activity has been observed in both schizophrenia-related and substance-induced psychoses (**Fig. 2D**). As the SN mediates the attentive processes connecting world- and self-oriented activity, an increased or decreased SN-rsFC may thus alter the communication between self-related and sensory-related networks in the form of a non-mediated interaction between the two. This may ultimately lead to a blurring of the world/self boundary and, consequently, increased world/self ambivalence.

7.2 World/self ambivalence as a core domain in psychosis

Ultimately, despite different aetiologies, we propose that the three forms of psychotic experiences described here share an altered world/self relationship by way of an imbalance towards either internal or external pressure. In line with the clinical and neurobiological findings previously discussed, we hypothesise that this imbalance is of crucial importance in the genesis of psychoses, as it may generate ambivalence by disrupting the flow of information provided by the interaction of world- and self-related activities.

From a phenomenological perspective, self-continuity and self-unity are preserved in healthy individuals by the presence of a self-oriented activity which is stable, yet capable to efficiently interact with the heterogeneity of the external contents continuously presented to the individual. If on the one hand this allostatic equilibrium ensures an optimal state, on the other it could be disrupted by imbalances generated either in the world- or self-related networks. Lebedev et al, (2015) describe the phenomenological self as *"the experience of being 'me' as being coherent in mental acts and distinct from the outside world"*; an excessive contamination of world- and self-related contents (i.e. world/self ambivalence) may lead to the arrest of both the integrative and segregative functions, as self and non-self would no longer be perceived as distinct entities. Following the loss of the world/self boundary, the dysregulated interference of world- and self-related processes may trigger two parallel, interconnected phenomena. First, a sense of the world contaminating the self; second, a projection of the subjective instances on the objective ones. The former phenomenon finds its clinical expression in symptoms like passivity or the presence of intrusive thoughts and perceptions, whereas the latter is prominent in the case of hallucinations, where subjective mental contents acquire a perceptual valence and substitute the objective stimuli.

8 Conclusions

Our model of world/self ambivalence offers an explanation of the similar phenotypes observed in multiple conditions, characterized by psychotic experiences, using a single construct. As the disruption of the world/self boundaries originates either from a neural imbalance between internal and external pressure or from an unmediated world/self interaction, the world/self boundary itself can be considered a reflection of the dynamic but regulated interaction of self- and world-related activities. The world/self boundary and its absence, leading to ambivalence, may hence be considered as useful clinical constructs to describe the complex pictures observed in different, but related conditions. The proposed operational framework stems from the clinical and neurobiological findings collected, providing insights into the mechanisms regulating brain dynamics and consequently generating subjective experience. In addition, it helps to define the complex concepts of self- and world-related activities, with major implications for both research and clinical practice. Furthermore, considering the world/self relationship when interpreting the often cryptic fMRI findings may promote novel approaches focused on regulating the brain dynamics in the circuits described above. Clinically, an understanding of the qualitative aspects of the world/self ambivalence such as similarities and differences between conditions may help to refine the currently available procedures of assessment, consequently improving diagnostic accuracy and specificity. The integration of these theoretical insights with recently developed techniques such as co-activation patterns (Liu et al., 2018) and multimodal imaging microstates (Musso et al., 2010) may further help in unraveling the relationship between world- and self- related activities.

Lastly, considering the role of world/self ambivalence in psychosis may allow re-interpretation of key psychopathological stances in a fresh light. The 'loss of vital connection to the world' described by Minkowski in relation to schizophrenia (Sass, 2001) may be an active attempt to reduce the confusion generated by the unmediated exchange of information between world- and self- related contents. Likewise, the Bleulerian autism can be seen as a secondary

withdrawal, a defensive mechanism acted by the patient to defend his own self from the ambivalence given by its interaction with the world: *''The professionals call it apathy and lack of motivation. But they don't understand that giving up is a highly motivated and highly goal-directed behavior. For us giving up, refusing to hope, not trying, not caring; all these were ways to protect the last fragile traces of our spirit and our selfhood from undergoing another crushing''* (Deegan, 1994).

Table 1

Psychotic experience	First-person perspective	World/self alteration	Reference
Schizophrenia-related	*I am no longer myself (. . .) I feel strange, I am no longer in my body, it is someone else; I sense my body but it is far away, some other place. Here are my legs, my hands, I can also feel my head, but cannot find it again.*	Altered bodily boundaries → world/self ambivalence.	*(Parnas and Handest, 2003)*
	Am I here or there? Am I here or behind?		
	What should I do with a clock? I must look at it all the time. Am I myself not a clock? One is so engrossed in looking at the clock and loses the thread to oneself. Because I am myself a clock, everywhere in me, because it is always so confused.	Lack of differentiation between world and self → world/self ambivalence.	*(Boss, 1977)*
	I become everything I experience to a point where it ultimately resolves into a state of considering myself the universe. I can open myself completely.		*(Frosch, 1983)*
	I mean you get messed up over about interacting with others, seems like it swings both ways.		*(Lysaker et al., 2006)*
	...it was as if I was not "thinking the delusion," the delusion was "thinking me!" I was totally enslaved by the belief system.	Excessive impact of the internal predisposition → increased internal pressure?	*(Chadwick, 2007)*
	I hear my voice when I speak, but the voice seems to originate from some other place.	Self-originating functions attributed to the world → confused attribution of agency to self or world.	*(Parnas and Handest, 2003)*
Substance induced (mescaline)	*For a moment, I randomly pulled on my earlobe and scratched at it. Then, it seemed that my entire bodily feeling was only my earlobe, which being enormous, I held in my hand. The entire rest of my body had disappeared...*	Altered bodily boundaries → world/self ambivalence.	*(Mishara et al., 2016)*
	Only the object in front of me exists; I forget myself and everything else around me.	Excessive impact of the world-related over self-related activity → increased external pressure?	*(Mayer-Gross and Stein, 1926)*
	If I see a soupbowl in front of me, there exists only this soupbowl.		
	The colors are so forceful; all the objects seem newly painted.		
	Perception, thought, movements and volition are no longer experienced as my own, and with that, the feeling that thinking is not initiated by me, but someone else, a foreign agency.	Self-originating functions attributed to the world → confused attribution of agency to self or world.	
Sensory deprivation	*My hands are really floaty like [they're] not attached to my body...my hands feel really numb like they're floating...my head feels really heavy like my neck can't hold it up.*	Altered bodily boundaries → world/self ambivalence.	*(Lloyd et al., 2011)*
	I see shadows and shapes when there is nothing there.	Self substitutes the world in producing perceptions → reduced external pressure?	
	It feels as if I am sinking, I don't know why.	Self disruption in absence of stimuli → confused attribution of agency to self or world.	

Table 2

Psychotic experience	Reference	rsFC findings	Relation with symptoms	Experimental condition
Schizophrenia	*(Hu et al., 2017) (review)*	DMN↑ (10 studies)	PS, NS, CF, self-insight	Chronic and acute SCH (vs healthy)
	(Mwansisya et al., 2017) (review)	DMN-SN↑ (1 study)		First-episode SCH (vs healthy)
	(Alderson-Day et al., 2015) (review)	AUD↑ (1 study) AUD↓ (2 studies)	PS*	Chronic and acute SCH (vs healthy)
	(Karbasforoushan and Woodward, 2012) (review)	Within DMN↑ DMN↑ (3 studies) DMN↓ (2 studies)		Chronic SCH (vs healthy)
	(Palaniyappan and Liddle, 2012) (review)	SN↑↓		Chronic and acute SCH (vs healthy)
	(Huang et al., 2019)	SN↓ SN-DMN↑		First-episode SCH (vs healthy)
	(Rodriguez et al., 2019)	DMN↑↓ SN-DMN↓		First-episode SCH (vs healthy)
	(Li et al., 2015)	DMN↑ SN-DMN↑ SN-VIS↓ VIS↓ AUD↓		First-episode (vs chronic SCH)
	(Hare et al., 2019)	DMN-SN↑	PS, NS	Chronic SCH (vs healthy)
	(Lee et al., 2018)	SN↑ DMN= SN-VIS↑ SN-DMN↓		Chronic SCH (vs healthy)
	(Wang et al., 2016)	SN↓	Illness severity	Chronic SCH (vs healthy)
	(Krishnadas et al., 2014)	DMN↑ SN↑	NS PS	Paranoid SCH (vs healthy)
Substance-use	*(Carhart-Harris et al., 2016)*	Within DMN↓ DMN↓ VIS↑	Ego-dissolution Hallucinations	After LSD administration (vs before)
	(Preller et al., 2018)	DMN↓ VIS↑ AUD↑ SN↓		LSD (vs placebo, vs LSD+ketanserine administration)
	(de Araujo et al., 2012)	VIS↑		After ayahuasca administration (vs before)
	(Palhano-Fontes et al., 2015)	DMN↓		After ayahuasca administration (vs before)
	(Tagliazucchi et al., 2014)	VIS↑ AUD↑ DMN, SN (density)↑	Ego-dissolution	LSD (vs placebo administration)

	(Carhart-Harris et al., 2015)	DMN↓ VIS↑		MDMA (vs placebo administration)
	(Carhart-Harris et al., 2012)	SN↓ (activity) Within DMN↓		Psilocybin (vs placebo administration)
	(Lebedev et al., 2015)	SN↓	Ego-dissolution	Psilocybin (vs placebo administration)
Sensory-deprivation	*(Xu et al., 2014)*	VIS↓ Exteroceptive↓ Interoceptive↑		Eyes closed (vs eyes open)
	(Zou et al., 2015)	VIS↓ (cerebral blood flow)		Eyes closed (vs eyes open)
	(Agcaoglu et al., 2019)	VIS↓ AUD↑		Eyes closed (vs eyes open)

NOTE: when the name of a network is used alone it denotes the rsFC (resting state Functional Connectivity) of that particular network with areas other than DMN (Default Mode), SN (Salience), VIS (Visual), and AUD (Auditory) networks; between-network rsFC is denoted by joining the names of the respective networks with a hyphen. *Anticorrelation. SCH: patients with schizophrenia. LSD: Lysergic Acid Diethylamide; MDMA = 3,4-Methylenedioxymethamphetamine. PS: Positive Symptoms; NS: Negative Symptoms; CF: Cognitive Functioning.

Tables captions

Table 1: World/self relationship alterations as described in first-person perspectives.

Table 2: Summary of cited studies on resting-state functional connectivity in schizophrenia, substance use and sensory-deprivation (eyes closed).

Figures captions

Fig.1 *1) Spontaneous activity. 2) Self-related activity. 3) World-related activity. 4) Global subjective experience* produced by self-related and world-related activity, their interaction being mediated by salience processing. The graphical representation puts world-related networks on the external layers as they are the first step when processing incoming external stimuli. 5) *Psychotic experiences:* Alterations of the world/self boundary due to different mechanisms might lead to an insufficient differentiation of self-related and world-related activity and, thus, ambivalence. Networks elaborated from (Power et al., 2014). DMN=default mode network, AUD=auditory network, VIS=visual network, SN=salience network.

Fig.2 A-B-C) the imbalance between internal and external pressure may account for the similarities found in different subsets of psychotic experiences such as confusion of world/self boundaries and ambivalence of the mental contents. A) Increased internal pressure → DMN overwhelms sensory networks. B) Increased external pressure → sensory networks overwhelm DMN. C) Reduced external pressure →DMN overwhelms sensory networks. D) An altered filter of the information flow leads to a loss of the directionality in self- and world-related activities, and thus to ambivalence of the world/self boundaries. The inability to selectively attribute the correct attentional valence to stimuli and self has been found in both schizophrenia and substance induced psychosis.

Glossary

Spontaneous activity: generated intrinsically by each single neuron. It is a permanent, ubiquitous and fundamental feature of the brain (Tsodyks et al., 1999).

Self-related activty: generated by the integration of spontaneous activity and the events within the individual such as his own mental processes and interoceptive functions (heartbeat, respiration, proprioception, etc). This is what is usually observed *in vivo* when the individual is not involved in specific tasks, that is, at rest. Initial attempts have been made to assess the dynamics characterizing self-continuity and self-coherence according to the self-related activity's structure (Schneider et al., 2008; Wolff et al., 2019).

World-related activity: generated by the integration of spontaneous activity and external stimuli. Neural activity in sensory areas increases when the individual interacts with external stimuli.

World/self relationship: Interaction between self-related and world-related activities. On a phenomenological level, the integration/segregation of these complex dynamics contributes to generate the global subjective experience of the individual.

World/self boundary: the distinction between the individual and his own sorroundings. We hypothesize that an altered world/self boundary may be 1) shifted, due to an imbalance between external and internal pressure or 2) blurred, due to an unmediated interaction between world-related and self-related activities.

World/self ambivalence: a reciprocal contamination of world-related and self-related contents which may alter the ability of the individual to differentiate them. The degree of world/self ambivalence is proportional to the shifting/blurring of the world/self boundary.

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