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Dissociation as a disorder of integration – On the footsteps of Pierre Janet

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ABSTRACT

At the end of the 19th century Pierre Janet described dissociation as an altered state of consciousness manifested in disrupted integration of psychological functions. Clinically, such disruption comprises compartmentalization symptoms like amnesia, detachment symptoms like depersonalization/derealization, and structural dissociation of personality with changes in the sense of self. The exact neuronal mechanisms leading to these different symptoms remain unclear. We here suggest to put Janet's original account of dissociation as disrupted integration of psychological functions into a novel context, that is, a neuronal context as related to current brain imaging. This requires a combined theoretical and empirical approach on data supporting such neuronal reframing of Janet. For that, we here review (i) past and (ii) recent psychological and neuronal views on dissociation together with neuroscientific theories of integration, which (iii) are supported and complemented by preliminary fMRI data. We propose three neuronal mechanisms of dynamic integration operating at different levels of the brain's spontaneous activity - temporo-spatial binding on the regional level, temporo-spatial synchronization on the network level, and temporo-spatial globalization on the global level. These neuronal mechanisms, in turn, may be related to different symptomatic manifestation of dissociation operating at different levels, e.g., compartmentalization, detachment, and structural, which, as we suggest, can all be traced to disrupted integration of neuronal and psychological functions as originally envisioned by Janet.

> Unable to integrate the traumatic memories, they seem to have lost their capacity to assimilate new experiences as well. It is … as if their personality which definitively stopped at a certain point cannot enlarge any more by the addition of new elements.” (Pierre Janet, 1911, p. 532).

1. Introduction

Dissociation has early been described at the end of the 19th century by Pierre Janet. He highlighted the abnormalities in the subjects' coordination and integration of their different psychological functions whose contents are operated in a more compartmentalized, disrupted, or dissociated way, e.g., “out of consciousness” (see below for details). The central role of disrupted coordination and integration of psychological functions and their contents also resurfaces in more recent characterizations of dissociative disorders (Lanius et al., 2005; Liotti, 2004; Farina and Liotti, 2013; Van der Hart et al., 2006; Reinders et al., 2019). Dissociation is nowadays considered as a disruption and/or discontinuity of ordinarily integrated functions in processing of mental contents as in consciousness, perception, memory and identity (DSM-5; APA, 2013).

Dissociation is manifested in several stress-related psychiatric dysfunctions such as post-traumatic stress disorders, dissociative disorders and borderline personality disorders (Lyssenko et al., 2018; Scalabrini

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et al., 2017a; Scalabrini et al., 2018; Lanius et al., 2010; Schimmenti and Caretti, 2016; Mucci, 2018; Farina et al., 2019). However, the nature and mechanism of dissociation remains unclear.

Dissociative manifestations are characterized by (a) *compartmentalization symptoms* that are experienced as unbidden intrusions into awareness and behaviour, with accompanying losses of continuity in subjective experience (i.e., amnesia, flashbacks, sudden emotional and behavioral dysregulations); and/or (b) *detachment symptoms* characterized by a sense of separation from certain aspects of everyday like the body (out-of-body experiences), the sense of self (depersonalization), or the external world (derealization; Holmes et al., 2005).

Other investigators suggest additional symptoms that concern the whole personality. Specifically, Janet spoke of abnormal mental integration of the different contents resulting in a lack of integration among two or more "*systems of ideas and functions that constitute personality*" (Janet, 1907). This is well in accordance with more recent studies that also point out abnormal integration as a structural pathology of personality (theory of structural dissociation of the personality – TSDP, Van der Hart et al., 2006). Accordingly, Liotti's model of dissociation (Liotti, 1992), derived by disorganization of attachment, is characterized by mutually incompatible and incoherent internal working models that cause a fragmented and compartmentalized organization of self-consciousness encompassing the whole personality. Similarly, the *parallel-distinct structures model* by Şar (2017) postulates the predominant role of disturbed mutuality between internal world and external reality in trauma-related dissociation. One can thus speak of structural symptoms in dissociation that complement compartmentalization and detachment symptoms.

Neuronally, a variety of different regions and most notably the insula, a crucial hub involved in intero-exteroceptive integration (Craig, 2003; Critchley et al., 2004), have been found to be abnormal in dissociative-based disorders (Van der Kolk, 2015; Nicholson et al., 2016; Hopper et al., 2007). What remains unclear is how the intero-exteroceptive integration on the neuronal level relates to the disrupted integration on the psychological level as so well described by Janet.

We here aim to contribute in filling that gap between the current views of dissociation, that is, the gap between abnormal intero-exteroceptive integration on the neuronal level on the one hand and disrupted integration on the psychological level on the other.

Neuronally, we will propose that dissociation may be related to a failure in the integrative mechanisms at three different levels of neuronal activity, e.g., regional, network, and global. In addition, the psychological level may mirror the disruption of integration on the neuronal side: consequently leading to compartmentalization, detachment, and structural symptoms. The attempt to link Janet's original psychological description of dissociation as disorder of integration to specific neuronal mechanisms requires a combined theoretical, i.e., reframing, and empirical, i.e., data presentation, approach.

Our paper will hence include a narrative review of (i) past and (ii) present psychological and neuronal views on dissociation, as well as (iii) preliminary empirical, i.e., neuronal data from brain imaging intending to provide support to our proposal and interpretation of literature findings.

2. Theoretical review - dissociation as disorder of integration on psychological and neuronal levels

2.1. Historical background – Pierre Janet: dissociation as disorder of integration

The very first author who used the concept of dissociation per se was Moreau de Tours in France (Moreau, 1845) in experimental studies on the effect of hashish. He used the term dissociation or disintegration (*désagrégation*) to describe the splitting off or isolation of ideas, which if had been aggregated or integrated would have formed a whole harmonious system. Thus, the term dissociation has been primarily used to describe a system whose ideas and contents are not integrated and no longer exhibit internal continuity and coherence. However, it is only with Pierre Janet (1859–1947) that dissociation was systematically studied and was considered a crucial and basic psychological process leading to experiences that may be expressed as sensory perceptions, affect states, and behavioral re-enactments.

Janet's view on dissociative phenomena was mainly influenced by the neurologist Hughlings Jackson (1835–1911) and his model considering dissociation as a loss of integration between hierarchical levels. The Jackson's work is prevalently based on the hypothesis that the mind, rooted in the body's natural world, consists of a hierarchical organization of several functions reflecting the evolutionary development of the specie, which integrates increasingly complex, mutually coordinated levels. The mind produces the consciousness, expressed as the integration of lower and higher levels, through works and functions such as Janet's personal synthesis, i.e., the ability to interpret in a unified and consistent way, the parts of one's own body and the memories of the self (Meares, 2012).

Janet in his major work, *L'automatisme psicologique* (Janet, 1973) introduces the three foundations of his theory: 1) sensory perception and mental integration, 2) dissociative reactions as failures of integration processing, and 3) their relations with consciousness. Intriguingly, Janet operationalized consciousness as a product of a larger regulating system comprising and integrating outer exteroceptive environmentally oriented movements and inner interoceptive (or proprioceptive) regulating systems.

When this internal-external regulating system is unbalanced or disrupted by, for instance, overwhelming emotional experiences (usually traumatic), the result is a subconscious psychological automatism: the contents remain un-integrated in the field of consciousness such that the individual lacks proper attention, judgement and agency to navigate and interact with the environment. Janet therefore speaks of a "*disaggregation of the psyche*". Following Janet, dissociation is based on the disruption of internal-external stimulus integration, which, in turn, leads to uncoordinated psychological functions and the various dissociative symptoms (Fig. 1).

2.2. Present view: dissociation as disrupted integration on the psychological level

Pierre Janet's characterization of dissociation as a disorder of integration strongly surfaces in our current view of dissociation (see Mucci et al., 2019; Farina et al., 2019; Frewen and Lanius, 2006; Reinders et al., 2003, 2006,; Schlumpf et al., 2013). Several scholars have hypothesized that dissociative responses to trauma are similar to the freezing response observed in animals: in situation that cannot be controlled (or that were not able to be controlled in the past and are perceived as still present by the individuals), the threatening organism may be engaged in a kind of passive defense mode, accompanied by a shut down of the arousal system and an increased parasympathetic activity (Gershuny and Thayer, 1999; Schauer and Elbert, 2015; Hagenaars et al., 2014; Liotti, 1992; Cantor, 2005; Schore, 2009). Therefore, according to Farina et al. (2019), dissociative non-integrative processes lead affective dysregulation together with the fragmentation of mental and behavioral activities, as well as of the sense of self and autobiographical memory (Carlson et al., 2009; Liotti, 2009; Schore, 2009; Teicher et al., 2010; Braun and Bock, 2011; Meares, 2012).

Like Janet, present descriptions clearly point out that dissociation concerns isolated contents, e.g., information, that are not connected, linked, integrated with other contents. Dissociation may thus be characterized by an abnormal high degree of non-integrated information that does not become conscious. Even worse, the integration of these contents into the ongoing consciousness seems to be blocked in dissociation with such blockade being apparently related to the severity of the traumatic experience as marked by non-integrated contents. The

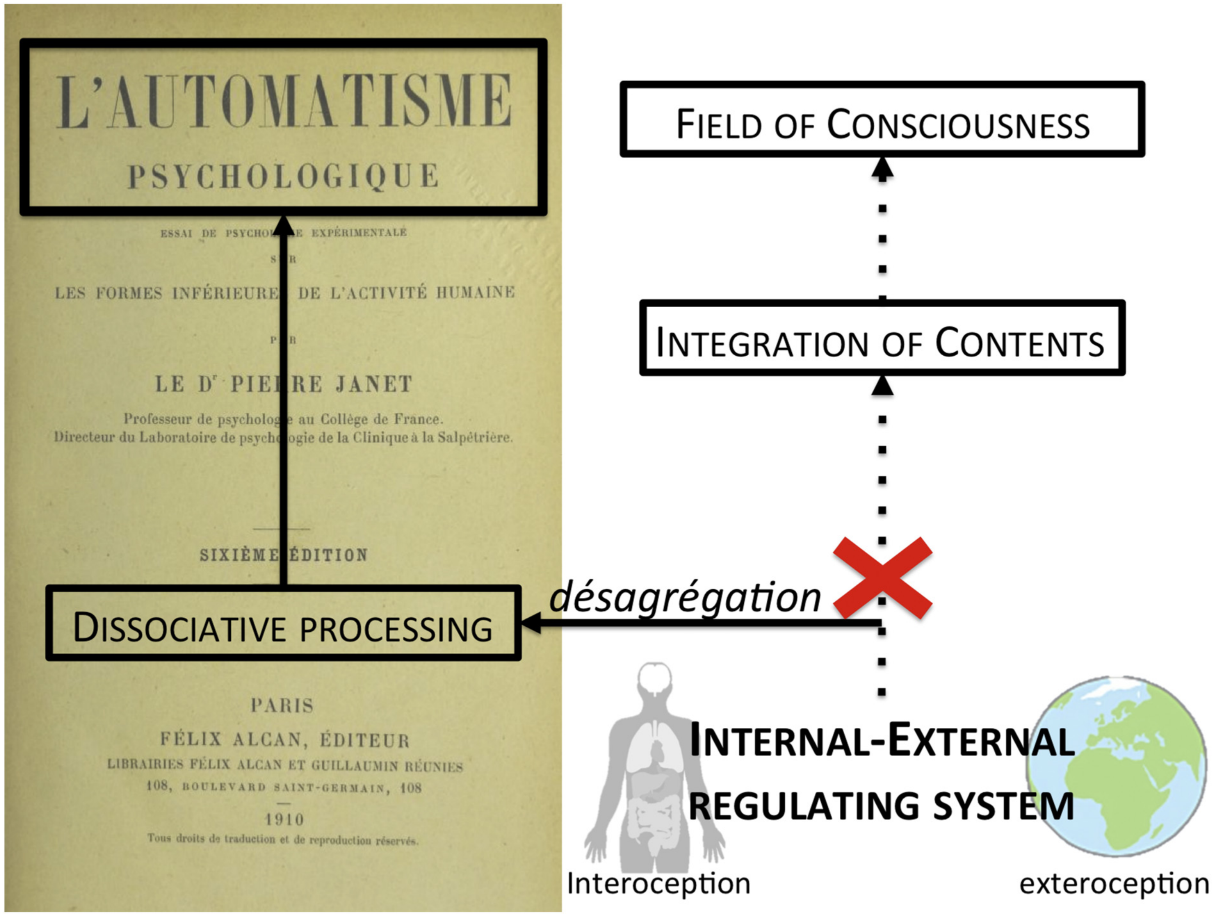

Fig. 1. Pierre Janet's theory of dissociation as a mechanism of un-integration (or *"Désagrégation"*) of contents in the field of consciousness. This process leads to unconscious psychological automatisms.

parts or elements themselves are still present but remain un-integrated. Accordingly, on a psychological level, dissociation can be characterized as a disorder of integrated contents while, at the same time, un-integrated contents still remains present.

Disruption in integration interferes with a coherent encoding of salient events (Petersen and Posner, 2012; Conway and Pleydell-Pearce, 2000). That, in turn, leads to an un-integrated perception where different aspects of the event (such as sensory, affective and cognitive) are encoded separately rather than being connected and integrated. In this regard Farina et al. (2014) found a disruption in functional connectivity between networks in dissociative patients when compared with healthy controls after the recall of traumatic attachment memories. The lack of connection and integration of sensory, affective, and cognitive aspects of events can distort one's perception including its various aspects, e.g., time (e.g., acting or feeling as if a traumatic event that is experienced in the past is still present), body (e.g., depersonalization and out of body experiences), thought (e.g., voice hearing in second-person perspective), and emotional numbing (Frewen and Lanius, 2014; Frewen and Lanius, 2006). Therefore, in line with the original view of Jackson and Janet, we might hypothesize that dissociation could be considered as an integrative failure at different levels (Van de Hart, 2006; Farina et al., 2019).

This view is well in line with the clinical observations made for dissociative symptoms. In fact, compartmentalization symptoms like intrusions can be featured by the perception of isolated, un-integrated sensory stimuli as if the respective event is still present in time (Van der Kolk, 2015; Van der Kolk et al., 1996; Foa and Riggs, 1995). Similarly, in the case of detachment symptoms, one may assume that the traumatic events and their contents simply "*fall through the cracks of consciousness*" in a rather literal way as they are no longer integrated with others, i.e., non-traumatic ones, for which reason they cannot be perceived anymore, e.g., they are no longer associated with consciousness at all. This is paradigmatically reflected in the loss of awareness with a continuum of different forms of des- or un-integrated contents starting from absorptions and mild gaps in awareness (Butler, 2006) to more pathological manifestations such as depersonalization and derealization (Putnam, 1995). This, as we will postulate later, may be related to *"cracks in the temporo-spatial structure of the brain's spontaneous activity"*.

2.3. Neuronal level of dissociation

The neurobiological process of dissociation can be related to the lack of integration among psychobiological systems (see for instance Putnam, 1997, in his theory of dissociation of discrete behavioral states). Indeed, recent studies proposed dissociation as a psychobiological mechanism (Frewen and Lanius, 2006; Siegel, 1999; Putnam, 1997), related to functional dissociation among brain structures. In a recent article, Krause-Utz et al. (2014) provided a systematic review of recent neuroimaging studies about disorders characterized by dissociation, like depersonalization disorder, dissociative identity disorder, post-traumatic stress disorder and borderline personality disorder. Their findings on the neurobiological underpinnings of dissociation emphasized the role of altered co-activity in brain regions involved in: i) emotion processing and memory (e.g. amygdala, hippocampus, parahippocampal gyrus and middle/superior temporal gyrus); ii) interoception regulation (insula); iii) self-referential processes and iv) emotional/cognitive regulation (PACC, PCC, mPFC; see the review for more details). In this context, intriguingly, Lanius et al. (2010) showed that PTSD individuals with dissociation might be characterized by an excessive corticolimbic inhibition (i.e. emotional over-modulation) in response to exposure to traumatic memories (the opposite pattern was found in individuals with PTSD without dissociation). Dimensionally, it has been shown (Hopper et al., 2007) how dissociative response to trauma reminders negatively correlated with right anterior insula activation and positively with medial prefrontal cortex and anterior cingulate cortex. Another fMRI study comparing aversive versus neutral images (Phillips et al., 2001) showed how chronic depersonalization disorder patients reported less arousal and showed diminished activity in the occipito-temporal cortex, anterior cingulate cortex (ACC), and insula compared to obsessive compulsive disorders and healthy controls. Lemche et al. (2014) showed that altered anterior insula (AI) and dorsal ACC reactivity to sad emotional expressions were associated with the difficulty to identify and describe one's own feelings.

These findings seems to be coherent, in case of dissociative processing, with the disengagement and un-integration of internal-external stimuli through the abnormal AI activity, a key hub for intero-exteroceptive processing and a crossroads through the processing of feelings and the sense of self-continuity, that constitutes the basis for the subjective evaluation of one's internal-external condition, that is "how you feel" (Craig and Craig, 2009; Craig, 2010; Craig, 2011) and moreover, is related to the regulation of sympathetic and parasympathetic systems. Interestingly, the insula's involvement in interoceptive, self-referential and emotional processing relies not only on its task activation but also on its wider functional connectivity to other networks (Couto et al., 2013). Indeed, the insula seems to be a shared region in most of the investigations previously reported and, moreover, has been demonstrated lately that insula resting state functional connectivity is able to distinguish PTSD and its dissociative subtypes from healthy participants with high predictive accuracy through a machine learning approach (Harricharan et al., 2020).

2.4. From the neuronal to the psychological level – disrupted integration as "common currency" in temporo-spatial dynamics of brain and mind

As proposed by Mudrik et al. (2014) integration might be seen as a ubiquitous phenomenon that comprises several types of characterization (e.g. spatio-temporal, multisensory, semantic, cognitive). In order to understand how we can link and trace the disrupted integration on the psychological level to the brain and abnormal integration on the neuronal level, we first have to briefly determine integration in a most basic and general sense (e.g., independent of either psychological or neuronal levels). Here we consider integration as the combination of different features, or objects into one unified whole or unity. The different features or parts that are integrated can concern different psychological functions, e.g., affective, sensory, and cognitive, including their respective contents. From a neuronal perspective we account for a temporo-spatial integration where the different elements refer to the different regions' and networks' neuronal signals and how they are connected with each other. The spatial component refers to the relationships between different brain regions that is constituted and measured by so-called 'functional connectivity' (FC), shaping various neural networks in the brain's resting state (Menon, 2011, for a review). The temporal component refers to the neuronal synchronization that allows integrating neuronal activity from different brain regions (and their respective psychological functions and contents) over longer stretches of time and distant regions/networks. Together, this constitutes a complex elaborated temporo-spatial structure and dynamics in the brain's spontaneous activity (Northoff, 2014a and 2014b, Northoff et al., 2019).

To better elucidate the intrinsic connection between the neuronal synchronization and the concept of integration we might consider the example of the visual binding problem, that is, how different properties of an "object" might result in a unified global representation. One of the proposed solutions is based on the idea that visual objects are coded by a firing synchronization of cell assemblies (Roskies, 1999). Following this hypothesis, this refers to the 'local' integration of neuronal properties, that is the synchronization with neighbouring cortical regions (deputed to the same function), to the 'long distance' integration, that is the synchronization with long distant cortical regions (deputed to different functions) and 'global' integration, that is the synchronization at the global level of the brain activity, which is necessary for the vision of the object within a more complex context of a global conscious experience. Departing from this example, one may want to distinguish between different neuronal levels of synchronization in fMRI, as on (i) local or intra-regional level; (ii) network or inter-regional level; and (iii) global level of the whole brain. Integration in this case means that neuronal activities at different discrete points in time and space are related and processed in dependence of each other; we now assume that neuronal synchronization and integration are central in constituting the spontaneous activity's temporo-spatial structure of the brain. Thus, these different levels of integration will serve as roadmap for our investigation of altered integration in dissociation.

Even more important, based on recent data, we propose that neuronal synchronization is integrated on regional, network, and global levels of the brain's neural activity which, in turn, leads to disruption of integration on the psychological level resulting in compartmentalization, detachment, and structural symptoms of dissociation. Hence, we propose that integration or better "disruption of integration" provides a link or bridge and thus a "common currency" (see Northoff et al., 2019; as well as Northoff and Huang, 2017) of neuronal and psychological levels in dissociation, where symptoms are related with the intrinsic tempo-spatial organization of spontaneous brain's activity. This temporo-spatial approach to the brain provides the dynamic framework to further investigate different functions related to the dissociation phenomena, which are the sensory, cognitive and affective features. Conceived in a historical perspective, our proposal of disrupted integration providing a "common currency" extends Janet's proposal from the psychological to the neuronal level (Fig. 2).

3. Resting state fMRI empirical data

3.1. Aim

Following our recently developed temporo-spatial approach to brain, consciousness, and psychopathology (Northoff, 2013, Northoff, 2014a; Northoff and Duncan, 2016, Northoff and Huang, 2017; Northoff, 2018), we here assume distinct mechanisms of temporo-spatial integration to operate on different levels of the brain's spontaneous activity including (i) temporo-spatial binding on the regional level; (ii) temporo-spatial synchronization on the network level; and (iii) temporo-spatial globalization on the global level of the whole brain. For that purpose we analysed our preliminary rs-fMRI data and according to our hypotheses we tested for their association with dissociative proneness scores. Thus, our findings will be compared and combined with review findings for a broader discussion.

3.2. Methods

Our sample was constituted by 32 right-handed male participants (age 21–33; mean = 25.4; standard deviation = 2.82). They are the same as those included in previous studies (for more detail see Scalabrini et al., 2017b; Scalabrini et al., 2019). All participants had normal or corrected-to-normal vision capabilities. None of the participants reported a history of neurological or psychiatric disease, or substance abuse. All subjects completed the resting state fMRI acquisition and fulfilled the PID-5 (Personality inventory for DSM-5, Krueger et al., 2012; for more details on the psychometric properties of the Italian version see Fossati et al., 2013). In order to assess dissociative

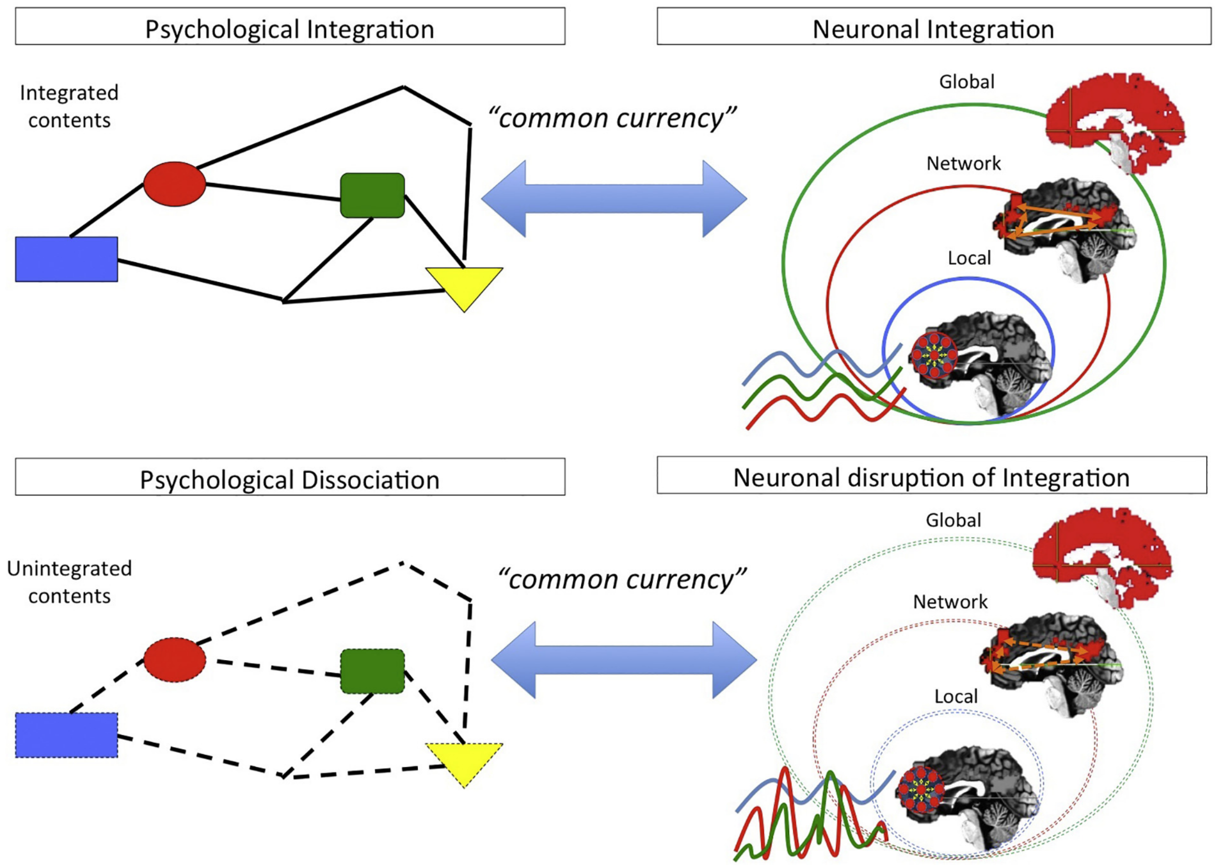

Fig. 2. The figure shows our hypothesis: the degree of synchronization of the time-series within and between different regions of the brain (from local to global) can be used as a proxy to test the level of integration of neuronal and, subsequently mental features.

proneness, we relied on the PID-5 facet "*perceptual and cognitive dysregulation"* that is considered the most representative one to account for dissociative tendencies or dissociative proneness (Ashton and Lee, 2012; Ashton et al., 2012). Specifically, following the DSM-5 (2013), "perceptual and cognitive dysregulation" includes: *Odd or unusual thought processes and experiences, including depersonalization, derealization, and dissociative experiences; mixed sleep-wake state experiences; thought-control experiences* (2013, p. 781).

Written informed consent was obtained from all participants after full explanation of the study procedure, in line with the Declaration of Helsinki. The Ethics Committee for Biomedical Research of the provinces of Chieti and Pescara approved the experimental protocol. (For more detailed sample and scanner characteristic see Table 1; for more detailed methods see *Supplementary materials*).

3.3. Resting state fMRI analysis

Regional homogeneity (ReHo). Following our hypothesis of the relation between dissociative proneness and abnormalities in resting state local FC, we calculated the whole brain Regional homogeneity (ReHo). ReHo analysis was performed for each subject by AFNI program: 3dReHo. As spatial smoothing could artificially enhance ReHo intensity and reduce its reliability (Zuo et al., 2013), we calculated ReHo based on unsmoothed BOLD time series. Specifically, for each voxel, Kendall's coefficient of concordance (KCC) was calculated between the BOLD time series for the voxel and those of its nearest neighbour voxels (Zang et al., 2004; Zuo et al., 2013), focusing on the range of 0.01–0.01 Hz. This gave a voxel-wise ReHo map. Spatial smoothing was then performed with a 8-mm full-width at half-maximum (FWHM) Gaussian kernel. All individual ReHo map were computed and standardized into ReHo *Z*-values by subtracting the mean voxel-wise ReHo obtained for the entire brain (i.e., global ReHo), and then dividing by the standard deviation. This subject-wise ReHo normalization has been shown to improve both normality and reliability across subjects (Zuo et al., 2010, 2013).

Functional Connectivity. We performed a seed-based functional connectivity (FC) analysis for the resting-state, using as seed the networks that may be relevant for symptoms of dissociation, for instance: in our hypothesis sensorymotor network may be related to out of body experiences, depersonalization and derealization, auditory network may

Table 1
Sample and scanner characteristics

Subj (n)	Mean age (SD)	Sex (M)	fMRI acquisition	Psychological measure
32	25,4 (± 2.82)	All	2 session resting state eyes open (fixation cross)	Dissociative proneness measured with PID-5 – "*perceptual and cognitive dysregulation*".
Scanner/Software	Anatomical resolution	Scan duration	TR – TE – Flip angle	Resolution
Philips Achieva scanner - 3 T	1 mm × 1 mm × 1 mm	6 min	2000 ms – 35 ms – 90°	2.875 mm × 2.875 mm × 2.875 mm

Note: PID-5 = Personality inventory for DSM-5.

be related to voice hearing in a second-person perspective, dorsal attention and salience network may be connected to problems related to attention, encoding of salient events and symptoms like absorption and daydreaming, while fronto parietal task control and limbic network can be related to cognitive and emotional dysregulation (see also Lanius et al., 2005; Tursich et al., 2015 for similar hypothesis).

These networks were taken from a well-established node template from previous studies (Power et al., 2011; Cole et al., 2014) containing 264 putative functional areas (10 mm diameter spheres, 30 voxels per sphere) across the whole brain. A voxel-wise FC map for each seed was computed as a map of temporal correlation coefficients between BOLD time course in each brain voxel and BOLD time course averaged across voxels in the network of interest. The correlation coefficients were then transformed into z-values by means of the Fisher r-to-z transformation, to improve normality for group-level analysis (Power et al., 2012). This procedure produced spatial maps in which the values of voxels represented the strength of the correlation with the networks.

Global signal correlation (GScorr). The GS was calculated by averaging time courses across all voxels in the gray matter after the band-pass filter (0.01–0.1 Hz). A voxel-wise GScorr map was computed as a map of temporal correlation coefficients between BOLD time course in each brain voxel and the GS-BOLD time course (Zhang et al., 2018b). The correlation coefficients were then transformed into z-values by means of the Fisher r-to-z transformation, to improve normality for group-level analysis (Power et al., 2012). This procedure produced spatial maps in which the values of voxels represented the strength of the correlation with the global activity of the brain.

Degree centrality (DC). In graph theory, a complex system is modelled as a "graph", which is defined as a set of "nodes" linked by "edges". For a binary graph, degree of centrality (DC) is the number of edges connecting to a node. For a weighted graph, DC is defined as the sum of weights from edges connecting to a node, which is also sometimes referred to as the node strength (Zuo et al., 2012). In our voxel-wise analysis, each voxel was considered as a node, obtaining a binary and a weighted value for each voxel. The DC analysis was performed for each subject by AFNI program 3dDegreeCentrality. For an overview of resting state measures characteristics see Table 2.

3.4. Relationship between different levels of resting state analyses and dissociative proneness

To establish if there was an association in functional areas of the brain and dissociation we therefore tested, at a group level, for the co-variance between the individual dissociative proneness values and the different individual maps obtained from the different resting state analyses, i. e. ReHo, functional connectivity, GScorr, and DC. All results were corrected using 3dClustSim in AFNI. Setting a threshold of $p < .001$ and a cluster size > 20 voxels, to obtain a corrected significance level of $\alpha < 0.05$.

3.5. Results

3.5.1. Relationship between ReHo and dissociative proneness

In order to assess the association between local connectivity and dissociative tendencies we conducted a whole brain voxel-wise correlation analysis. Testing the co-variance between the individual dissociative proneness values and the whole brain ReHo map we observed a significant and negative co-variance of dissociative proneness in right anterior insula (AI), in left postcentral gyrus and in right inferior frontal gyrus ($t = 3.646$ $p = .001$, $\alpha < 0.05$; see Table S1 in Supplementary material for more information).

3.5.2. Relationship between networks-FC and dissociative proneness

In order to assess the association between networks FC and dissociative tendencies, we analysed the rs-FC in various networks and we tested for their relationship with the rest of the brain by the co-variance

Table 2
Resting state measures and their temporo-spatial mechanisms.

rs-fMRI	Neuronal level	Dynamic integration level	Phenomenological level	Symptoms level
ReHo	Regional/Local	Temporo-spatial binding	Loss of contents and "objectual unity	Comparmentalization symptoms of dissociation
FC	Inter-regional/Network	Temporo-spatial synchronization	Loss of first person perspective and disaggregation of functions	Detachment symptoms of dissociation
GScorr and DC	Global	Temporo-spatial globalization	Discontinuity and narrowing of the field of consciousness	Structural dissociation of personality

Note: rs-fMRI = resting state fMRI; ReHo = Regional Homogeneity; FC = Functional Connectivity; GScorr = Global Signal correlation; DC = Degree Centrality.

with dissociation scores. Fixing the threshold at $t = 3.646$ ($p = .001$, $\alpha < 0.05$), we found a significant negative relationship of the various networks with the right AI as modulated by dissociative proneness (entered as co-variate). Specifically, i) for the auditory network we found a significant relation with dissociative scores in right AI; right medial frontal gyrus, right cingulate gyrus and right inferior parietal lobule; ii) for the visual network we found a significant relation with dissociative scores in right AI, right cuneus, left cuneus; iii) for subcortical network we found a significant relation with dissociative scores in right insula, left cingulate gyrus, left insula, righ precuneus; iv) for fronto-parietal task control we found a significan relation with dissociative scores in right AI; v) for cerebellum we found a significant relation with dissociative scores in right AI; vi) for dorsal attention network we found a significant relation with dissociative scores in right AI, right precentral gyrus, right inrior-parietal lobule; vii) for cingulo-opercular task control network we found a significant relation with dissociative scores in right AI, right precuneusm right inferiori parietal lobule; viii) for salience network we found a significant relation with dissociative scores in right AI, right middle occipital gyrus and left declive; ix) for somatomotor network we found a significant relation with dissociative scores in right AI; right inferior parietal lobule, left cingulate gyrus, left superior temporal gyrus (See Table S1 in Supplementary material for more details).

3.5.3. Relationship between GScorr / DC and dissociative proneness

In order to assess the association between global connectivity and dissociative tendencies we conducted a whole brain voxel-wise correlation analysis. Our GScorr results show that, by including the dissociative proneness scale as a covariate, we obtained abnormal distribution of GS in the right AI ($t = 3.646$ $p = .001$, $\alpha < 0.05$). This finding of is further supported by degree centrality (DC, Zuo et al., 2012; Hudetz and Mashour, 2016). As GScorr, DC showed a negative relation in right AI when co-varying with the individual dissociative proneness values ($t = 3.646$ $p = .001$, $\alpha < 0.05$; See Table S1 in Supplementary material for more information).

4. Discussion of review and empirical findings

4.1. Temporo-spatial binding and Regional homogeneity (ReHo) – loss of "objectual unity" in psychological contents leading to compartmentalization symptoms

The first level of dynamic temporo-spatial integration occurs on the level of the regions themselves where different stimuli are bound together. We therefore speak of "temporo-spatial binding", which is meant in a purely neuronal way as the binding of distinct stimuli within and by the local region's neural activity (Northoff and Huang, 2017; Northoff, 2018). The concept of binding is also used often on the psychological level where it describes the linkage, e.g., binding between different stimuli into one content by means of which the latter is supposed to become conscious (Crick and Koch, 2003; Revonsuo, 2006). This has been called the "binding hypothesis" (Crick and Koch, 2003). For instance, stimuli are supposed to be bound together by 40 Hz (i.e., gamma band) oscillations in the visual cortex that allow the stimuli to be synchronized, amounting to "binding by synchronization" (Mudrik et al., 2014; Zmigrod and Hommel, 2011).

Binding by synchronization already occurs in single regions' spontaneous activity: the different continuous intero-exteroceptive and neural inputs are temporally and spatially linked and thus bound together resulting in the contents of consciousness. Such "binding by synchronization" can be measured in fMRI on the neuronal and intra-regional level by what is described as "Regional Homogeneity" (ReHo, Zang et al., 2004; Zuo et al., 2013). ReHo is defined as functional connectivity at a local or intra-regional spatial scale where it measures functional interactions or synchronizations between the neighbouring voxels or vertices. Operationally, ReHo is characterized by two important features: i) the definition of neighbouring as determined by spatial adjacency, and ii) the functional homogeneity of the time-series from these neighbouring voxels.

Taken together, ReHo reflects local or intra-regional synchronization between different voxels on the neuronal level. A single voxel contains several millions of neurons (Logothetis, 2008). Given that different population of neurons in a region process distinct stimuli (Ruben et al., 2001), ReHo, describing neuronal synchronization, can serve as temporo-spatial mechanism to allow for the binding of different stimuli into contents. For that reason, the temporo-spatial synchronization of neuronal activity on the intra-regional level may lead to binding between different stimuli or contents on the psychological level, e.g., "binding by synchronization".

Given that un-integration in the context of dissociation can be described by the loss of contents, e.g., compartmentalization symptoms, we now assume that such temporo-spatial binding is disrupted on the neuronal intra-regional level, as measured by ReHo. Our results on ReHo and the association with dissociative proneness scores might support this hypothesis: individual characterized by higher levels of dissociative proneness showed decreased local connectivity in right anterior insula (AI), in left postcentral gyrus and in right inferior frontal gyrus (Fig. 3).

These findings raise the following question: how can binding by synchronization on the intra-regional level yield the integration of contents? We suppose that the contents are constituted or generated on the basis of the binding between different stimuli in temporo-spatial terms, that is, by connecting their different points in time and space by temporal synchronization. By binding together different stimuli in terms of their different points in time and space, a temporo-spatial unity of the different stimuli is constituted. Such temporo-spatial unity provides the dynamic basis for the unity of different objects or stimuli on the psychological level, the objectual unity (as philosophers would call it, e.g., Bayne and Chalmers, 2003). Our findings now suggest that such temporo-spatial unity and consequently objectual unity and its underlying temporo-spatial binding seem to be disrupted in dissociation. Decreased ReHo in insula indexes decreased binding by synchronization of interoceptive stimuli from the body and exteroceptive stimuli from the environment. Intero-exteroceptive binding is thus disrupted in dissociation such that the respective contents, as featured by their "temporo-spatial and objectual unity", are lost leading to the compartmentalization symptoms in dissociation. Such loss of contents and their "objectual unity" might, for instance, be manifested in the perception of single non-integrated exteroceptive or interoceptive stimuli in terms of strongly isolated sensations or impressions (deriving from overwhelming traumatic experiences) of either the external world or the own body in dissociative states (Van der Kolk, 2015; Mucci, 2018; Schore, 2011; Lanius et al., 2010).

4.2. Temporo-spatial synchronization and inter-regional functional connectivity – "Désagrégation" of affective, cognitive, and sensorimotor functions resulting in detachment symptoms

Temporo-spatial integration also occurs between different regions on a network level. This can be measured by functional connectivity that is based on the correlation of the time series of different brain regions. If different brain regions share similar patterns of variance in activity over time, they can be identified as belonging to a network (Hacker et al., 2013; Smith et al., 2009). Since the correlation between the time series entails synchronization between the different regions' neuronal activity (see Weaver et al., 2016; Huang et al., 2017), one can characterize rs-FC as temporo-spatial synchronization. Recent studies on rs-FC demonstrated how individuals diagnosed as PTSD with dissociation (vs. PTSD without dissociation) are characterized by rs-FC changes in different regions and networks. These include mainly rs-FC from prefrontal cortex to amygdala (Lanius et al., 2010) as well as rsFC of the insula with various cortical and subcortical regions (Nicholson

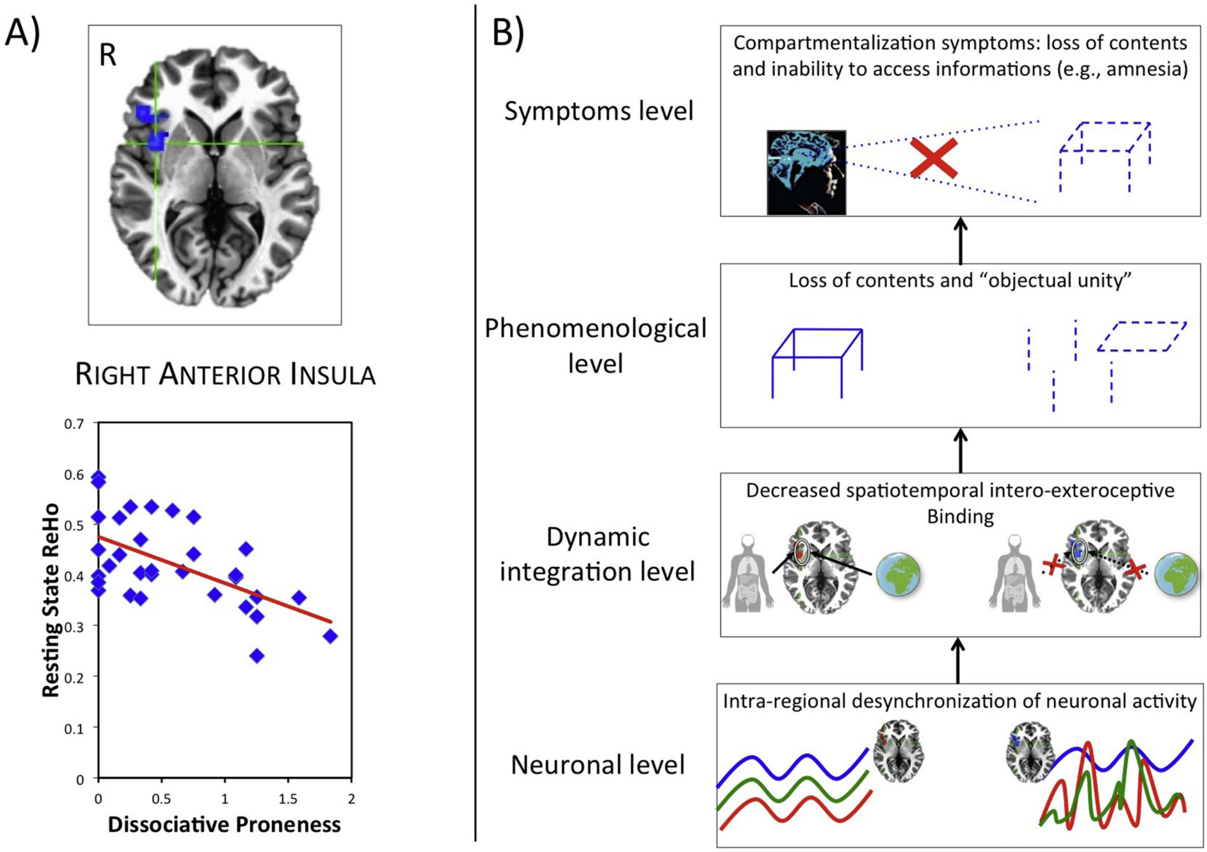

Fig. 3. A) Group statistical map of a whole brain voxelwise resting state region of homogeneity (ReHo) covarying with dissociative proneness scores ($t = 3.646$ $p = 0.001$, $\alpha < 0.05$). B) Schematic illustration of different levels of binding, e.g. neuronal, information, phenomenological, symptoms.

et al., 2015; Tursich et al., 2015).

Following the different results, we analysed the rs-FC in various different networks and tested for their relationship with the rest of the brain by the co-variance with dissociation scores. Intriguingly, we found a significantly negative relationship of the various networks, in particular with the right anterior insula as modulated by dissociative proneness. The networks being related to insula in dependence on the level of dissociation included the auditory, the visual, the subcortical, the fronto-parietal task control (FPTC), cerebellum, the cingulo-opercular task control (COTC) and the salience network (See Table S1 in Supplementary materias for more details) (Fig. 4).

Based on our neuronal findings, we assume that more the networks are desynchronized from the insula, the higher the degree of dissociation. We assume that the reduced temporo-spatial synchronization in neuronal activity prevents the integration of the different functions including sensorimotor, perceptual, cognitive, and affective ones. The different functions are thus no longer synchronized, e.g., they remain non-integrated, with specifically the insula and its intero-exteroceptive function: affect is not coordinated and thus integrated anymore with cognition and perception, and so on. This amounts to what Pierre Janet originally described as "*désagrégation*" which now can be specified as temporo-spatial desynchronization between different psychological functions including their des-integration from the more basic intero-exteroceptive integration on the level of body and world.

A specific instance of non-integration at the network level may consist in the integration between somatic information from the own body on the one hand and cognitive, affective, and sensory information on the other. The group around Tallon-Baudry demonstrated body-brain coupling by temporal synchronization of interoceptive stimuli from heart and stomach with the brain's spontaneous activity in specifically the insula and other regions like anterior midline regions and visual cortex (Park and Tallon-Baudry, 2014; Park et al., 2014). These findings show that the brain and the temporal structure of its neural activity align themselves to the ongoing temporal structure of the body and its ongoing visceral activity in stomach and heart (Northoff and Huang, 2017; Northoff, 2018). Following Tallon-Baudry and colleagues (Tallon-Baudry et al., 2018), such "temporo-spatial alignment" (Northoff, 2018; Northoff and Huang, 2017) of the brain to the body, e.g., neuro-visceral monitoring as they say, is central for constituting the first-person perspective. Our first-person perspective is thus not based in the brain itself but rather in how its neural activity is aligned to and thus synchronized with the body, and ultimately the environment or world (Northoff, 2018).

Our findings show that dissociation is related to temporo-spatial desynchronization between insula, as mediating the body's interoceptive stimuli, and the various cortical networks involved in different psychological functions, e.g., cognition, emotion, perception, etc. These and other findings highlight the central role of the insula in dissociation and PTSD (Lanius et al., 2010; Tursich et al., 2015; Nicholson et al., 2015; Lemche et al., 2014). Importantly, the central role of the insula strongly suggests that the temporo-spatial synchronization between body and brain is disturbed in dissociation. Such temporo-spatial desynchronization of the body-brain connection should disrupt the first-person perspective (Tallon-Baudry et al., 2018): instead of being perceived in relation to the own person (in a first-perspectival mode), the contents would remain detached from the self and its bodily-based first-person perspective: the contents will then be perceived as such but in such way that they remain unrelated to the person and its bodily-based first-person perspective - the contents will consequently be perceived as foreign, e.g., as non-self-related, thus reflecting what, on the symptomatic level, is described as detachment symptoms.

The "*désagrégation*" of contents from the first-person perspective and

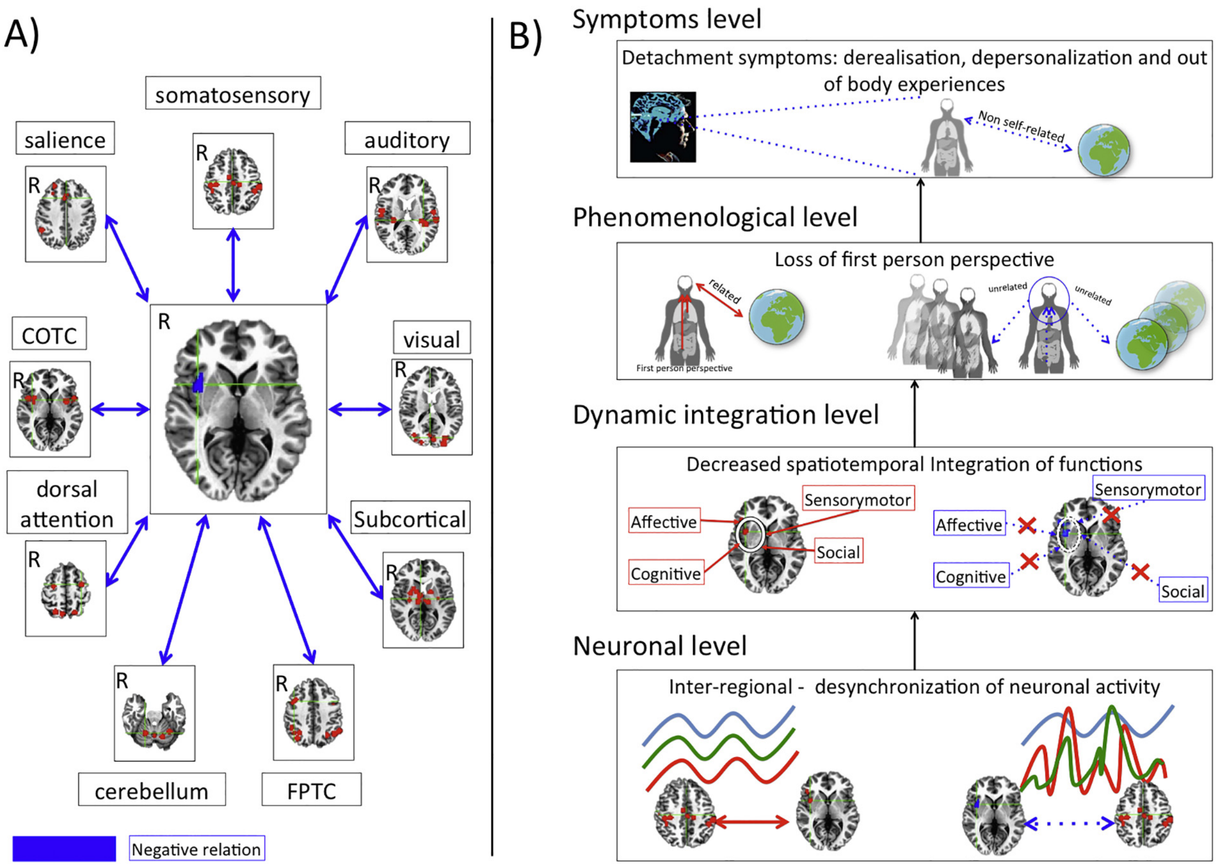

Fig. 4. A) Group statistical map of a whole brain voxelwise network resting state functional connectivity (FC) covarying with dissociative proneness scores for the different networks ($t = 3.646$, $p = 0.001$, $\alpha < 0.05$). B) Schematic illustration of different levels of synchronization e.g. neuronal, information, phenomenological, symptoms.

their subsequent manifestation as detachment symptoms can occur on both cognitive and somatic levels. On the cognitive level, this process is manifested in derealization, depersonalization. Analogous symptoms can be observed on the somatic level of the body. This may result in somatization with various body's symptoms like unspecific pain, hyperreactivity to external stimuli, and abnormal heartbeat awareness (Van der Kolk, 2015; Nijenhuis, 2001; Brown et al., 2007). On a more general level, such body-brain disruption reflects what Pierre Janet described as "*désagrégation*" between body and mind, which can also be referred to the loss of first-person perspective.

4.3. Temporo-spatial globalization – Dissociation between level/state and contents of consciousness and the structural dissociation of personality

Dissociation does not only affect specific psychological contents or the coordination of psychological functions. It goes beyond that by affecting the whole personality, that is, its structure leading to structural symptoms. One would consequently assume that, analogously, the whole brain and its global brain activity and thus what could be described as "temporo-spatial globalization" (Northoff and Huang, 2017) is also altered in dissociation.

Global activity of the brain and thus temporo-spatial globalization can be measured in fMRI using the global signal correlation (GScorr, Yang et al., 2014). The global signal, as obtained in fMRI, refers to the average of the time courses in the resting state activity of all voxels and thus measures the global distribution of neuronal activity across all regions in the brain (Yang et al., 2014; Turchi et al., 2018). Despite controversy that GS may, in part, reflect unwarranted noise in the fMRI signal (Power et al., 2017a; Power et al., 2017b), recent studies in animals and modelling demonstrated the physiological basis of global signal in resting state (Liu et al., 2013; Murphy and Fox, 2017; Turchi et al., 2018; Pisauro et al., 2016; Ponce-Alvarez et al., 2015). Finally, GScorr has been shown to be abnormal in psychiatric disorders like schizophrenia (Yang et al., 2014; Yang et al., 2016) and bipolar disorder (Zhang et al., 2018a) (Fig. 5).

We took GScorr as proxy of the brain's information integration on a global level, e.g., temporo-spatial globalization of neuronal activity. Our GScorr results show that, by including the dissociative proneness scale as a covariate in our GScorr map, we again obtained abnormal distribution of GS in the right AI. Our analysis on DC also showed a negative relation in right AI when co-varying with the individual dissociative proneness scores (See Table S1 in Supplementary materials for more information).

Taken in a more general way, our results suggest that the right anterior insula and ultimately intero-exteroceptive binding are not properly connected to the brain's global activity. Global activity and local intero-exteroceptive binding are thus decoupled from each other. Our results might carry major implications for the personality and its structure in dissociation. The contents may be "lost" for the personality which can no longer be linked to the more concrete and specific levels of both intero-exterocpetive binding with "objectual unity" and inter-regional coordination of different psychological functions. The field of the personality or, the field of consciousness as Janet says, becomes discontinuous, narrowed, and fragmented which, as we propose, might result in global temporo-spatial fragmentation of self and personality. Symptomatically, such temporo-spatial fragmentation of self and personality might amount to what has been described as the structural dissociation of the personality in dissociation (Nijenhuis and Den Boer, 2009; Van der Hart et al., 2006; Reinders et al., 2003; Schlumpf et al., 2013).

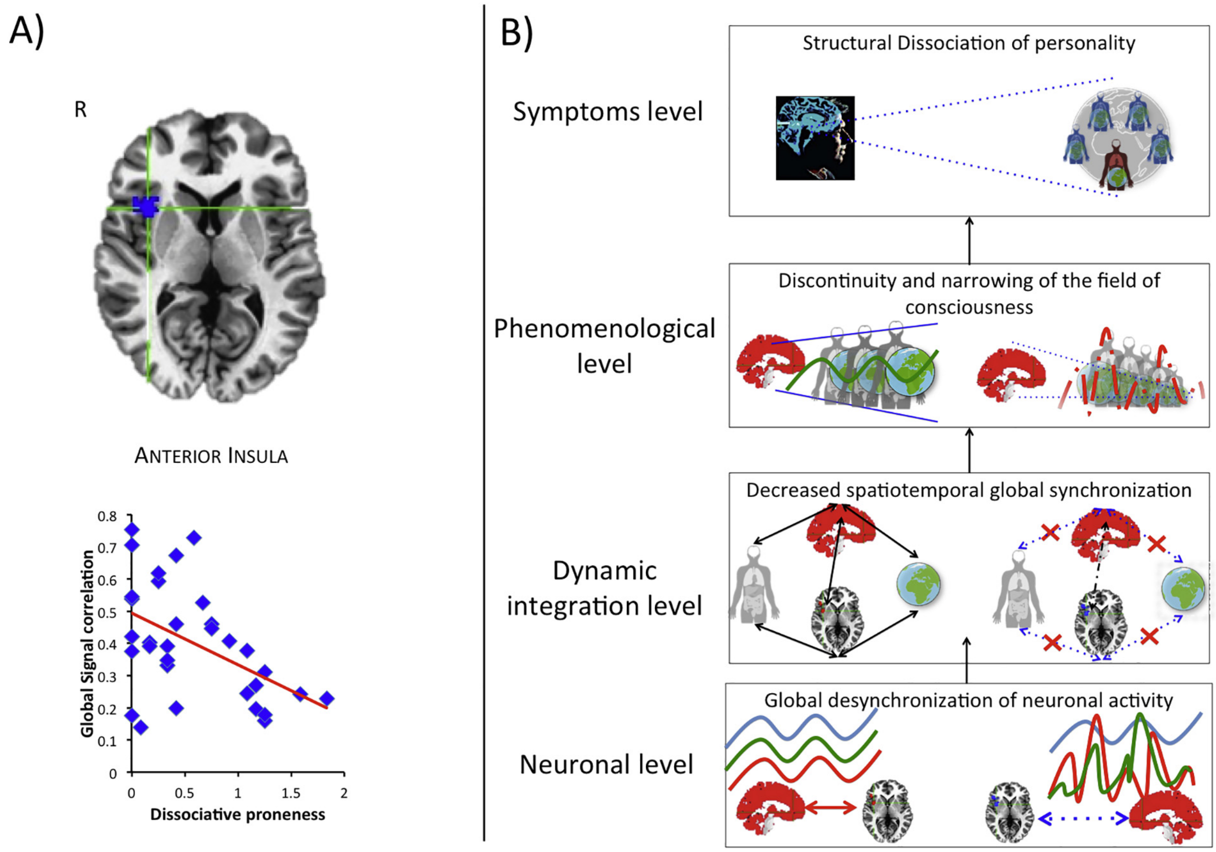

Fig. 5. A) Group statistical map of a whole brain voxelwise resting global signal correlation (GScorr) covarying with dissociative proneness scores ($t = 3.646$, $p = 0.001$, $\alpha < 0.05$). B) Schematic illustration of different levels of globalization, e.g. neuronal, information, phenomenological, symptoms.

5. Limitations

Some limitations of our investigation need to be mentioned. It can be argued that the empirical section of the paper is represented by a small sample that was not constituted by clinical participants; indeed further research needs to expand this investigation on larger and clinical samples characterized by dissociative-based disorders. However, our data lend support to the construct of dissociation as a continuum between healthy and pathological manifestations. Moreover our investigation aimed to support the actualization of the mechanism of dissociation, as originally described by Janet, while our analysis, together with the review of the psychological and neuroscientific literature, are intended to give a framework to our hypothesis based on the temporo-spatial features of the spontaneous brain activity. Hence, the empirical data do not provide substitute for a full-fledged study by itself but are included as a possible proof for a clinical informed manifestation of the mechanism of dissociation and its underlying neuronal processing. Future research needs to confirm the reliability and reproducibility of these preliminary findings and, moreover, need to test our perspective and interpretations investigating task-evoked neuronal activity and their relationship with the spontaneous activity of the brain.

6. Conclusion

Following and extending the original description by Pierre Janet, we here propose that dissociation is a disorder of integration on both psychological and neuronal levels. Several lines of evidence form the literature including our data lend support to the assumption that intero-exteroceptive integration function, in dynamic and temporo-spatial terms, is disrupted on all three levels of the brain's neuronal activity, i.e., regional, network, and global, in dissociation. We assume that temporo-spatial binding of different stimuli/contents on the regional level, temporo-spatial synchronization of different functions on the network level, and temporo-spatial globalization of linking contents to level/state of consciousness on the global level are disrupted in dissociation. Importantly, we here posit that the three temporo-spatial mechanisms on the neuronal level might be associated to the different symptoms, i.e., compartmentalization, detachment, and structural, in dissociation. Hence, extending Pierre Janet original concept of dissociation as a disorder of integration, we conceive disruption in temporo-spatial integration as "common currency" (Northoff et al., 2019) of neuronal and psychological levels in dissociation.

Author's contribution

AS and GN designed the combined theoretical-perspective review, and interpreted the data. AS, RE and SD analysed the data. AS, GN and CM, wrote the manuscript that was critically revised by RE and SD. All authors approved the final version of the manuscript.

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Declaration of Competing Interest

The authors declare no competing financial interests.

Appendix A. Supplmentary data

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Further Reading

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