

Neurobiological Correlates of Core Symptoms in Anorexia: Abnormal Spatiotemporal Structure in the Resting-State Activity and Troubles of the Self

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The debate about the psychopathological nature of body dysmorphia and delusion-like thought in anorexia nervosa is still open. The intensity and the stability of the misperception of body shape and of the thought distortions related to weight gains which are present in many subjects affected with anorexia nervosa supports a parallelism between these symptoms and the psychotic symptoms which are expressed in subjects affected with schizophrenia or other major psychosis. Generally the body dysmorphism in anorectic subjects is considered a clearly distinct entity with respect to delusions in schizophrenic subjects even though it can reach delusional characteristics (Delsedime et al., 2011; Seeman, 2014) [1]. Nevertheless, recent studies on the phenomenological aspects of anorexia evidenced a certain overlap of the body dysmorphism in anorectic subjects with the delusional symptoms in psychosis (Mountjoy et al., 2014) [2]. These new evidences give room to a new conceptualization of dysmorphic symptoms in anorexia nervosa. Some authors argue that in the most severely disturbed anorectic subjects a possible deficit in the structure of the Self may be strictly related to a perception of the body with delusional characteristics (Delsedime et al., 2013) [3]. It is thus possible that a common basis for the expression of the psychotic-like symptoms in anorexia nervosa and the psychotic symptoms in the major psychosis may reside in deficits related to the structure of the Self.

At this regard it is expected that the in-depth exploration of brain functioning by means of the newest imaging techniques may shed a light in the shared and unshared circuits which are involved in the psychopathological processes in eating and psychotic disorders.

Recently Northoff (2015) [4] proposed a general theory of the neurobiology of schizophrenia based on alterations in the spatiotemporal structure of resting-state activity. Recent studies on the functional resting-state alterations in schizophrenia suggest a fragmentation in the "stream of consciousness" in schizophrenic subjects, i.e. a disruption of the continuity of the Self (Doering et al., 2012) [5]. This supports the abovementioned conceptualization of the schizophrenia as a disorder of the Self (Sass and Parnas, 2003; Schneider, 1959; Northoff & Bermpohl, 2004, Northoff, 2015) [6-8, 4]. At the moment no study evidenced

a strong correlation between the symptoms of the anorexia nervosa and those of the schizophrenia, and there is no sufficient imaging material concerning anorexia nervosa to compare directly the resting-state activity of the two disorders. On the other hand an indirect support to this line of interpretation derives from the recent findings obtained exploring electrophysiological brain activity in anorectic and depressed subjects which do not support the hypothesis of a strict relationship between symptoms of anorexia nervosa and mood disorders, and instead suggest that the delusion-like symptoms of anorexia nervosa may represent a monosymptomatic psychosis (Jàuregui-Lobera, 2012) [9]. This opens the possibility of a more strict link with other psychopathological models.

The neurobiologic model accounting for a deficit of the Self functioning in the subjects affected with schizophrenia represents, at least partially, a possible template for a parallel neurobiologic interpretation of the deficit of integration of the Self in subjects with anorexia nervosa.

A recent meta-analysis of resting-state studies in schizophrenia has observed an hypoactivity in various anterior and posterior midline regions of the DMN which are supposed to be strictly related to the integration of the inputs related to the Self including the PACC, the ventromedial prefrontal cortex (VMPFC), the precuneus, the posterior cingulate cortex (PCC), and the hippocampus (Kuhn & Gallinat, 2013) [10]. Also in the subjects affected with anorexia nervosa the anterior and posterior midline regions are also altered, both morphologically and functionally (Amianto et al., 2013a; Joos et al., 2010) [11, 12]. As an adjunct,

in both the schizophrenia and the anorexia nervosa these regions evidence a reduced activity (Amianto et al., 2013a; Joos et al., 2010), while directly comparing the resting-state activity between schizophrenia and major depressive disorder (MDD) the PACC and VMPFC showed reduced resting-state activity in schizophrenia and increased in MDD (Kuhn & Gallinat, 2013) [10].

Another clear alteration in the resting-state functional connectivity in schizophrenic subjects is represented by the decreased cross-network connectivity, with widespread reduction in the degree of small worldness, number of hubs, and modularity (Karbasforoushan & Woodward, 2012) [13]. Functional connectivity of the resting-state within the midline regions and the DMN tends to increase, instead lateral prefrontal cortical and sensorimotor functional connectivity is rather decreased in schizophrenia (Whitfield-Gabrieli et al., 2009; Karbasforoushan & Woodward, 2012; Yu et al., 2012) [13-15]. These findings supporting the alteration of the resting-state's spatial structure in schizophrenia coupled with the evidences of abnormal activity balances between different regions, abnormal functional connectivity within and between networks, and abnormal frequency fluctuations in midline regions lend support to the assumption that schizophrenia is a "dysconnectivity syndrome" that affects the whole brain including its various regions and networks (Stephan, Friston & Frith, 2009) [16].

The current findings on resting-state in anorexia nervosa are not so extensive as those on schizophrenia, nevertheless some signs of dysconnectivity have been evidenced. In particular, intrinsic connectivity within the cerebellar network of anorectic subjects shows some peculiar alterations compared to healthy subjects. They have been evidenced a greater connectivity with insulae, vermis, and paravermis and a lesser connectivity with parietal lobe (Amianto et al., 2013b) [17]. Even though these evidences do not overlap those of schizophrenia, they may support the hypothesis of a "cerebellar disconnection" syndrome possibly related to integrative deficits in Self functions.

As concerns the processing of the external and the internal stimuli the research in healthy subjects associated the anticorrelation between DMN and executive network, in particular between PACC/VMPFC and DLPFC, with the balance between internal (i.e. Self-related) and external (i.e. environment-related) mental contents (Vanhaudenhuyse et al., 2011; Wiebking et al., 2014) [18, 19].

According to this interpretation, the stronger is the resting-state/DMN activity and functional connectivity in medial regions, the more the focus of mental activity will be on internal mental contents e.g. those which are related to the Self, like thoughts on own self and the body (Vanhaudenhuyse, et al. 2011) [18]. Symmetrically, the stronger is the resting-state activity and functional connectivity in the lateral regions/CEN the more

it increases the activity concerning external mental contents originated in the interaction with environment, like perceptions. It thus happens that when internal mental contents are highly represented the ones on external are reduced and vice versa (Vanhaudenhuyse, et al. 2011) [18]. The balance between internal and external mental contents is thus mediated by the anticorrelation or orthogonality between midline regions/DMN and lateral regions/CEN.

Up to now no study systematically explored a deficit of orthogonality between DMN and CEN in anorexia nervosa. Nevertheless the review of Jàuregui-Lobera (2012) [9] underlines that AN subjects present neural disturbances in response to stimuli that are relevant to the disorder like food exposure, different emotional situations, or body images. This nearly supports a selective blurring of the boundary between self- and external stimuli pertinent to body image and body functioning in these subjects. In addition, a recent study confirmed a higher amount of attentional biases related to the external food related stimuli in anorectic subjects (Novosel et al., 2014) [20], suggesting a focal deficit in internal and external stimuli distinction. Moreover the study of Lee and coworkers (2013) [21] explored the resting-state synchrony between anterior cingulate cortex and precuneus and found that it is increased in AN subjects. The authors relate this kind of over activity to the rumination on eating, a mechanism which may be an attempt to overbalance the deficit of Self-coherence in these subjects as a response to an alteration in the integration of perceptual stimuli (Favaro et al., 2011; Harvey et al., 2013) [22, 23].

At the present moment the brain imaging evidences linking the psychotic-like symptoms of anorexia nervosa, namely the body misperception and the irrational fear of weight gain, to the abnormal resting-state activity in schizophrenia are still poor. Nevertheless the hypothesis that also the core symptoms of anorexia nervosa may be related to a "dysconnectivity syndrome" and to an unbalance between the processing of external and internal stimuli which is consequent to the alteration of the resting-state is suggestive and supported by some initial literature evidences. The possibility that these resting-state alterations may be clinically and phenomenologically perceived as disorders of the integration of the Self it is also suggestive. In particular it supports old (Bruch, 1982) [24] and new theories (Skarderud, 2010) [25] on the pathogenesis of anorexia nervosa and may thus be helpful in directing psychotherapy interventions and the possibility to gather new proofs of their efficacy. Much research should be spent exploring neuroimaging of anorectic subjects to go deep through this line of thought, but it might not be so far off the time when the intricate neurobiological network of symptoms in these subjects can be exposed to the neurobiological level with possible unexpected progress in the therapeutic approach to these disorders.

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