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Commentary

Insular Dysfunction in People at Risk for Psychotic Disorders

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Abstract: In response to the review article written by Pavuluri and May [1] and to the original article by Tomasino et al [2] we will comment the recent neuroimaging findings of insular dysfunctions in Schizophrenia and Bipolar Disorders, focusing on people at genetic risk for developing psychotic symptoms. A disrupted insular functioning was reported in several studies, even though the results were not univocal with respect to the direction of the effect (some studies reported a reduced activation, other an augmented activation) and the lateralization of the observed alterations (left, right or bilateral). We will conclude that an altered function of the insula during both cognitive and emotional task may be a candidate vulnerability marker for psychotic disorders.

Keywords: insula; psychotic disorder; bipolar disorder; schizophrenia, vulnerability marker; first-degree relatives; fMRI

1. Introduction

The role of the insula in integrating complex brain functions is today a hot topic in neuroimaging research.

In their interesting review, Pavuluri and May [1] described the crucial influence of the insula on the development and outcome of severe neuropsychiatric conditions, such as frontoparietal dementia, attention deficit hyperactivity disorder (ADHD), major depressive disorder (MDD) and pediatric Bipolar Disorder (BD). They highlighted that the insular cortex showed structural similarities and strong functional connections with the ventrolateral prefrontal cortex (VLPFC) and the anterior cingulate cortex (ACC), two areas strictly involved in emotion processing and salience detection.

Pavulury and May also focused on left/right differences in insular functions, with the right insula more involved in emotional tasks and left insula in cognitive control.

A lateralization of insular cortex was reported by Tomasino et al [2] in their case series of 40 neurological patients affected by lesions of anterior insula. Even though the authors pointed out that lesions limited to the insular cortex were extremely rare and also the surrounding cortical areas were usually involved, their results are intriguing. Right/left differences were found for cognitive alterations (left > right) and anxiety symptoms (right > left). Moreover, the nature of the observed cognitive changes were not the same: confusion and altered attention for right lesions, language alterations for left ones. Another interesting result is the 10 % of auditory experiences in right insular lesions.

In a recent systematic review we conducted on fMRI correlates of sustained attention tasks in psychosis [3], we found that a disrupted functioning of the insular cortex was commonly observed in both affective (Bipolar Disorder type I, BDI) and non-affective (Schizophrenic Disorder, SCZ) psychosis.

On the contrary, other cortical and subcortical structures seemed to differentiate the groups: amygdala alterations were more frequent in BDI, dysfunctions of cingulate cortex and thalamus in SCZ. Significant alterations of the insula have also been reported in MDD with psychotic features [4] (see also Busatto for a review) [5].

An interesting model to understand the role of the insula in psychotic symptoms has been proposed by Palaniyappan and Liddle [6]. According to this model, the insular cortex, as a part of the salience network (which is also composed of ACC, MPFC, amygdala and hypothalamus) is disrupted in psychotic disorders. The salience network is involved in processing of internal and external stimuli and in providing a correct response to rapid changes in the environmental conditions. So, an inappropriate judgment of internal stimuli and self-generated motor response may result in hallucinations and passivity experiences, whereas an incorrect salience given to complex external events, especially in uncertainty contexts, may lead to false beliefs and delusions.

An altered functioning of the salience network could also explain the symptoms of non-psychotic conditions such as ADHD and MDD without psychotic features.

The core symptoms of ADHD (inattention, impulsivity and hyperactivity) are, as a matter of fact, related to impaired attention, emotion processing and motor control, all functions performed by the salience network. On the other end, the depressed mood observed in MDD, even in absence of delusions, significantly affect the salience given to internal stimuli or environmental conditions, thus leading to a mood-congruent bias in interpreting reality.

2. Insular dysfunction in people at risk for psychotic disorders

Are insular alterations observed only after the clinical onset of psychosis, therefore associate with disease manifestations, or also in unaffected family members of psychotic probands, thus indicating a potential association with illness risk? Candidate vulnerability markers (or endophenotypes) must be associated with illness, heritable, state independent and found in unaffected relatives of patients at a higher rate than in general population [7].

In two of our previous studies, we enrolled healthy relatives of SCZ patients [8] and healthy relatives of BDI probands [9] to perform a fMRI adapted sustained attention task. Both behavioral and neuroimaging data were obtained. The paradigm we used was a visual degraded Continuous

performance task (deg-CPT), with different levels of difficulty. CPTs are particular kinds of “oddball paradigms”, and they are worldwide used to assess sustained attention and executive functions. In a oddball task, subjects are required to identify rare and unpredictable target stimuli presented among a stream of frequent non-target “distracting” stimuli [10,11]. To increase the attentional load, stimuli may be manipulated in speed (slow or rapid presentation), sensory modalities (visual, auditory), perceptual characteristics (blurred or degraded stimuli, use of digits, symbols or letters) or required response (only on targets, only on non-targets, on both targets and non-targets). If an event-related design is used, the pattern of functional activation during wrong and correct response may be separately analyzed.

In our study on unaffected adult siblings of schizophrenic patients [8] we found significant different activations of several brain regions, despite a comparable performance with respect to normal controls. A bilateral insular dysfunction was detected, but the differences were particularly evident in the left hemisphere and during the most difficult task level: an augmented activation during wrong responses and a reduced activation during correct responses on targets.

A similar reduced activation of the left insula during target recognition was reported by Hart et al [12] in a sample of unaffected pediatric subjects (mean age 14) with at least one schizophrenic family member.

Van de Meer et al [13] recently found that both adult schizophrenic patients and their unaffected siblings hypoactivate the left anterior insula, VLPFC, and middle temporal gyrus during an emotion regulation task, whereas subcortical deficits (hypoactivation of caudate and thalamus) were limited to the patient group.

Chamgong and colleagues [14] analyzed the pattern of functional activation during a volitional saccades task in adult schizophrenic patients and their healthy first-degree relatives. The bilateral insula was one of the five brain region of interest (together with ACC, prefrontal cortex, middle occipital gyrus and cuneus) where a decreased activation, when compared to normal controls, was observed in both patients and relatives. In these five regions relatives tended to show intermediate task-related signal change.

In their study on spatial working memory, Choi et al [15] enrolled 4 groups of subjects: patients with schizophrenia, first-degree relatives of schizophrenia (genetic high risk, GHR), ultra-high risk (UHR) subjects, and healthy controls. GHR were free of any clinical manifestations, whereas UHR subjects had no family history of schizophrenia but experienced prodromal symptoms considered strongly associated with imminent development of psychotic disorders [16]. In terms of behavioral accuracy, schizophrenic patients performed worse than controls, whereas GHR and UHR did not show any significant deficit. During the maintenance phase of working memory, a significant different activation of the insular region was observed between-groups: an augmented activation of left insula was observed in GHR subjects, whereas UHR subjects showed a bilateral hyperactivation. The authors speculated that at-risk subjects used compensatory activity for decreased efficiency to achieve a similar level of performance as healthy controls.

For what regard people at risk for Bipolar Disorder, we found an altered insular functioning during a sustained attention task) [9]: unaffected first-degree relatives of BDI and euthymic BDI shared a reduced accuracy in target detection and an abnormal activation of the bilateral insula during the wrong responses on targets. On the other hand, during correct responses to targets patients failed to activate the right insula and relatives hyperactivated the left one. During a block-design negative emotion task conducted on the same subjects [17] an augmented activation of the left insula

was reported in both patients and relatives, with respect to controls, even after controlling for difference in behavior performance (accuracy was significantly reduced in the patients group) and subclinical mood symptoms.

Whalley et al [18] observed that young relatives of BD patients who later developed a MDD demonstrated an increased activation of the bilateral insula during a executive / verbal fluency task when compared to those relatives who remained well overtime. The authors speculated that an altered insular function can differentiate individual at high risk for BD who later develop MDD from those at familiar risk who remain well.

During a facial emotional go/no go task, when inhibiting response to fearful faces, relatives of BD probands failed to recruit a cluster that extended from the left inferior frontal gyrus into the adjacent portion of the insula [19].

Analyzing the brain activation pattern of young unaffected relatives of psychotic BD patients during a working memory task, Thermenos et al [20] reported a lack of task-dependent modulation of activity in the insular cortex, especially during the lower level of difficulty run.

3. Conclusion

Several studies reported altered pattern of functioning in the insular regions during both cognitive and emotional tasks not only in patients suffering of affective or non affective psychotic disorders, but also in clinically intact subjects at augmented genetic risk for psychotic disorders. The dysfunctions were more frequently located in the left hemisphere, even though other studies reported right or bilateral alterations. The direction of the effect was also controversial, with some studies detecting a reduced level of activation and other studies reporting an hyper activation with respect to comparison groups. The heterogenic results may partially depend on the different paradigms used and other studies are needed to better address this topic. In conclusions, altered functioning of the insular region may represent a candidate vulnerability marker for psychotic disorders. Being the insula is part of the salience network, we also hypothesized that a disruption in this brain network could account for a significant impairment in attention, emotion processing, motor control and judgment of complex environmental stimuli, thus providing a shared risk factor for developing both psychotic and non-psychotic disorders.

Conflict of Interest

All authors declare no conflicts of interest in this paper.

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