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Neurobiological Approach to Paranoid Spectrum Disorders

Review Article

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Summary

In Kraepelin's psychiatric nosology three types of paranoid conditions are described, that conceptually approach diagnostic entities according to modern classification systems: paranoid schizophrenia, delusional disorder, and paranoid personality disorder. A lengthy debate, maintained until today, is whether less 'serious' paranoid disorders, such as paranoid personality disorder and delusional disorder are included in schizophrenia spectrum, or if they form a distinct nosological entity which is different from schizophrenia. Genetic epidemiological, neuropsychological, neurophysiological and neuroimaging studies have been gathered to review the research data available to date regarding the question on the paranoid spectrum disorders.

Key words: schizophrenia, delusional disorder, paranoid personality disorder

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INTRODUCTION

An as-yet unsettled issue concerns the relationship among paranoid personality, delusional disorder, and paranoid schizophrenia. This is an issue that, regardless of any taxonomic approaches and theoretical differences, is important to the daily clinical practice, as it is related to the most common, perhaps, clinical cases found in mental health institutions. Therefore, an effective differential diagnosis which goes beyond the symptom phenomenology, is a sine qua non prerequisite for the direction of treatment.

One theoretical approach shows that the paranoid personality disorder belongs to the schizophrenic spectrum, with delusional disorder being placed in an intermediate degree of severity in the same spectrum. However, according to an earlier approach, the disorders in question belong to the paranoid spectrum that differs from the schizophrenic spectrum in its distinct cognitive profile (Figure 1).

The concept of spectrum suggests that discrete psychiatric disorders have similarities to one another either at the clinical level or at the level of aetiopathogenesis and pathophysiology. In addition, more and more evidence suggests that psychotic symptoms are present in the general population on a continuum of graded severity rather than as a 'whole or none' phenomenon.

Genetic epidemiological, molecular genetics, neuropsychological, neurophysiological and neuroimaging studies have been collected as a review. The rationale is that if the diagnostic categories represent biological entities, then biological markers such as genetic alleles, genetic expression products, brain structure or cognitive functionality will converge to related psychiatric disorders and will diverge in discrete disorders.

GENETIC EPIDEMIOLOGICAL STUDIES

FAMILY, ADOPTION

It has long been argued that characteristics such as suspiciousness, referential thinking, and peculiar ideas are prevalent among relatives of schizophrenic patients (Bleuler, 1922; Kretschmer, 1925; Ray, 1863/1968).

The widely known adoption study of the 1960s, the Danish Adoption Study (Kety et al., 1968), was the first methodologically robust attempt to detect subsyndromal schizophrenialike traits in the adopted biological offspring of schizophrenic probands. The findings of the study supported the existence of a "schizophrenia spectrum"—a continuum of schizophrenialike characteristics in the nonpsychotic relatives of schizophrenic individuals. Kendler et al. 1984, re-analyzing the data by Kety et al. and confirmed the proposed genetic relationship of paranoid personality disorder with schizophrenia.

Subsequently, two family studies and one adoption study (Stephens, 1975; Kendler, 1982; Baron, 1985) showed prevalence of paranoid personality disorder in relatives of schizophrenic patients compared to normal controls. Studies (Kendler, 1993; Parnas, 1993) have also shown that all three personality disorders of Cluster A, namely paranoid, schizoid, and schizotypal personality disorder, are present at increased rate in relatives of schizophrenic patients. A Study by Varma et al. in 1992 reported that all 3 Cluster A personality disorders are present at increased rate in first degree relatives of schizophrenic patients with paranoid type schizophrenia rather than in relatives of schizophrenic patients with non-paranoid schizophrenia.

However, a study by Erlenmeyer-Kimling et al. in 1995 reported that all three Cluster A personality disorders occur to both offspring of schizophrenia patients and offspring of patients with emotional disorders. A review article by Webb et al. in 1993 reported that 3 of the 6 studies supported the familial association between paranoid personality disorder and schizophrenia, but an extended study argued an increased risk of paranoid personality disorder in relatives of patients with emotional disorders rather than schizophrenia. In two recent well-designed studies (Asarnow et al., 2001; Nicolson et al., 2003) with conflicting findings: the former demonstrated a relatively small non-statistically significant risk of developing paranoid personality disorder in relatives of early childhood onset schizophrenia patients compared with relatives of ADHD patients and normal controls; however, the latter showed a high and statistically significant risk of paranoid personality disorder in parents of schizophrenia patients with both early childhood and adulthood onset compared to parents of normal controls.

In addition, Chang et al. in 2002 reported that 3.4% –8.6% of first-degree relatives of schizophrenic patients had a paranoid personality disorder. Tienari et al. in 2003 reported that in adopted children of mothers with schizophrenia, paranoid personality disorder was the disorder that occurred less frequently compared to other disorders of the schizophrenic spectrum.

Thus, to the question whether paranoid personality disorder belongs to the schizophrenia or delusional spectrum, other genetic epidemiological studies (Kendler, Gruenberg, & Strauss, 1981; Kendler & Hays, 1981; Kendler, Masterson, 1985; Winokur, 1985, de Portugal, 2008) argue that it belongs to the spectrum of delusional disorder, while other researchers (Maier, Lichtermann, Minges, and Heun (1994); Corruble, 1996) report that paranoid personality disorder was more common in relatives of patients with unipolar depression compared to relatives of patients with schizophrenia.

TWIN STUDIES

Twin studies using self- report questionnaires to measure the traits of Cluster A personality disorders have nearly uniformly demonstrated significant heritability for these traits, that typically ranged between 35% and 60%, and failed to find shared environmental effects (Claridge & Hewitt 1987; Kendler & Hewitt, 1992; Kendler et al. 1987a; Linney et al. 2003; Jang et al. 2005).

In a clinical sample-based twin study using the Structured Clinical Interview for DSM-III-R Personality Disorders (SCID-II), lower rates of heritability for paranoid personality disorder have been reported (28%) (Torgersen et al. 2000). A more recent twin study using Structured Interview for DSM-IV Personality Disorders (SIDP-IV) reported a rate of 21% for paranoid personality disorder. The proportion of genetic liability shared with all Cluster A disorders was estimated at 100, 43 and 26% respectively for schizotypal, paranoid and schizoid PDs (Kendler et al. 2006).

These results are consistent with the assumption that common genetic risk factors for Cluster A personality disorders reflect the general population's susceptibility to schizophrenia. The extended phenotype corresponding to this genetic vulnerability is often described with the term schizophrenia spectrum.

Since unreliability of measurement will decrease the heritability estimates and the test-retest reliability or stability of measurement for personality disorders (with questionnaires and semi-structured interviews) has been shown to be imperfect, both measurement scales were used over time to account for unreliability of evaluation; and results indicated that the liability to cluster A personality disorders was substantially higher than in the first study, with estimated heritabilities of 66% for paranoid personality disorder, (Kendler et al. 2007). In a 10-year longitudinal study investigating the temporal stability of genetic risk factors for Cluster A personality disorders, they reported that 68% of susceptibility to paranoid personality disorder derives from the effects of genetic factors (Kendler et al. 2015).

DELUSIONAL DISORDER

Kraepelin clearly depicted delusional disorder (paranoia) and included it in the spectrum of disorders with delusional features, which comprised paraphrenia and paranoid schizophrenia. Since Kraepelin era, many psychiatrists have argued that paranoia and paranoid schizophrenia were the opposite ends of a psychotic disorders spectrum with delusions as the dominant symptom. However, the controversy continues as to whether the delusional disorder - paranoid (delusional) psychoses - belongs to the schizophrenia spectrum or it is a distinct nosological entity (Riecher-Rossler et al. 2003).

Delusional disorder is usually included in schizophrenia spectrum disorders and may be placed in a continuum with paranoid schizophrenia. Although paranoid schizophrenia is grouped with other types of schizophrenia, perhaps Kraepelin's primary conceptualization that it belongs to the same spectrum with delusional disorder is justified. Kahlbaum's observations that paranoid disorders are distinct nosological entities may be accurate since they appear genetically distinct from other psychoses.

GENETIC EPIDEMIOLOGY STUDIES

Genetic studies of families of patients with delusional disorder do not support the theory of the schizophrenia spectrum. Schanda et al. (1983) reported that the risk of 'atypical psychosis' was higher for first degree relatives of patients with delusional disorder compared to relatives of patients with paranoid schizophrenia. Kendler et al. (1985) reported that paranoid personality disorder may have a greater familial effect in patients with delusional disorder than in patients with schizophrenia. Some studies found that relatives of patients with delusional disorder show increased rates of suspiciousness, jealousy, paranoid personality disorder, and delusional disorder compared to normal control relatives (Winokur 1985), but did not show increased rates of schizophrenia or emotional disorder.

Additional cases of patients in schizophrenia spectrum prevailed among the biological relatives of adopted patients with schizophrenia. This genetic profile was not found for delusional disorder, and in that sense of genetic causality, the delusional disorder did not appear to belong to the schizophrenia spectrum disorders. It is argued that delusional disorder as a nosological entity emphasizes what we call heterogeneity within the schizophrenia spectrum (Rosmondetal., 2001; Kendler et al. 1981).

MOLECULAR GENETIC STUDIES

PARANOID PERSONALITY DISORDER

In agreement with the hypothesis that schizophrenia and related personality disorders is associated with dopaminergic dysregulation, Rosmond et al. (2001) reported that a polymorphism in the D2 receptor (DRD2) gene is involved in Cluster A personality disorders. In addition, a study by Roussos (2013) reported that allele A of the calcium channel gene-rs1006737 CACNA1C was associated with paranoid ideation in the Schizotypal Traits Questionnaire (STQ). Also recent studies (Roussos, 2011; Pasparakis, 2015) reported that allele A of the rs1006737 CACNA1C gene was associated with lower extraversion and increased harm avoidance, trait anxiety, and paranoid ideation in healthy young males and gene alleles of rs10994336 ANK3 and rs1006737 CACNA1C are associated to increased

startle response, implying a possible role of these polymorphisms in the detection and processing of stressful or threat stimuli from the hippocampus/amygdala neurocircuit.

The study by Golimbet et al. (2003) in patients with emotional disorders, schizophrenia and normal controls reported a correlation between the short “s” allele and the “ss” genotype of 5-HTTLPR gene polymorphism (lower expression of serotonin transporter) with low scores in paranoia in MMPI.

A study by Smyrnis et al. (2007) reported that individuals with val / val genotype of the COMT gene had higher scores on the ‘paranoia’ factor in the schizotypal personality disorder questionnaire compared with those with the Met / Val genotype, suggesting a positive association between the allele Val and the factor “paranoia”.

MOLECULAR GENETIC STUDIES

DELUSIONAL DISORDER

Catalano et al. (1993) reported that polymorphism in the D4 receptor encoding gene (DRD4) was highly significant in patients with delusional disorder compared to schizophrenic patients and normal controls. Zenner et al. (1998) reported multiple genetic polymorphisms in the gene encoding the D4 receptor (DRD4) to be associated with delusional disorder. Di Bella et al. (1994) demonstrated a significant association of the Ser9Ser allele with the D3 receptor (DRD3) gene in patients with delusional disorder. Serretti et al. (2000) demonstrated a significant association between the Ser311Cys allele in the D2 receptor (DRD2) gene and delusional ideas in major psychotic disorders (including delusional disorder and schizophrenia).

This is an indication that this mutation may be related to delusional symptomatology regardless of diagnosis.

Morimoto et al. (2002) suggested that delusional disorder, particularly the persecutory type, was related to a dopaminergic psychosis and that polymorphisms of the DRD2, DRD3 and / or TH genes were part of the genetic etiology that caused dopaminergic hyperactivity and thus paranoid symptoms. In a molecular genetics study for delusional disorder, Morimoto et al. (2002) demonstrated a high frequency of the genotype which encodes the Ser311Cys D2 (DRD2) receptor in patients with delusional (ICD-10) persecutory type (21%), compared to schizophrenics and controls (6%). In addition, there was also a significant positive association between the TH allele gene and pretreatment levels of plasma pHVA in delusional disorder.

Debnath et al. (2006) proposed an immunogenetic approach for the causality of paranoid spectrum disorders. Investigating genetic correlations between delusional disorder and paranoid schizophrenia they reported that the HLA-A * 03 gene is significantly associated with both delusional disorder and paranoid schizophrenia. Wilke et al. (1996) highlighted the possibility of immunologic dysfunctions in paranoid disorders. In their study they reported significantly reduced production of γ-interferon in patients with acute phase paranoid schizophrenia.

ELECTROPHYSIOLOGICAL STUDIES

STUDIES WITH EVOKED POTENTIALS

PARANOID PERSONALITY DISORDER

Liu et al. (2007) found a normal range of MMN (mismatch negativity) in patients with paranoid personality disorder, and not reduced, which is in agreement with a previous study in patients with paranoid schizophrenia (Sato et al. 2003). This result implies that patients with paranoid personality disorder do not have stimulus processing impairment and show a normal performance in filtering irrelevant stimuli. But they show hypervigilance as indicated by the reduction in latency of the N1 potential, meaning they showed faster automatic processing of auditory stimuli and their alterations, with maximum amplitude of approximately 135–140 ms, but with normal ability to filter irrelevant stimuli.

Electrophysiologically N1 potential occurs earlier in patients with paranoid personality disorder compared to the general population, at Fz and Pz electrodes. In a recent study by Xue-bing L et al. (2011), the neuronal mechanism of suspiciousness was investigated with EEG in people who were predisposed to schizotypy and people who were not predisposed to schizotypy, provoking a feeling that they were being ‘perceived’. The results showed a positive deviation at 250–400 ms after the stimulus in both control groups. However, P3 potential was sig-

nificantly reduced in people with a schizotypy predisposition compared to the other group. Further analysis has shown hypoactivity in the frontal and temporal regions in individuals with a predisposition to schizotypy, suggesting that the frontotemporal neurocircuit holds a role in initiating suspicious thoughts. The difference in P3 potential was negatively associated with suspicion / paranoid ideation.

STUDIES WITH EVOKED POTENTIALS

DELUSIONAL DISORDER

A study of auditory evoked potentials in patients with delusional misidentification syndrome reported a significant decrease in P3 amplitude in right frontal areas and a significant prolonged P3 latency in the midline compared with normal controls (Papageorgiou et al., 2003). In a follow-up study, the same research group attempting to determine whether delusional syndromes and schizophrenia are discrete nosological entities studied with evoked potentials schizophrenic patients with and without delusional misidentification syndrome and reported significant reduction in P3 amplitude in frontal lobe of schizophrenic patients without the delusional misidentification syndrome and smaller reduction in schizophrenic patients with delusional misidentification syndrome compared to normal controls (Papageorgiou et al. 2005).

In addition, in patients with delusional misidentification syndrome there was a significant increase in P3 latency in the midline as compared to normal controls. Patients without delusional misidentification syndrome showed a significant decrease in P3 amplitude in the left frontal areas compared to patients with delusional misidentification syndrome (Papageorgiou et al. 2005).

ELECTROPHYSIOLOGICAL FINDINGS: STUDYING EVOKED POTENTIAL IN *SCHIZOPHRENIA*

O'Donnell et al. (1993) with auditory event-related potentials in schizophrenic patients reported a bilateral decrease in N2 amplitude which was associated with a decrease in cortical volume in the upper left temporal gyrus as well as with the reduction of the medial temporal structures, related to chronic course of the disease. In contrast, the amplitude of P3 was only related to cortical volume in the left upper temporal gyrus in the posterior region and clinically with delusions and formal thought disorders. Impairments in the 'syntactic' dimension of each response (N400) reflect the dysfunction of the implicated neuronal circuits and studies by Prueter et al. (2002) and Kiang et al. (2008) indicated indirect deficits in semantics in patients with delusional ideas without formal thought disorders. This deficit was related to the severity of the delusional ideas indicating a possible role in aetiopathogenesis.

Studies on prepulse inhibition (Perry and Braff 1994) have reported a correlation between delusional ideas in schizophrenia and sensorimotor deficits, and Dawson et al. (2000) reported associations among delusional ideas and suspiciousness and prepulse inhibition abnormalities only when the responder was encouraged to attend and not when he was instructed to ignore the prepulse, suggesting that anticipatory modifications trigger attention mechanisms under the influence of delusional ideas.

A study by Louzã et al. (1989) which attempted to highlight differences in P3 in somatosensory evoked potentials between paranoid and non-paranoid schizophrenic patients reported that after nerve stimulation on the right side, the non-paranoid group exhibited a significant increase in latency but normal P3 amplitude; however the paranoid group showed a tendency to decrease P3 amplitude with normal latency. After stimulation on the left side a P3 latency increase was observed in the paranoid patient group with an amplitude decrease, whereas the non-paranoid group showed similar performance to the normal control group.

Generally, patients with paranoid schizophrenia tend to show fewer reductions of cognitive event-related potentials than do non-paranoid schizophrenia patients and impairments in P1, N1, P2, MMN are mostly bilateral, whereas in patients with non-paranoid schizophrenia show lateralization. This means that patients with paranoid schizophrenia retain a better preservation of the frontal-temporal dialogue allowing them to distinguish between relevant and irrelevant stimuli (Oades et al. 1996).

NEUROPHYSIOLOGICAL FINDINGS

PARANOID PERSONALITY DISORDER

Studies have reported that patients with Cluster A personality disorders with positive family history of schizophrenia exhibit schizophrenic-like laboratory findings (Thaker et al. 1996, 2000). Studying the prosaccadic and antisaccadic eye movements in 55 first-degree relatives of schizophrenia patients (21 belonged to Cluster A personality disorders) and 62 other individuals in the general population (25 belonged to Cluster A personality disorders) they concluded that relatives of patients with schizophrenia, especially those belonging to Cluster A, showed significant impairments in antisaccadic tasks. Also studying eye-tracking movements in 32 first-degree relatives of schizophrenia patients (13 belonged to Cluster A of personality disorders) and 75 other individuals in the general population (24 belonged to Cluster A of personality disorders) concluded that relatives of patients with schizophrenia, especially those belonging to Cluster A, had significant smooth pursuit eye abnormalities.

NEUROPHYSIOLOGICAL FINDINGS

DELUSIONAL DISORDER

Gambini et al. (1993) studied smooth pursuit and voluntary saccadic eye movements in patients with delusional disorder, schizophrenia, and normal controls. They found that schizophrenic patients differed from normal controls in some smooth pursuit eye movement characteristics, while both groups of patients showed more saccades compared to normal controls during the smooth pursuit test. In addition, they found that patients with delusional disorder differed in some voluntary saccadic eye movement characteristics compared to controls. The data supported the idea of a biological dysfunction in eye tracking in delusional disorder.

The same research group in another study reported (Campana et al. 1998) impairment in eye tracking performances in patients with delusional disorder indicating a cerebral dysfunction similar to those detected in schizophrenic patients. They also reported that normal smooth pursuit eye movement performance in delusional disorder patients was associated with an improvement in psychopathology probably due to the effect of antipsychotic drugs.

NEUROPSYCHOLOGICAL FINDINGS

PARANOID PERSONALITY DISORDER

Similar cognitive deficits but minor in severity to those observed in schizophrenia characterize schizotypal personality disorder (Siever et al., 2002). There are no studies on cognitive deficits in people with paranoid personality disorder, but deficits in learning and information processing appear to be risk factors for paranoia, most notably in the realm of impaired hearing where paranoia can be evoked by both experimental (Zimbardo et al., 1981) and natural conditions (Sanchez Galan, Denez Sanchez, Llorca Ramón, & del Caarizo Fernández-Roldan, 2000; van der Werf et al., 2007).

Besteiro-González et al. 2004 reported that Cluster A personality disorders were characterized by deficits in executive functions according to neuropsychological tests. Coolidge et al. (2009) studied 49 college students using the Coolidge Axis II Inventory Personality Disorder Questionnaire and neuropsychological tests and reported that the Digits Backwards subtest was the strongest predictor for personality disorders (negative correlation). In a study by Coolidge et al. (2004) that examined whether personality disorders are psychological manifestations of executive dysfunctions, investigating the bivariate heritability between executive function deficits and the personality disorder scales in 314 twins-96 monozygotes and 61 dizygotic-they reported that the proportion of observed correlations attributed to heritable factors ranged from 0.27 for schizoid personality disorder to 0.64 for histronic. For paranoid personality disorder it was 0.43.

Consequently there are significant genetic effects (co-heritability) between executive function deficits and personality disorders, which may indicate that some of the characteristic symptoms of personality disorders may be present due to executive function deficits.

Hypervigilance of the paranoid seems to lead them to attend and recollect (in a biased way) the threat-related stimuli. This type of process has been reported for populations with clinical (Garety 1999) and sub-clinical (Combs 2004) paranoia.

Functional deficits in social skills have also been reported, such as deficits in neuropsychological tests of emotional and social perception and behav-

ior (Combs 2004), as well as in 'theory of mind' (Kinderman 1998), which may contribute to the inherent tendency of paranoid to personalize negative social interactions.

NEUROPSYCHOLOGICAL FINDINGS

DELUSIONAL DISORDER

It has been proposed that patients with delusional disorder should not have a significant decrease in neurocognitive functions, and many argue that this is a prerequisite for the diagnosis, since systematized delusional ideas seem inconsistent with neurocognitive deficits (Kunert et al. 2007).

Besides, one of the clinical features of delusional disorder is the absence of significant functional impairment. Although there is extensive literature on neurocognitive deficits in schizophrenia, few studies have evaluated neurocognitive deficits in patients with delusional disorder. Some of these studies report mild deficits in executive function and memory between patients with delusional disorder and normal controls, but other studies show slight differences between patients with delusional disorder and patients with paranoid schizophrenia, supporting the continuum of psychotic spectrum. While previous studies did not show differences between patients with delusional disorder and normal controls (Conway et al., 2002; Evans et al., 1996), recent studies support the existence of cognitive deficits in executive and memory functions in patients with delusional disorder (Ibanez-Casas et al., 2013; Leposavic et al., 2009; Yesilyurt et al., 2008).

Recent and more extensive studies (Lapcin et al. 2008; Grover et al. 2011) report that patients with delusional disorder showed similar neurocognitive deficits compared with patients with paranoid schizophrenia. They suggested that the similarity of neurocognitive profiles likely suggests that similar underlying biological underpinnings are responsible for the deficits in the two paranoid spectrum disorders. Patients with delusional disorder had a reduced ability of cognitive flexibility, slower speed processing, restricted capacity for learning, updating and inhibiting inappropriate information and poorer memory and reasoning (Ibanez-Casas et al. 2013).

The results of the study are not in line with the traditional notion of cognitive preservation in patients with delusional disorder. On the contrary, if compared with previous studies on schizophrenia, executive function in delusional disorder could be postulated as being half-way between that of patients with schizophrenia and controls (Oflaz et al. 2014). It has been suggested (Hui et al. 2015) to evaluate the neurocognitive dimension in both disorders. The same was proposed by de Portugal et al. (2012), referring to the inclusion of neurocognitive deficits within the spectrum of psychopathology of delusional disorder.

NEUROIMAGING FINDINGS

PARANOID PERSONALITY DISORDER

No neuroimaging studies have been performed exclusively in people with paranoid personality disorder although in case reports, in trauma patients, brain injury may contribute to paranoid symptoms or features such as jealousy. In a 30 year prospective study in patients with brain injury a high incidence (8.3%) of paranoid personality disorder has been reported (Koponen et al., 2002).

Suspiciousness is considered a major feature of paranoid personality disorder. There is evidence that it is related to right temporal brain activity, to areas that have also been associated with vigilance (Robertson and Garavan, 2004). Using the tractography technique Nakamura et al. (2005) showed the correlation of suspiciousness with reduced connectivity of right frontotemporal structures through the right uncinate fasiculus. Fisher's study et al. (2014) in a non-clinical population, reports that suspiciousness is associated with early detection of emotional information during a neuropsychological test with a version of the Stroop task, which reflects right temporal brain activation. Increased suspiciousness was associated with enhanced N200 observed over right temporal-parietal cortex during an auditory oddball task (Sumich et al., 2014), suggesting increased early attentive processes, which is consistent with a tendency toward vigilance.

Paranoia is also considered as the common manifestation of early dementia (Eustace et al., 2002), and appears to be prevalent in older adults (95 years) and at younger ages appeared to be a precursor of dementia (Ostling & Skoog, 2002).

ANATOMIC NEUROIMAGING FINDINGS IN *DELUSIONAL DISORDER*

Neurological studies that aimed to elucidate the pathophysiology of delusional disorders have reported the presence of ischemic temporoparietal lesions (Braun and Suffren, 2011; Vallar and Ronchi, 2009).

According to a recent (2015) review article, from 14 studies that reported structural brain changes in patients with delusional disorder, in 4 cases of patients with delusional disorder somatic type, MRI did not reveal structural brain alterations (Ota et al. 2003; Akahane et al. 2003, Freudenmann et al., 2010, Uezato et al., 2012). Several other studies have shown diffuse cerebral atrophy (Miller et al., 1989; Wada et al., 1999; Huber et al., 2008), as well as enlargement of ventricles (Narumoto et al., 2006).

Concerning the brain areas where structural brain changes occur in the white matter conflicting findings are presented. White matter deficits in the frontal lobes were reported in 3 patients, in 2 in parietal and in 1 on the right temporoparietal area. In a recent study (Wolf et al., 2013) a volumetric decrease in gray matter frontotemporally on the right side of the striatum and on the left side of thalamus and an increase of white matter in striatum was reported in 16 patients with delusional disorder compared to normal controls.

FUNCTIONAL NEUROIMAGING STUDIES IN *DELUSIONAL DISORDER*

Functional neuroimaging case studies with SPECT have shown changes in blood flow in the temporoparietal areas (Hayashi et al., 2004; Narumoto et al., 2006; Wada et al., 1999). According to a recent review article (González-Rodríguez et al., 2015), reduced cerebral blood flow was reported in 5 patients in temporoparietal areas (Wada et al., 1999; Ota et al., 2003). , Hayashi et al., 2004; Akahane et al., 2009; Hayashi et al., 2010), right temporal lobe (Horikawa et al., 2006; Narumoto et al., 2006), left temporoparietal areas (Caliyurt et al., 2004; Hayashi et al., 2004; Wada et al., 1999) and increased cerebral blood flow in one patient in right temporal lobe (Uezato et al., 2012), and in another total frontotemporal asymmetry was revealed (Umezaki et al. al., 2013).

In addition, prefrontal dysfunction (reduced activation of the left posterior prefrontal cortex) was reported in 9 patients with delusional disorder using fMRI during an n-back neuropsychological test (Oflaz et al., 2014). The same study reported increased activation of the temporal lobe as well as increased activation in the fusiform gyrus and the posterior area of the cingulate gyrus.

CHANGES IN NEUROIMAGING IN *DELUSIONAL DISORDER*

In a study by Vicens et al. (2016) using voxel-based morphometry and functional neuroimaging during n-back neuropsychological testing, as well as in a functional connectivity study with BOLD fMRI in default state, 22 patients with delusional disorder were studied. Regarding the volume, patients showed grey matter reductions in the medial frontal/anterior cingulate cortex and bilateral insula on unmodulated (but not on modulated) voxel-based morphometry analysis, failure of de-activation in the medial frontal/anterior cingulate cortex during performance of the n-back task, and decreased resting-state connectivity in the bilateral insula.

ANATOMIC NEUROIMAGING FINDINGS *IN SCHIZOPHRENIA*\

Ha et al. (2004) using MRI in 35 patients with paranoid schizophrenia reported significant cortical atrophy in the insula, left posterior prefrontal cortex, medial frontal and temporal structures as well as in the anterior region of the cingulate gyrus. In MRI studies in schizophrenic patients decrease in volume of left upper temporal gyrus was associated with positive symptoms (Barta et al., 1990; Gaser et al., 2004; Nestor et al., 2007), formal thought disorder, delusions (McCarley et al., 1993; Shenton et al., 1992), and neurocognitive deficits in executive functions (Nestor et al., 2007, 1993).

Cascella et al. (2012) using MRI in 43 patients with schizophrenia reported a negative correlation between the severity of delusional ideas and the size of left claustrum and right insula. Atrophy of gray matter of insula bilaterally, in dorsal frontal areas, superior temporal gyrus, anterior cingulate gyrus, medial frontal cortex, thalamus and left amygdala have been reported in schizophrenia. In white

matter a decrease in interhemispheric communication has been reported, in inferior longitudinal fasciculus, occipitofrontal fasciculus, corpus callosum and fornix (Bora et al. 2011).

FUNCTIONAL NEUROIMAGING STUDIES IN *SCHIZOPHRENIA*

Most studies in schizophrenic patients with fMRI (Barch et al., 2001; Callicott et al., 1998; Driesen et al., 2008) show reduced prefrontal activation during neuropsychological tasks testing working memory and executive functions. Previous studies have reported that symptoms of disorganization and formal thought disorder in schizophrenic patients were associated with decreased activation of the posterior prefrontal cortex (Menon et al., 2001; Perlstein et al., 2001; Yoon et al., 2008).

Functional neuroimaging studies in schizophrenia have reported impairments in the activation of the superior temporal gyrus during executive functions (Gur et al., 2007), which were associated with formal thought disorder (Kircher et al., 2001; McGuire et al., 1998). Other studies support that patients with schizophrenia display a decrease in the activation of the anterior cingulate gyrus (Honey et al., 2005; Neuhaus et al., 2007; Yücel et al., 2002), and an increase in the activation of the posterior region which has also been related to delusional persecutory ideas (Blackwood et al., 2004).

Menon et al. in 2011 using MRI reported that delusional ideas of association-reference in patients with schizophrenia were associated with increased activation of the medial ventral and posterior medial prefrontal cortex, the anterior and posterior cingulate gyrus and the paracentral lobe, namely brain regions with thick interconnections with the limbic and striatal dopaminergic pathway. Activation of the insula and ventral striatum was related to the severity of the delusional ideas.

FUNCTIONAL NEUROIMAGING FINDINGS IN *SCHIZOPHRENIA*

Although schizophrenic patients activated the posterior prefrontal lobe less than controls, they strongly activated the anterior cingulate gyrus, indicating that in schizophrenia the functional connectivity of the frontal structures is impaired or reversed (Glahn et al. 2005).

FMRI findings show that there are areas with significant differences between schizophrenia and controls during neuropsychological tests with n-back task. They show deactivation in schizophrenia, namely in areas that were significantly activated in normal controls (Pomarol-Clotet, E. et al, 2010). For instance, a failure to inhibit the default network in schizophrenic patients compared to their first degree relatives and controls has been displayed in posterior cingulate, medial prefrontal cortex and the praecuneus lobule (Whitfield-Gabrieli et al., 2009).

FUNCTIONAL CONNECTIVITY FINDINGS IN PATIENTS WITH *SCHIZOPHRENIA*

Studies testing functional connectivity during default states have identified significantly increased functional connectivity in medial prefrontal cortex in relatives and patients compared to controls and significantly increased functional connectivity in posterior cingulate gyrus and the praecuneus lobule in patients compared with controls (Whitfield-Gabrieli et al. 2008). In addition, a reduced connectivity between right insula regions and resting- state areas in patients with schizophrenia has been found. (Moran et al, 2013)

CONCLUSIONS

Paranoid personality disorder is genetically and epidemiologically related to schizophrenia less strongly compared to schizotypal personality disorder.

Few neurobiological studies focused exclusively or primarily upon paranoid personality disorder and inconclusive evidence of the reliability and validity of the disorder (mainly due to the idiosyncratic paranoia of psychiatric patients that seems to be better explained from other psychiatric diagnosis) excluded paranoid personality disorder, as a distinct personality disorder, from the revised personality disorders model of DSM-V, and included it into the "Personality Disorder Trait Specified" category, where idiosyncratic paranoia is categorized according to clinical criteria.

Genetic epidemiology studies support famil-

ial association of paranoid personality disorder with delusional disorder but in the sense of genetic etiopathogenesis, delusional disorder does not appear to belong to the schizophrenic spectrum. However, when investigating the genetic associations between delusional disorder and paranoid schizophrenia an immunogenetic approach to the pathogenesis of paranoid spectrum disorders has been suggested.

Molecular genetic studies suggest that DRD2, DRD3 gene polymorphisms are part of the genetic etiology leading to hyperactivation of the dopaminergic pathways resulting in paranoid symptoms. Neurophysiological studies report smooth pursuit eye impairments in patients with delusional disorder suggesting brain dysfunction similar to that of schizophrenia patients. Neuropsychological studies report that patients with delusional disorder had similar neurocognitive deficits compared with patients with paranoid schizophrenia, and the similarity of neurocognitive profiles probably suggests that similar biological underpinnings are responsible for the deficits in the two disorders of the paranoid spectrum.

In neuroimaging studies, the structural and functional alterations observed in patients with delusional disorder are similar to those observed in patients with schizophrenia but they are less extensive.

Due to the significant heterogeneity observed in the diagnostic category of delusional disorder, a different way of classification has been proposed than that used in the classification system based on the content of delusional ideas (de Portugal et al. 1012).The paranoid dimension of delusional disorder is associated with premorbid paranoid personality disorder, adverse childhood experiences, legal problems, severe functional impairment, and poor therapeutic compliance and response. The cognitive dimension is associated with cognitive impairment, substance use disorders, physical comorbidity, possible visual hallucinations, decreased comorbidity with depressive disorders, and severe functional impairment. Schizoid dimension presents in single patients and is associated with a family history of schizophrenia, a premorbid personality mostly schizoid or schizotypal type and the possibility of auditory hallucinations and dysthymia. Emotional dimension is related to family history of depression, premorbid obsessive compulsive personality, somatic delusional ideas, absence of delusional ideas of reference, tactile and olfactory hallucinations, depressive and anxiety disorders, and suicidality.

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