Neurobiology of Psychosis. Clinical and Psychosocial Implications

This is a Section of *Epidemiologia e Psichiatria Sociale*, that regularly appears in each issue of this Journal to describe relevant neuroscience topics. In particular, studies investigating the relationship between neurobiology and psychosocial psychiatry in major psychoses will be debated. The aim of these short articles is to provide a better understanding of the neural basis of psychopathology and clinical features of these disorders in order to raise new perspective in every-day clinical practice.

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Twin studies in psychotic disorders

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Genetic factors are recognized to be involved in the etiology of major psychoses, particularly schizophrenia and bipolar disorder. Nevertheless, little is known about the nature and extent of the specific genetic contribution to disease liability (Kendler *et al*., 1993; Danese, 2008). Twin studies can provide crucial insights regarding the etiology of sub-threshold and clinical psychosis, and represent an extraordinarily powerful design to establish the role of genes and environment both in the expression of a trait (e.g., development of a disease) and in the co-expression of multiple traits (e.g., comorbidity of multiple diseases). By comparing the correlation for a trait between genetically identical monozygotic (MZ) twins with that between dizygotic (DZ) twins who represent full sibs, and assuming that MZ twins share relevant environmental exposures to the same extent as DZ twins ('equal environments assumption'), it is possible to estimate the contribution of genetic factors ("heritability") and environmental influences to the expression of the trait. Furthermore, when multiple phenotypes are studied, cross-twin/cross-trait correlation (i.e., between a given phenotype in a twin and another phenotype in his/her co-twin) in MZ and DZ twin pairs provides information on genetic or environmental influences common to the phenotypes (genetic or environmental correlation between the phenotypes), which could play a role in their co-expression (Boomsma *et al*., 2002; Spector *et al*., 2000). The potential of the twin design enormously increased after the implementation of population-based registries of data on twins in several countries (Busjahn & Hur, 2006), including Italy (Fagnani *et al*., 2006; Stazi *et al*., 2002).

A large body of twin studies aimed at unraveling the genetic and environmental architecture of major psychoses and psychotic symptoms. Although results vary

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Table I – *Published twin studies on schizophrenia, bipolar disorder and psychotic symptoms, showing estimates of genetic and environmental effects based on biometric modelling.*

Major psychoses (dichotomous diagnosis)

Study	Trait, Country, Setting	Diagnostic criteria, Age	Sample	Estimates from best-fitting univariate (liability-threshold) models
Cannon *et al.*, 1998	Schizophrenia, Finland, Population	DSM-III-R, ICD-8 Mean age at 1st treatment contact: 27.2 years (males), 28.0 years (females)	7873 pairs (total screened); 253 affected pairs identified	A=83%; E=17%
Cardno *et al.*, 1999	Schizophrenia, England, Clinical	RDC lifetime-ever Mean age at 1st psychiatric contact: 24.2 years; Mean age of co-twins at last follow up: 46.5 years	98 pairs	A=82%; E=18%
		DSM-III-R	90 pairs	A=0%; D=84%; E=16%
		ICD-10	93 pairs	A=0%; D=83%; E=16%
Sullivan *et al.*, 2003	Schizophrenia, Multinational meta-analysis, Various (Population and Clinical)	Various (DSM-III-R, ICD-8, ICD-10, plus others unstated)	Data from 12 studies	A=81%; C=11%; E=8%
McGuffin *et al.*, 2003	Bipolar disorder, England, Clinical	DSM-IV Mean age at 1st psychiatric contact: 24.2 years; Mean age of co-twins at last follow up: 46.5 years	67 pairs	A=85%; E=15%
Kieseppa *et al.*, 2004	Bipolar disorder, Finland, Population	DSM-IV Mean age of co-twins at last follow up: 48.0 years (range 35-57)	7873 pairs (total screened); 25 affected pairs identified	Bipolar I: A=93%; E=7%
Edvardsen *et al.*, 2008	Bipolar disorder, Norway, Population & Clinical	DSM-III-R Mean age: 48.6 years (range 19-83)	Bipolar I: 21 affected pairs Bipolar II: 25 affected pairs	Bipolar I: A=73%; E=27% Bipolar II: A=58%; E=42%

Psychotic symptoms (symptom dimensions as quantitative traits)

Study	Trait, Country, Setting	Assessment tool, Age	Sample	Estimates from best-fitting models
Gillespie *et al.*, 2001	Psychoticism, Australia, Population	Self-report (EPQ) Age range: 18-28 years	3269 pairs	A=40%; E=60%
	Interpersonal sensitivity	Self-report (IPSM)		A=36%; E=64%
Gillespie *et al.*, 2004	Psychoticism, Australia, Population	Self-report (JEPQ) Age at baseline: 12 years	1342 twins at baseline	Longitudinal Males 12 years: A=47%; E=53% 14 years: A=41%; C=11%; E=48% 16 years: A=41%; E=59% Females 12 years: A=41%; E=59% 14 years: A=35%; C=11%; E=54% 16 years: A=41%; E=59%
Bratko & Butkovic, 2007	Psychoticism, Croatia, Population	Self-report (EPQ) Mean age at baseline: 17 years	160 pairs at baseline	Longitudinal (2 measures, 4 years apart) 1st time point: A=46%; E=54% 2nd time point: A=46%; E=54%
Hur, 2007	Psychoticism, South Korea, Population	Self-report (EPQ) Adolescents and young adults	765 pairs	A=0%; D=39%; E=61%
Kendler *et al.*, 2006	Paranoid personality disorder, Norway, Population	Structured interview (SIDP-IV) Mean age: 28.2 years (range 19-36)	1386 pairs	Multivariate A=21%; E=79%
	Schizoid personality disorder			Multivariate A=28%; E=72%
	Schizotypal personality disorder			Multivariate A=26%; E=74%

Table I

Psychotic symptoms (symptom dimension as quantitative traits)				
Study	**Trait, Country, Setting**	**Assessment tool, Age**	**Sample**	**Estimates from best-fitting models**
Hay *et al*., 2001	Perceptual aberration – Magical ideation, Australia, Population	Self-report (Chapman & Chapman) Age range: 18-25 years	3685 twins	A=33%; E=67%
	Hypomania – Impulsivity/Nonconformity			A=28%; E=72%
	Social anhedonia			A=0%; D=50%; E=50%
	Physical anhedonia			A=36%; E=64%
McDonald *et al*., 2001	Perceptual aberration, USA (Pennsylvania), Population	Self-report (Chapman) Age range: 18-27 years	157 pairs	A=33%; C=9%; E=58%
	Magical ideation			A=0%; C=41%; E=59%
	Social anhedonia			A=27%; C=0%; E=73%

In the reported twin studies, biometric model-fitting was used to estimate the effect of additive genetic (A), either shared environmental (C) or non-additive genetic (D), and unshared (individual-specific) environmental (E) factors. Multivariate or longitudinal models are identified as such; otherwise, the models refer to cross-sectional univariate designs.
RDC: Research Diagnostic Criteria; EPQ: Eysenck Personality Questionnaire; IPSM: Interpersonal Sensitivity Measure; JEPQ: Junior Eysenck Personality Questionnaire; SIDP-IV: Structured Interview for DSM-IV Personality.

greatly, depending on population, design, diagnostic criteria and symptom assessment tools, these studies are very consistent in suggesting that psychotic traits may be mainly influenced by additive genetic and unshared (individual-specific) environmental factors, while environmental exposures that are shared within the family may play only a marginal role. Several twin studies on schizophrenia have been conducted up to this date. A meta-analysis that combined information from 12 studies adopting heterogeneous diagnostic and ascertainment strategies showed strong additive genetic effects on liability to this disease, with a joint heritability estimate of 81% (Sullivan *et al*., 2003). For bipolar disorder, heritability was estimated at 85% by McGuffin *et al*. (2003) and at 73% (bipolar I) and 58% (bipolar II) by Edvardsen *et al*. (2008) in clinical samples. Genetic effects were reported to explain 93% of individual differences in liability to bipolar I disorder by Kieseppa *et al*. (2004) in a Finnish population sample.

The twin method has also been extensively used to investigate psychotic symptom dimensions in general population samples. Heritability estimates of about 40% have been reported for psychoticism, and a similar genetic contribution (36%) has been shown for interpersonal sensitivity (Gillespie *et al*., 2001; Hur, 2007). Recently, two studies (Gillespie *et al*., 2004; Bratko & Butkovic, 2007) reinforced the concept that personality traits stability, including psychoticism, is primarily influenced by genetic factors. In addition, in our Italian sample of around 700 young adult twins, we found that genetic factors explained approximately 50% of individual differences in psychotic symptoms (i.e., interpersonal sensitivity, paranoid ideation, and psychoticism), and that shared genetic effects played an important role in the co-occurrence of such symptoms, including, for the first time, obsessive symptoms (Fagnani *et al*., submitted for publication). By performing a multivariate analysis on a large sample of Norwegian twins, Kendler *et al*. (2006) obtained modest estimates of genetic effects for paranoid (21%), schizoid (28%) and schizotypal (26%) personality disorder. Other twin studies aimed at quantifying the genetic load on perceptual aberration, magical ideation and anhedonia, reporting heritability estimates generally modest to moderate (Hay *et al*., 2001; McDonald *et al*., 2001).

Interestingly, recent epidemiological surveys (i.e., the Zurich Study, Rössler *et al*., 2007; the British National Survey of Psychiatric Comorbidity, Johns *et al*., 2004; the Nemesis Study, van Os *et al*., 2000 and the US-National Comorbidity Survey, Kendler *et al*., 1996) also suggested that psychotic symptoms are often sub-threshold features of the general population, indicating that psychotic disorders rarely adhere to a strict diagnostic definition. Instead, psychoses seem to be multi-dimensional, encompassing a broad spectrum of features centered around paranoid ideation, psychoticism, and interpersonal sensitivity (Long *et al*., 2007; Perugi *et al*., 2003; Rössler *et al*., 2007). Therefore, the clinical definition of psychosis may represent a rather small fraction of the total phenotypic continuum (van Os *et al*., 2000).

In conclusion, there is consistent validation from twin studies that psychotic traits are genetically distributed also in the general population. A small percentage of them may be related to psychotic disorders, specifically to schizophrenia and bipolar disorder. These findings, taken together, suggest that the study of large and well-characterized twin samples could highly contribute to delineate the etiology and pathogenesis of psychotic disorders, and thereby pave the way for major improvements in clinical management (Ricciardi *et al*., 2008).

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