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D. Talevi, A. Rossi

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The link between happiness and psychopathology

Why happiness?

Health is a dynamic "state of complete physical, mental and social well-being and not merely the absence of disease or infirmity". It is a basic human right, not seen as the final goal of human existence, but a resource for living a full life in society. Most of the scientific approaches adheres to the "disease model" of the mind, focusing on what makes human beings unhealthy. On the other hand, "Positive psychology" turned attention to qualities of optimal experience, including happiness [1]. The pursuit of happiness has been considered an essential human right since antiquity and its importance is not a new concept in anthropological sciences. The pursuit of happiness has been confined as an object of philosophical investigation until the 50s of the last century. During those years an array of humanist scholars underwent empirical studies that emphasized happiness as an important issue within the concept of health, since it helps produce wellbeing that fits the WHO definition of health. Moreover, happiness is recognized as an important concern in global public policy. Given that the objective of governments is to improve people's well-being, experts in education, development and economy stated that happiness, or related indices of wellbeing, might represent a more efficient and holistic indicator of quality of life and social progress than Gross Domestic Product (GDP). GDP relates just to the economic aspect of life; subjective well-being, in contrast, takes into account both economic and noneconomic concerns, including health, family, community and work. Although wealth and happiness were found to be correlated [2], the relation is not linear. Social inequality seems to lead to differences in quality of life and health more than income in itself. Depression is supposed to be the most disabling disease in the world in 2030, leading to higher rates of mortality and lost productivity per person. Turning the question on its head, might it be more useful to promote health by promoting happiness, instead of treating depression?

What is happiness?

Happiness can be defined as a fundamental lasting affect characterized by preponderance of positive over negative emotions and presence of life satisfaction, social engagement, and objectives in life. The concept encompasses three elements: evaluative, hedonic, and eudaimonic [3]. The first concerns wellbeing-life satisfaction. The hedonic aspect focuses on seeking positive feelings and avoidance of the negative ones. The eudaimonic feature is about having a sense of meaning and purpose in life. The pursuit of happiness guides human behavior and enhances the development of personal resources useful for living in harmony with the surrounding environment. Happier people show to have habits connected to close relationships, kindness, physical wellbeing, experience of "flow", spiritual engagement, virtues and positive mindset [1].

Among exponents of Positive psychology, Abraham Maslow [1] defined the "hierarchy of needs", a hierarchical list of basic human needs that had to be fulfilled for maximum psychological health and for increasing life satisfac-

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tion. On the top of the pyramid there are morality, creativity, spontaneity, problem solving, lack of prejudice and acceptance of facts. Below those, he put needs connected to esteem, love, safety and survival. Martin Seligeman [1 4] postulated the stages of happiness: the pleasant life, the good life and the meaningful life. In the final stage, personal strengths and virtues are mobilized for a purpose much greater than the self. He classified, through cross-cultural studies, six virtues, that are wisdom, courage, humanity, justice, temperance and transcendence, and twenty-four human strengths which are the "route" trough which individuals achieve virtues in their life. Ed Diener [1 4] coined the expression "subjective well-being" (SWB) as the aspect of happiness that can be empirically measured. The three major components of SWB are pleasurable and painful feelings (affective component) and life satisfaction (cognitive component). He argued for a strong genetic component to happiness. His researches found that social relationships are highly correlated with happiness, supporting the notion that unhappy people can raise their level significantly by closely interacting with good friends and family.

From "being happy" to "being healthy"

Scientific research confirmed that happiness is closely related with health [5]. This link is bidirectional: happier population show lower rates of chronic illnesses and live longer; at the same time, negative emotions and depression are frequent sequelae of these diseases [6 7]. Happiness has been found to have both direct and indirect effect on the body, involving changes in the neuroendocrine, immune and cardiovascular systems [6 7]. It is pretty obvious that "feeling good" promote positive emotions.
There are several reasons that make happiness a good marker of mental health: above all, it concerns the affective domain of the psyche, especially the balance between positive and negative emotions. Positive emotions have been confirmed to increase prosocial outcomes and enhance affiliations [8]. Reduced amounts of negative emotions have also been associated with reduced risk for certain mental disorders like anxiety, depression and borderline personality disorder [8]. In fact, happier people score lower on psychopathology scales [4]. Furthermore, happiness deals with some important factors for psychiatry, like the concepts of resources, resilience, and social network. Especially, it is conceivable that resilience may be fostered by the presence of lasting positive affects and, in turn, work as a protective factor against stressful life events. In this sense, it may explain the pathway to positive mental health outcomes. unhappiness also leads to risky or maladaptive behaviors, as some studies found: people who feel unhappy tend to engage in smoking, high alcohol or drugs consumption or physical inactivity [7 9]. Interpersonal violence might be another negative outcome: lower levels of happiness seems to be related to a lower self-control and to a propensity to physical and verbal aggression [10]. The relationship between violence and happiness appears to be relevant in terms of outcome, given the strong impact that violence has on world public health [11 12]. Given all of the above, identifying "what makes happy people happy" instead of focusing on "what makes depressed people depressed" might be the next challenge for psychiatry. According to a bio-psychosocial model, determinants of subjective wellbeing include personal and environmental factors. Some studies invoke psychological features like personality, both the aspects of temperament and character such as self-direction [6 13]. These features may mediate the relation between life events and response. Basic human values could be involved in this link as well, having individualistic and collectivist values A different impact [14].

Conclusions

The science of happiness gives prominence to human strengths, leaving the "problem-based" focus in favor of the "resources-based" focus. Being happy may make an impact on mental and physical health through biopsychosocial mechanisms. Since a more holistic approach to promote health is desirable and possible, psychiatry may walk the pathway of promoting mental health through the promotion of happiness. As Seligman said, treatment is not just fixing what is broken; rather, it involves nurturing what is best within ourselves.

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Original article

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Mediating role of lack of support for the relationship between extraversion and sense of loneliness in parents of children with autism spectrum disorder and parents of children with intellectual disability

Summary

Objectives

Parents of children with autism spectrum disorder (ASD) as well as parents of children with intellectual disability (ID), in addition to stress related to a child's disability, may experience loneliness and social isolation. The purpose of this study was to verify the mediating role of actually received and perceived available social support in relationship between extraversion and sense of loneliness in parents of children with ASD and parents of children with ID.

Methods

168 parents of children with ASD and 111 parents of children with ID, without autistic traits, participated in the study. The following research tools were used: De Jong Gierveld Loneliness Scale (DJGLS) in the Polish adaptation; Polish adaptation of Ten Item Personality Inventory (TIPI): TIPI-PL; Berlin Social Support Scales (BSSS) – Polish version and a survey questionnaire.

Results

It was shown in group of parents of children with ASD that extraversion weakens the sense of loneliness through the perceived available social support (Z = -3,846, p = 0.001, C.I. [-1.608; -0.496]). In this sample, the analogous, mediating role of actually received support in the relationship between the distinguished variables was also identified (Z = -2.970, p = 0.003, C.I. [-1,364; -0.249]). In turn, in the group of parents of children with ID, the existence of a mediating role of only perceived available support in the relationship between extraversion and a sense of loneliness was noticed (Z = -2.799, p = 0.005, C.I. [-1,625; -0.236]).

Conclusions

The research results indicate that extraversion participates in complex mechanisms of regulating the sense of loneliness in parents of children with ASD and parents of children with ID, in which the perceived and received support plays an important role as intermediary variables. It is advisable to sensitize parents to the importance of social support and help in building resources, and to inform about possible and available forms of assistance in the immediate environment.

Key words
Autism spectrum disorder • Intellectual disability • Parents • Sense of loneliness

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Introduction

Sense of loneliness is a subjectively felt discomfort resulting from the unsatisfactory state of interpersonal relations [1 2]. It does not have to be synonymous with social isolation, but it is associated with perception (indifferently, objectified or not) of being lonely and dissatisfied with the current quality of social relations [3]. Loneliness – as speculated – fulfills important evolutionary functions as an "alarm" against social isolation and a moti-

vating factor for establishing and nurturing social contacts [4]. At the same time, it should be emphasized that the persistent, chronic sense of loneliness has negative health consequences, such as depression and anxiety disorders, suicidal thoughts [5], coronary heart disease [6], and it increases mortality risk for various reasons [7].

According to the results of many studies, the most important factors affecting the sense of loneliness are, on the one hand, the quality of social support [8-10], and on the other, personality traits [11 12]. However, so far, apart from general mentions [13 14] and exploratory research, which are mentioned below, these relationships were not verified in the case of parents of children with neurodevelopmental disorders, such as the autism spectrum disorder (ASD) and intellectual disability (ID). According to the DSM-5 [15], symptoms of ASD mainly concern deficits in the field of social communication and social interactions, as well as limited, repetitive patterns of behavior, interests or activity. The classification distinguishes three levels of depth of the disorder, based on the criterion of the severity of clinical symptoms present and – what is connected with this – the required support. ID includes deficits in the field of intellectual functioning (confirmed by both clinical assessment and standardized intelligence testing) and adaptive deficits (leading to the inability of a person to meet the developmental and sociocultural standards of personal independence and social responsibility), the beginning of which first appears in the developmental period. Raising a child with neurodevelopmental disorders is a great challenge for parents, associated with the feeling of chronic stress [16 17] and, sometimes, the experience of social stereotypes and misunderstanding [18]. Parental role is often carried out at the expense of important social activities, natural for families with neurotypical children [19].

The results of exploratory research on loneliness of parents of children with neurodevelopmental disorders [20] allowed to identify predictors of a sense of loneliness in the group of parents of children with ASD and parents of children with ID. In both groups, extraversion was such a role. When it comes to variables related to social support, in the group of parents of children with ASD, a statistically significant predictor appeared to be perceived available support, and in the case of parents with children with ID - actually received support.

There are premises to assume that the covariation of extraversion and sense of loneliness does not result (in whole or in part) from the direct cause-and-effect linking between them, but from the mediation of the third variable related to support. For example, it was explained that extraversion is related to loneliness through the mediation of social network variables [21]. Again, however, this problem was not analyzed in the group of parents of children with neurodevelopmental disorders. The problem is important because both parents of children with ASD [22] and ID [23] experience different quality of support, and loneliness is one of the most serious aggravating factors.

Objectives

The aim of the study was to verify the mediating role of actually received and perceived social support in relationship between extraversion and sense of loneliness in parents of children with ASD and parents of children with ID.

On the basis of the considerations presented above, and above all the results of the preliminary research devoted to this problem, the following research hypotheses were formulated:

- H1: In the group of parents of children with ASD extraversion weakens the sense of loneliness through perceived available support;
- H2: In the group of parents of children with ID extraversion weakens the sense of loneliness through actually received support.

Methods

The following measures were used in the study:

1. De Jong Gierveld Loneliness Scale (DJGLS) in the Polish adaptation of Grygiel et al. [24], in order to diagnose the sense of loneliness of parents. The scale is one-dimensional and measures a generalized sense of loneliness. Internal consistency determined by Cronbach's α for the Polish adaptation of the scale is 0.89; the value of the average inter-position correlation $r = 0.42$; and the homogeneity coefficient H Loevinger = 0.47. The scale correlates with the UCLA loneliness scale ($r = 0.82$).
2. Polish adaptation of the Ten Item Personality Inventory (TIPI) – TIPI-PL [25], in order to measure personality traits included in five-factor model: extraversion, emotional stability, agreeableness, conscientiousness and openness to experience [26]. All TIPI-PL scales are characterized by similar or higher reliability in relation to the original version (Cronbach's α = 0.44-0.83). In order to verify the validity of TIPI-PL, the relationships of personality traits measured with the TIPI-PL and the NEO Five-Factor Inventory (NEO-FFI) were analyzed. The following values of the correlation coefficient were obtained: for extraversion $r = 0.68$ ($p < 0.001$); for agreeableness $r = 0.61$ ($p < 0.001$); for conscientiousness r = 0.74 ($p < 0.001$); for emotional stability $r = 0.72$ ($p < 0.001$); for openness to experience $r = 0.49$ ($p < 0.001$).
3. Berlin Social Support Scales (BSSS) – Polish version [27], which allow measuring: Perceived Available Support (PAS) – subjective belief, without a specific

time context, concerning availability of help from other people; Actually Received Support (ARS) – perception of help currently provided by other people; Need for Support (NFS) – the need to use support in a crisis situation; Support Seeking (SS) – the frequency and scope of seeking assistance; and Protective Buffering Support (PBS) – protecting relatives from negative news. Reliability measured by Cronbach's α coefficient for individual scales was from 0.71 to 0.90.

4. Survey questionnaire – containing questions about sex and age of the parent, education, material status, number of children and the age of the child with a specific neurodevelopmental disorder.

Participants and procedure

Ethical approval was obtained from the Research Ethics Committee of the Faculty of Pedagogy and Psychology at Maria Curie-Sklodowska University in Lublin, Poland, to conduct this study. Parents of children with ASD and ID were reached through institutions supporting the development of their children (foundations, associations, schools and kindergartens) located in four provinces of Poland: Podkarpackie, Warmian-Masurian, Gdansk and Lublin. The sets of measures were provided to the respondents and received from them by therapists and teachers working with their children. The survey was anonymous, each set was in an envelope and contained written instructions explaining the purpose of the project. Parents were informed about the possibility to withdraw from research at any time.

The results obtained by 168 parents of children with ASD and 111 by parents of children with ID, without autistic traits (in total 279 participants, including: 231 mothers and 48 fathers) were qualified for the analysis.

TABLE I. *The number of parents of children with ASD and parents of children with ID, including the sex of the respondents.*

Disorder in the child	Mothers	Fathers	In total
ASD	129	38	168
ID	96	12	111
In total	225	50	279

Detailed information on the number of respondents, taking into account their gender and disorders of the child, are presented in Table I.

Table II compares the average age of the parents of children with various developmental disorders, while Table III contains information on their level of education. Parents of children with ID were older than the parents of children with ASD; in their case, the average age was about 44 years, and in the group of parents of children with ASD – nearly 38 years. Both tested samples were different in this respect, as evidenced by relatively high values of standard deviations.

The group of parents of children with ASD was dominated by participants with higher and secondary education, and the group raising children with ID – by participants with vocational and secondary education.

Results

Using the Hayes' PROCESS macro [28], it was examined whether BSSS scales are mediators of the relationship between extraversion and the sense of loneliness in parents of children with ASD. The results are shown in Table IV.

On the basis of statistical analysis, the existence of a mediating role of perceived available support in the relationship between extraversion and a sense of loneliness in the parents of children with ASD was confirmed ($Z = -3.846$, $p < 0.001$, C.I. [-1.608; -0.496]). The model with the mediator explains 36.4% of the variance of the sense of loneliness. The introduction of a mediator weakens ($R^2med = 0.140$) the negative relationship between extraversion and a sense of loneliness, as illustrated in Figure 1.

Subsequently, the mediation role of actually received support in the relationship between extraversion and the sense of loneliness in the parents of children with ASD was identified ($Z = -2.970$, $p = 0.003$, C.I. [-1,364; -0.249]). The model with the mediator explains 28.9% of the variance of the sense of loneliness. The introduction of a mediator weakens ($R^2med = 0.112$) the negative relationship between extraversion and sense of loneliness, as illustrated in Figure 2.

In this group, there was no significant mediation role of the following variables: need for support, support seeking and protective buffering support.

Then it was examined whether BSSS scales are media-

TABLE II. *Age of surveyed parents (n = 279).*

	Median	SD	t	df	p
Parents of children with ASD	37.95	6.789	6.320	265	.001
Parents of children with ID	43.80	8.207			

TABLE III. *Education of examined parents (n = 279).*

Education	Parents of children with ASD		Parents of children with ID		Parents in total	
	N	%	N	%	N	%
Basic education	4	2,4	7	6,3	11	3,9
Vocational education	25	4,9	38	34,2	63	22,6
Secondary education	62	36,9	36	32,4	98	35,1
Higher education	77	45,8	28	25,2	105	37,6
No data	0	0,0	2	1,8	2	0,7

TABLE IV. *Analysis of extraversion and loneliness regression with the mediation of BSSS scales in parents of children with ASD (n = 168).*

Mediator	Model without a mediator		Model with a mediator					Bootstrap (C.I. 95%)		Sobel's Test	
	B_c	R^2	$B_{c'}$	B_a	B_b	B_{ab}	R^2_{med}	Lower	Upper	Z	p
PAS	-2.799***	.223	-1.861***	1.542***	-0,606***	-0.934	.140	-1.608	-0.496	-3.846	.001
NFS	-2.799***	.223	-2.871***	0.252^	0.311	0.072	-.006	-0.025	0.334	0.893	.372
SS	-2.799***	.223	-2.824***	0.678***	0.040	0.023	.016	-0.250	0.317	0.169	.866
ARS	-2.799***	.223	-2.168***	3.041***	-0.206***	-0.668	.112	-1.364	-0.249	-2.970	.003
PBS	-2.799***	.223	-2,795***	-0.163	0.027	-0.004	.001	-0.166	0.064	-0.090	.928

Note: PAS: perceived available support; NFS: need for support; SS: support seeking; ARS: actually received support; PBS: protective buffering support
*p < 0.1; ** p < 0.01; *** p < 0.001*

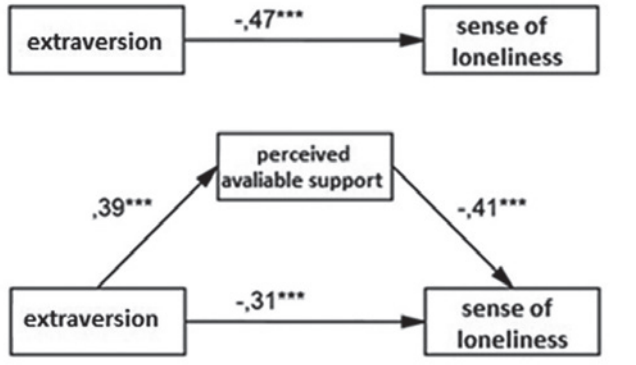

FIGURE 1. *Model of extraversion and sense of loneliness regression with a mediator – perceived available support, standardized coefficients, parents of children with ASD (n = 168). *** p < 0.001*

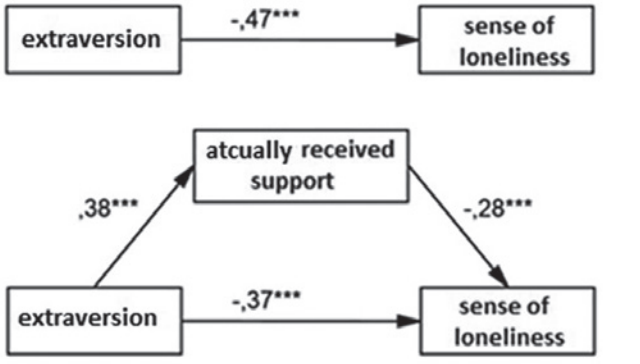

FIGURE 2. *Model of extraversion and sense of loneliness regression with a mediator – actually received support, standardized coefficients, parents of children with ASD (n = 168). *** p < 0.001*

tors of the relationship between extraversion and the sense of loneliness in the parents of children with ID. The results are shown in Table V.

Significant mediating role of perceived available support was noticed in the relationship between extraversion and a sense of loneliness in the parents of children with ID (Z = -2.799, *p* = 0.005, C.I. [-1,625; -0.236]). The model with the mediator explains 29.5% of the variance of the sense of loneliness. The introduction of a mediator weakens (R^2med = 0.099) the negative relationship between extraversion and sense of loneliness, as illustrated in Figure 3.

In the group of parents of children with ID there was no significant mediation role of such variables as: need

TABLE V. *Analysis of extraversion and sense of loneliness regression with the mediation of BSSS scales in parents of children with ID (n = 111).*

Mediator	Model without a mediator		Model with a mediator					Bootstrap (C.I. 95%)		Sobel's Test	
	B_c	R^2	$B_{c'}$	B_a	B_b	B_{ab}	R^2_{med}	Lower	Upper	Z	p
PAS	-1.576***	.109	-0.956*	0.864**	-0.687***	-0.813	.099	-1.625	-0.236	-2.799	.005
NFS	-1.576***	.109	-1.540***	0.039	-0.943**	-0.041	.006	-0.409	0.222	-0.258	.796
SS	-1.576***	.109	-1.511***	0.133	-0.467*	-0.120	.018	-0.518	0.030	-0.921	.357
ARS	-1.576***	.109	-1.556***	0.068	-0.318***	-0.283	.040	-0.976	0.056	-1.331	.183
PBS	-1.576***	.109	-1.609	-0.119	-0.279	-0.031	.004	-0.356	0.053	-0.375	.707

Note: PAS: perceived available support; NFS: need for support; SS: support seeking; ARS: actually received support; PBS: protective buffering support
** p < 0.05; ** p < 0.01; *** p < 0.001*

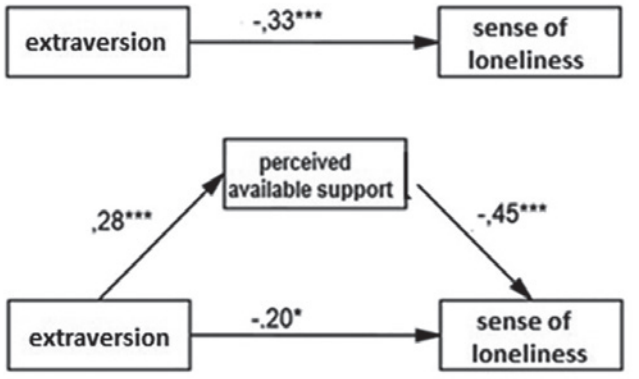

FIGURE 3. *Model of extraversion and sense of loneliness regression with a mediator – perceived available support, standardized coefficients, parents of children with ID (n = 111). *** p < 0.001*

for support, support seeking, actually received support and protective buffering support.

Discussion

The goal of the study was to answer the question whether perceived and actually received social support are mediators of the relationship between extraversion and a sense of loneliness in groups - respectively - of parents of children with ASD and children with ID. As a result of the analyzes carried out, the hypothesis 1 was positively verified. The mediating role of the perceived available support in the relationship between extraversion and a sense of loneliness in parents of children with ASD was confirmed. We are dealing with the situation of mediating the idea of the availability of help from others in a relationship between extraversion, as a personality trait of the parent, and the loneliness he or she feels. This group also showed the existence of a mediating role of currently received support in the relationship between extraversion and a sense of loneliness, which was not assumed at the level of hypotheses. In the case of parents of children with ID, it was not found that extraversion weakens the sense of loneliness through the actually received support. The hypothesis 2 was not confirmed. However, the existence of a mediating role of the perceived available support in the relationship between extraversion and the sense of loneliness was noticed.

Parents of children with neurodevelopmental disorders with low intensity of extraversion (introverts), presenting greater difficulties with establishing and maintaining social relationships, may feel a greater sense of loneliness, while extroverts, having a larger social network, experience less loneliness [21]. The results of the presented study additionally indicate that extraversion participates in more complex mechanisms of regulation of the sense of loneliness, in which the perceived and received support plays an important role as intermediary variables. Stokes [27] came to similar conclusions, discovering that variables related to the social network significantly reduce the relationship between extraversion and loneliness. It can therefore be assumed that this is a regularity for various social groups. The results obtained prove a particularly important role of the subjective conviction about the availability of help from other people, in the case of parents of children with ASD and parents of children with ID. It can be assumed that perceived social support is an important predictor of the psychological well-being of the parent, probably of greater significance than the support actually received [30 31] which, for example, may be inadequate to the needs, come from an inappropriate source or pose a threat to self-esteem [32].

The results obtained in the group of parents of children with ASD differ from the results obtained by parents of children with ID. In the parents of children with ASD, the relationship between the sense of loneliness and extra-

version is mediated by a greater number of variables associated with social support. It can be assumed that autism as a particularly disruptive disorder, mainly due to the frequent occurrence of challenging behaviors [33], requires multifaceted and diverse forms of assistance.
The most important limitation of this study is a relatively small group of examined fathers, which makes it impossible to perform analyzes with regard to the gender variable. Nevertheless, the results obtained allow for the formulation of practical conclusions regarding the support of parents of children with ASD and children with ID. It is advisable to sensitize parents to the importance of social support and help in building resources, including informing about possible available forms of assistance in the immediate environment. These goals could be implemented during workshops conducted by a psychologist or a social worker. Another important action is increasing communication skills of parents, including expressing their emotions and asking for help. Finally, support groups from the parents themselves, which can provide emotional and informational support, play an important role. It is worth initiating such activities at foundations or associations that care for the family of people with neurodevelopmental disorders.
In further studies devoted to this problem, it is worth considering attributions – for example the reasons that parents of children with ASD and ID perceive as conditions of experienced loneliness [34]. Also interesting would be a study involving parents of children with less frequent neurodevelopmental disorders, such as with the Tourette syndrome [35], where the social awareness of the problem is lower, the formal support deficit is higher and, as one can assume, the loneliness of families is greater.

Conclusions

1. Extraversion, as a personality trait related to attitudes towards social contacts, sociability and assertiveness, participates in complex mechanisms of regulating the sense of loneliness in parents of children with ASD and ID, where social support variables play an important mediating role.
2. Perceived and actually received support are mediators for the extraversion relationship with a sense of loneliness in the group of parents of children with ASD.
3. Perceived social support is a mediator for the extraversion relationship with a sense of loneliness in the group of parents of children with ID.
4. Based on the results obtained, as part of the prevention of loneliness of parents of children with ASD and ID, it is recommended to sensitize the importance of social support and help in raising awareness and building resources, including by informing about possible available forms of assistance in the immediate environment.

Conflict of interest

The Authors declare to have no conflict of interest.

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Original article

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Obsessive-compulsive symptoms and schizophrenia spectrum disorders: the impact on clinical and psychopathological features. A descriptive study on acute inpatients

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Summary

Objectives

Obsessive-compulsive symptoms (OCS) have often been described in schizophrenia spectrum disorders, contributing to the overall complexity of the clinical presentation, over and above the canonical symptom dimensions. The main aim of this study is to investigate the prevalence of OCS and its relationship with contextual psychopathology in a sample of acute psychotic inpatients within the schizophrenia spectrum.

Methods

76 subjects consecutively admitted with a diagnosis of schizophrenia spectrum disorder underwent a systematic psychopathological assessment including the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) and the Positive and Negative Syndrome Scale (PANSS). Descriptive and bivariate analyses were performed in order to identify clinical and psychopathological correlates of the schizo-obsessive subgroup, defined as a Y-BOCS score ≥ 17.

Results

44.7% of the participants revealed significant OCS. No significant differences were detected in terms of socio-demographic, diagnostic and treatment features. Subjects with clinically relevant OCS presented higher scores in the negative and general psychopathology subscales, as well as a higher PANSS total score (Tab. I).

Conclusions

High levels of OCS are relatively frequent in inpatients with schizophrenia and identify a subgroup with higher symptomatological severity. Screening for OCS in newly admitted subjects with schizophrenia might facilitate the timely identification of a subgroup with more intensive need of care.

Key words

Psychopathology • Obsessive compulsive • Schizophrenia spectrum • Psychotic disorders • Schizo-obsessive

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Introduction

The co-occurrence of schizophrenia and obsessive-compulsive symptoms (OCS) or obsessive-compulsive disorder (OCD) identifies a subpopulation of psychotic patients for which the term *schizo-obsessive* was coined [1-3].

The correlation of obsessions and psychotic symptoms was hypothesized since the foundation of the modern psychiatry, despite obsessive symptoms being initially considered a protective factor against psychosis. The possible transition from obsessions to delusional ideas or hallucinations at a certain stage of intensity during the course of illness was described by

several authors such Bleuler and Binswanger, considering the obsessive-compulsive syndrome as a possible variant of schizophrenia [4-6].

Although the two disorders represent different nosographic entities and OCS are not considered as primary features or clinical dimensions of schizophrenia [7], the coexistence of these conditions has been found to be critically frequent [2]. Indeed, previous studies evaluated the prevalence of OCS among patients affected by schizophrenia between 30 and 59% while OCD was estimated to occur in a percentage rate between 8 and 23% [3 8]. Recent literature describes schizo-obsessive disorder as a construct underlying several areas of overlap between schizophrenia and OCD, with a rising interest towards its neurobiological correlates, possibly connected with dysfunctions in basal ganglia and frontal lobe [9].

The association between these conditions can be considered as a continuum, where patients with primary diagnosis of OCD who develop psychotic features or schizophrenia at a later stage of the illness are included as well [10 11]. Furthermore, the schizo-obsessive framework has been more recently enlarged, with studies evaluating OCS also in subjects with a diagnosis of non-affective psychotic disorders, including schyzotypy [3 12 13]. Noteworthy, the likelihood of being affected by OCD has been shown significantly higher not only for schizophrenic patients, but for patients leaning on the whole spectrum [14]. Moreover, the hypothesis that treatment with second generation antipsychotics, especially clozapine, may induce or exacerbate obsessive-compulsive features in patients affected by schizophrenia provides further elements of complexity to the relationship of the two conditions, also in consideration of the need to address targeted treatment strategies in schizophrenic patients presenting OCS [15 16].

Recent studies investigated whether schizo-obsessive disorder identifies a population of patients with peculiar clinical and psychopathological features, without univocal results. Schizo-obsessive and schizophrenic patients seem to show no differences in the age at onset of psychotic symptoms, while OCS present an earlier onset in the schizo-obsessive group compared to patients diagnosed with OCD alone [17 18]. Patients with comorbidity of the two conditions seem to share a more significant social impairment, with lower level of education and higher rates of unemployment [16]. Similarly, OCS seem to show a significative impact on functioning in subjects affected by psychotic disorders other than schizophrenia [3 12]. However, other findings connect the presence of mild OCS with an improvement of social functioning in schizophrenia [19 20].

Clinically relevant OCS appear to be connected with psychopathological features of schizophrenia spectrum disorders with highly variable findings about the most represented symptomatologic dimensions [11 12 21]. On the other hand, some research failed to find any significant correlation between OCS and positive/negative symptoms, hypothesizing the independence of obsessions and compulsions from the core symptoms of schizophrenia [18 20 22 23]. In consideration of these conflicting results, how OCS interact with other clinical characteristics in schizophrenia spectrum disorders and their impact on the psychopathological presentation of the illness still represents a not fully addressed issue [12].

As a consequence, the present study examines the prevalence of OCS in a population of inpatients with diagnosis of schizophrenia spectrum disorders and investigates sociodemographic, clinical and psychopathological features of schizo-obsessive patients in order to better characterize this diagnostic construct and its relationship with other symptomatological constellations in schizophrenia spectrum disorders.

Materials and methods

This is an observational study assessing inpatients recruited at the Psychiatric Inpatient Unit in the General Hospital of Santa Maria della Misericordia in Perugia, Umbria, Italy, from January 2015 to December 2016. The sample consists of patients admitted to the unit both voluntarily or using compulsory treatment procedures after giving their writing consent, in full respect of ethical principles stated by the declaration of Helsinki. The research ethics committee of the Umbria region gave approval for the study. The whole sample consisted of 76 patients who fulfilled the inclusion criteria at their first admission during the study period.

Subjects aged 18-65, native Italian speakers, diagnosed with schizophrenia spectrum disorders according to DSM-IV-TR [24 25] were deemed eligible for the participation in the study. Patients with substance-induced psychosis or physical illnesses possibly affecting the psychopathological status were excluded.

Sociodemographic and clinical information was collected in specific paper records then entered into an electronic database. Symptom severity was rated by means of the Positive and Negative Syndrome Scale (PANSS) [26]. Patients were further tested with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) [27]. The presence of OCS was considered clinically relevant when patients scored 17 or more at the Y-BOCS, according to an operational criterion defined in previous literature [28].

Descriptive analysis and examination of the distributional properties of sociodemographic, clinical and living information variables were first carried out. Secondly, bivariate analyses were performed using chi-square tests for categorical variables and t-test for continuous variables. All analyses were performed

using the Statistical Package for Social Sciences (SPSS), 20.0 version for Windows Inc.

Results

Final sample consisted of 76 patients. Among these, 44 (57.9%) were males whilst 32 (42.1%) were females, with a mean age of 40.54 ± 12.06 years. The most common diagnoses according to the DSM-IV-TR [25] were Schizophrenia (29 patients, 38.2%) and Schizoaffective Disorder (25 patients, 32.9%).

In the present sample of patients affected by schizophrenia spectrum disorders, 34 (44.7%) patients presented clinically significant OCS, as defined by a Y-BOCS score ≥ 17. As for symptoms severity, 10 patients (13.2%) presented severe OCS and 1 (1.3%) showed extreme OCS, respectively defined by a Y-BOCS score included between 24 and 31 or between 32 and 40.

Patients diagnosed with schizophrenia spectrum disorders showing OCS (SCHZ-OCS) did not differ significantly from patients without OCS (SCHZ-OCS) in terms of socio-demographic characteristics such as gender, age, nationality, marital status, occupation, scholarity and living status.

No differences were found between SCHZ-OCS and SCHZ-NOCS groups for what concerns main psychiatric diagnosis according to DSM-IV-TR [25] and medical comorbidities. Substance misuse appeared to be more frequent among SCHZ-NOCS patients (p = 0.033). As for treatment features, the prescription of long-acting injectable antipsychotics, both typical and atypical, did not significantly diverge between the two groups.

Significant differences in psychopathological characteristics as measured by the PANSS were detected in the present study. Particularly, patients with clinically significant OCS presented higher scores in the negative (p = 0.003) and general psychopathology (p = 0.006) subscales, as well as a higher PANSS total score (p = 0.007) (Tab. I).

Discussion and conclusions

In the present study, near a half of the sample presented clinically significant OCS at the evaluation. This finding is partly consistent with the literature, where the prevalence of OCS in schizophrenia spectrum disorders can vary up to 59% [3 8 29]. Lower percentages could also be due to the heterogeneity of the samples, mainly considering outpatients [11 30], or to the evaluation of a co-morbid diagnosis of OCD and not the prevalence of OCS [21].

Between the two groups in analysis no differences were found about socio-demographic characteristics. This is consistent with part of the literature [17 30] where the lack of consensus is probably due to the different recruitment methods. In a previous study, psychotic patients with and without OCS did not differ from patients affected by OCD in absence of a schizophrenia spectrum disorder when compared on the basis of socio-demographic variables [23].

In the present study no differences were noted for what concerns clinical characteristics. In line with this finding, previous research elucidated that comorbidity between schizophrenia spectrum disorders and OCD did not represent a distinct nosographic entity on clinical bases [23]. Results about substance misuse in the schizo-obsessive subgroup are not fully consistent with literature findings, hypothesizing that comorbid OCD could increase the risk for some psychiatric comorbidities [3]. Anyway, although substance use disorders and OCD could share a common phenomenology with compulsivity at the basis, epidemiological findings about the co-occurrence of the two conditions are heterogeneous [31] and our results in the schizo-obsessive subgroup should thus be replicated.

Comparison of the psychopathological characteristics turned out to be statistically significant in our bivariate model. Particularly, psychotic patients affected by OCS showed more negative symptoms. This confirms some previous literature findings reporting a higher prevalence of negative symptoms [8 12 14 32 33], which are linked to a lower functioning and to the overall severity of the clinical presentation [34]. Similarly, general psychopathology symptoms were more represented in the schizo-obsessive sample. This could be consistent with the description of schizophrenia with OCS as a subtype presenting a major severity also in affective psychopathological domains, particularly anxiety and depression, which are included in this subscale of the PANSS [30 35]. The strong association as reported by negative and general psychopathology symptoms suggests a major complexity of schizophrenic patients presenting OCS, both in terms of clinical presentation and therapeutic strategies that should be addressed for this specific population. The higher PANSS total score confirms that the presence of OCS in schizophrenia spectrum disorder could significantly affect the overall severity of the clinical picture.

Data from the present study suggest that more pronounced OCS might define a pathomorphic expression of schizophrenia, with a negative impact on the clinical frame, on the quality of life and possibly on the whole outcome, although not representing a distinct syndrome in terms of socio-demographic and clinical characteristics [20 23 30].

As for methodological limitations, at least the following should be considered. First, our sample was recruited from people admitted in an inpatient unit, possibly characterized by a relatively high severity of illness, so our results should be generalizable with some cau-

TABLE I. *Socio-demographic and clinical characteristics in a population of psychotic inpatients (n = 76) with (SCHZ-OCS) and without (SCHZ-NOCS) obsessive-compulsive symptoms.*

	SCHZ-OCS (n = 34, 44.7%)	SCHZ-NOCS (n = 42, 55.3%)	χ^2	*p*
Socio-demographic characteristics	**n, %**	**n, %**		
Female gender	12 (35.3)	20 (47.6)	0.720	0.396
Italian nationality	33 (97.1)	39 (92.9)	0.089	0.765
Single	33 (97.1)	38 (90.5)	0.470	0.493
Scholarity > 13 years	14 (41.2)	26 (61.9)	2.460	0.117
Employed	14 (41.2)	21 (50)	0.287	0.592
	Mean (*SD)	**Mean (SD)**	**t**	**p**
Age	40.03 (12.77)	40.95 (11.59)	0.330	0.742
Socio-environmental status	**n, %**	**n, %**	χ^2	**p**
Conjugal family	2 (5.9)	2 (4.8)	0.000	1.000
Residential facility	5 (14.7)	5 (11.9)	0.000	0.986
Diagnostic features				
Schizophrenia	15 (44.1)	14 (33.3)	0.525	0.469
Delusional disorder	4 (11.8)	6 (14.3)	0.000	1.000
Schizoaffective disorder	8 (23.5)	17 (40.5)	1.737	0.188
Psychiatric comorbidity	6 (27.6)	5 (11.9)	0.144	0.704
Alcohol use	16 (47.1)	18 (42.9)	0.018	0.893
Substance use	4 (11.8)	15 (35.7)	4.542	0.033
Medical comorbidity	3 (8.8)	3 (7.1)	0.000	1.000
	Mean (SD)	**Mean (SD)**	**t**	**p**
Age at onset	25.53 (9.59)	25.41 (7.87)	-0.058	0.954
Therapeutic features	**n, %**	**n, %**	χ^2	**p**
LAI†	18 (52.9)	20 (47.6)	0.053	0.818
Atypical LAI	7 (38.9)	11 (55)	0.446	0.504
Psychopathological characteristics (PANSS‡)	**Mean (SD)**	**Mean (SD)**	**t**	**p**
Positive scale	21.56 (6.53)	21.26 (6.67)	-0.195	0.846
Negative scale	22 (6.27)	17.57 (6.33)	-3.045	0.003
General psychopathology scale	49.53 (10.13)	43.10 (9.67)	-2.822	0.006
PANSS‡ total score	93.09 (16.49)	81.93 (18.05)	-2.785	0.007

*Notes: *SD: Standard deviation; †LAI: Long acting injectable antipsychotics; ‡PANSS: Positive and Negative Syndrome Scale*

tions. Second, part of the sample was on psychotropic medications at the recruitment which could have interfered with the level of gravity of some of the symptoms evaluated by the scales since several authors reported that the use of second-generation antipsychotics might worsen OCS [3]. Moreover, in consideration of the observational nature of our study the discussion of possible causal interactions remains speculative.

The high prevalence of OCS in the present sample of acute inpatients diagnosed with schizophrenia spectrum disorders suggests the need for evaluating the presence of OCS as a distinct psychopathological domain in schizophrenic patients. The higher severity of the overall symptomatology, with particular relevance of negative and general psychopathology symptoms, could differentiate schizophrenia spectrum patients with OCS in a distinct subgroup, with the need of identifying targeted strategies in order improve quality of life and functioning of such patients.

Conflict of interest

The Authors declare to have no conflict of interest.

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Original article

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Effect on post-stroke anxiety and depression of an early neuropsychological and behavioural treatment

Summary

Objectives

Post-stroke depression and anxiety are common psychiatric symptoms that can interfere with the rehabilitation. This study aimed to examine the depression and anxiety levels in the sub-acute phase and at 2 months post-stroke evaluation in a sample of 50 inpatients. This study also evaluated the efficacy of an early neuropsychological and behavioral intervention on anxiety, depression and cognitive functioning. In addition the relationships between anxiety, depression and cognitive functioning were examined.

Methods

A convenience sample of 50 post-stroke patients was enrolled from an inpatient rehabilitation study. They completed the Mini Mental State Examination (MMSE), the Raven's Colored Progressive Matrix (RCPM), the Verbal Memory Span and Visuospatial Memory Span, the Hamilton Rating Anxiety Scale (HAM-A), and the Hamilton Rating Scale for Depression (HAM-D) in the subacute phase (T1) and 2 months after stroke (T2). Medical information about the stroke and its characteristics was provided. The neuropsychological part of the treatment was aimed to develop compensating skills, awareness of limits and improvement of cognitive deficits. The behavioral part of the treatment was aimed to teach appropriate behaviors and prepare social reintegration. A control sample of 50 orthopaedic patients well-matched for age, gender, and level of education was enrolled. The two sample were compared for anxiety, depression, and cognitive functioning at T1 and T2.

Results

Results showed significant differences between patients after stroke and control sample in anxiety and depression. These results persisted at two months after stroke evaluation. Moreover, the neuropsychological and behavioral treatment was efficacy to improve the cognitive functioning and reduce PSD and PSA.

Conclusions

Findings highlight the importance of anxiety and depression in post-stroke patients in the early phases. Multidisciplinary approach are necessary for a better functional outcome.

Key words

Anxiety • Cognitive impairment • Depression • Stroke • Treatment

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Introduction

Post-stroke depression (PSD) occurs frequently in stroke rehabilitation worsening the functional outcome. Past studies have investigated the prevalence for major depression founding a rates of 19.3% among hospitalized patients and 23.3% among outpatient samples [1]. PSD is a relevant complication of stroke because is associated with greater disability as well as increased mortality [2]. Cognitive disorder is another factor associated with PSD at follow-up [3]. However the relation between depression and cognitive impairment is still unclear [4]. Results of a recent study have shown that the

severity of depressive symptoms assessed in the acute phase or 4 years after stroke is not a predictor of the length of survival at 18-year follow-up [5]. In addition, PSD and others mood disorder post-stroke growth in prevalence over the initial weeks post-stroke, suggesting their dynamic nature in the early stages [6]. It could reasonable to hypothesize that PSD is a multi-factorial and complex phenomenon. A more deeply knowledge of the mechanism of PSD may lead to tailored treatments. Hence, several studies have examined the underlying mechanisms with often contradictory results. Literature regarding therapy did not product reliable results and only a minority of patients are properly treated [7].

PSD has been identified in the clinical practice for more than 100 years and the most of past studies have focused on depressive symptoms. Nonetheless depression is not the only psychiatric symptom after stroke. Recently literature has begun to recognize and explored the post-stroke anxiety (PSA). The prevalence for any anxiety disorder in post-stroke patients is common with a rate of 22% and phobic disorder as the predominant diagnosis [8]. Anxiety and depression persist at 5-year follow-up in about a third of post-stroke patients [9]. However risk factors for anxiety and effects with depression remain still unclear. On one hand PSA has a negative effect on quality of life of post-stroke patients; on the other this negative effect is independent from depression [10].

Psychological interventions could help patients and clinicians to incorporate emotions into conversations and recognize decisional competences [11]. The relationship between clinicians, patients and their caregivers are often characterized by difficulties to recognize negative emotions [12]. Findings from other fields of research pointed out that the presence of a clinical psychologist as consultant can improve diagnostic and therapeutic practices [13]. Regarding non-pharmacological treatment, evidences from the literature have highlighted the efficacy of relaxation training to reduce anxiety after stroke [14]. Nonetheless there are few studies that have examine the efficacy of psychotherapy and pharmacotherapy treatments for PSA. A recent study has evaluated the clinical efficacy of a neuropsychological intervention for post-stroke patients and their relationship to cognitive functioning in the early stages after stroke [15]. Results pointed out the correlation between PSA and PSD. In addition the neuropsychological intervention was efficacy on anxiety but not on depression at 2 months post-stroke evaluation.

The first aim of this study was to examine the prevalence of PSA and PSD in a sample of patients following a stroke in the subacute phase and two months from the onset. The second aim of this study was to evaluate the efficacy of two months of early neuropsychological rehabilitation on anxiety, depression and cognitive functioning.

Materials and methods

Study design and participants

Participants with a primary diagnosis of stroke and admitted to the "Villa Sofia" Rehabilitation Institute of Acireale, Italy, were enrolled in this study. In addition, a control sample of orthopaedic patients admitted to the same rehabilitation unit for two months of treatment were enrolled. Participants of this study were selected to achieve group-wise matching on average chronological age, level of education, and balanced gender percentage. Inclusion criteria for stroke patients were first-ever stroke; sufficient comprehension assessed with neuropsychological tests; able to be assessed. Inclusion criteria for orthopaedic patients were no stroke in anamnesis; sufficient comprehension assessed with neuropsychological tests; able to be assessed. Exclusion criteria both for stroke sample and orthopaedic sample were a positive anamnesis for any psychiatric disorder included in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [16].

Ethical approval was obtained from the Ethics Committee of the hospital. Patients were included in this study from January 2018 to June 2018. An expert neuropsychologist explained that consent was voluntary and that participation in this study did not influence the rehabilitation program. Finally, informed written consent was obtained was obtained from participants.

At the time they were first approached, participants were about 10 days post-stroke. Patients were evaluated in the sub-acute phase and at 2 months post-stroke. This period was chosen because cognitive functioning enhanced significantly between 2 and 6 months. The baseline evaluation was made before the beginning of the neuropsychological intervention. Neuropsychological assessment was conducted according to standardized procedures. Clinical and radiological parameters were obtained from medical records. The assessment was administered by an expert neuropsychologist and took about 120 minutes to complete.

In total, 109 patients were contacted in this study. Fifty-five patients were admitted at the rehabilitation center with a primary diagnosis of stroke. Fifty-four patients were admitted with an orthopaedic diagnosis. Regarding post-stroke sample, 5 patients declined further participation in the study after the first assessment. Regarding orthopaedic sample, 4 patients declared that were not interest to participate at this study.

Measures

The *Hamilton Rating Anxiety Scale (HAM-A)* [17] was used to assess anxiety symptoms during hospital stays. The HAM-A is administered by an interviewer who asks a semi-structured series of questions correlated to symptoms of anxiety. Seven of the items specifically assess

psychic anxiety and the others seven assess somatic anxiety. The interviewer rates the individual on a 5 point scale for each of the 14 items ranging from 0 (not present) to 4 (extreme symptoms). The interview and scoring takes about 15 minutes. Higher scores indicate high levels of anxiety.

The *Hamilton Rating Scale for Depression* (HAM-D) [18-19] was used to rate severity of depression. The HAM-D consists of 21 items and it is based on the clinician's interview with the patients and probes symptoms such as depressed mood, feelings of guilt, thoughts of suicide, sleep disturbances, and weight loss. The rater enters a number for each symptom that ranges from 0 (not present) to 4 (extreme symptoms). The interview and scoring takes about 15 minutes.

The *Mini-Mental State Examination* (MMSE) [20-21] was used to measure cognitive status. The *Raven's Colored Progressive Matrices task* (RCPM) [22-23] was used to assess abstract and logical reasoning. The RCPM consists of 36 items (three sets of 12) and involves completing a pattern or figure with a part missing by choosing the correct missing piece from among six alternatives. Patterns are arranged in order of increasing difficulty.

The *Verbal Span* and the *Visuospatial Span* (Corsi's block-tapping test, verbal span) [24] were used to assess the short-term memory. Specifically, the Verbal Span subtest is a short-term auditory memory task which requires the subject to repeat increasingly longer series of words. The series range in length from two to nine words. Two trials are presented for each series, and the subtest is discontinued after failure on both trials for a series. The Corsi block-tapping test was used to assess visuospatial memory and working memory. The examiner taps the blocks starting with sequences of two cubes. The subject has to reproduce a given sequence by tapping the blocks in the same sequence he see. If two sequences are correctly reproduced the sequence length increases by one item. The procedure ends when two sequences are reproduced erroneously. The Prose Memory task [24] was used to measure the long-term verbal memory. In this test, memory for details of a prose story is tested. The subject is asked to tell the story from memory and after 15 minutes to repeat the story to assess delayed prose recall.

Statistics

Statistical analysis was performed using IBM SPSS Statistics version 22 (IBM Corporation, Armonk, New York, USA). Descriptive statistics, such as the mean and SD of the variables, are reported below. The data showed a good range of variance and there were no univariate outliers for the variables considered.

An independent t-test was used to compare the levels of anxiety and depression in the sub-acute phase and at 2 months post-stroke with a control sample. This period was taken because cognition improved significantly between 2 and 6 months post-stroke and patients could engage thought acute care and rehabilitation [25]. The standardized mean difference effect size statistic was used to compare measures of anxiety and depression between the two samples at T1 and T2. An effect size value of 0.20 is considered small, a value of 0.50 is considered medium, and a value of 0.80 is considered large [26].

A paired t-test was used to assess the efficacy of rehabilitation intervention for stroke patients at T1 (subacute phase of stroke) and T2 (after 3 months).

The Pearson correlation coefficients were calculated between the T1 and T2 evaluations. Correlation coefficients were also calculated between the baseline evaluation and the changes over time between T2 and T1 (T2 minus T1).

In addition, the standardized mean difference was used to compare the magnitude of treatment effect for post-stroke patients.

Comparisons were computed with Student's t-test and the Bonferroni correction. Significance levels were set at $p < 0.05$ and $p < 0.01$.

Neuropsychological and behavioural treatment

Neurological patients underwent 45 minutes of neuropsychological rehabilitation four times weekly for two months. Neuropsychological treatment was aimed at developing compensating skills, recovery of cognitive deficit, awareness of limits and behavioral interventions. All cognitive exercises were planned after a first neuropsychological evaluation, where results defined different neuropsychological profiles. We proposed table exercises and cognitive rehabilitation software to stimulate selective language disorders, attention deficit disorders, apraxia, memory problems, and executive function disorders. To modify behavioural disorders demonstrated by patients, we also proposed behavioural interventions with the aim of teaching the patients to eliminate inappropriate behaviours and providing the means to prepare social reintegration designed to achieve a satisfactory degree of independence and the recovery of relational skills. After cognitive and behavioural treatment, the patients underwent a final neuropsychological evaluation in which changes in cognitive functions and any improvements achieved were recorded.

Results

Demographic and clinical characteristics

Socio-demographics and medical characteristics of the samples are presented in Table I. All patients were native Italian speakers and Italian nationals. The post-

TABLE I. *Baseline data of post-stroke patients and orthopaedic patients.*

	Post-stroke patients (n = 50) (mean ± S.D.) (min-max)	Orthopaedic patients (n = 50) (mean ± S.D.) (min-max)	t (df = 98)*
Age, years	60.14 ± 14.66	55.04 ± 17.07	1.60
	(21-81)	(21-81)	
Education, years	10.26 ± 3.83	10.26 ± 4.31	0.00
	(5-17)	(5-17)	
Gender			
Male	33 (66%)	28 (56%)	
Female	17 (34%)	22 (44%)	
Type of cerebral lesion			
Ischemic	32 (64%)		
Hemorrhagic	8 (16%)		
Neoplastic	5 (10%)		
Vasculopathy	3 (6%)		
Head injury	2 (4%)		
Hemispheric side of lesion			
Right hemisphere	34 (68%)		
Left hemisphere	14 (28%)		
Bilateral	2 (4%)		
Location of lesion			
Internal/pons/capsule	13 (26%)		
Frontal-parietal cortex	10 (20%)		
Frontal lobe	9 (18%)		
Temporal lobe	5 (10%)		
Fronto-temporal cortex	4 (8%)		
Parietal lobe	4 (8%)		
Cerebellum	3 (6%)		
Parieto-occipital cortex	1 (2%)		
Temporal-parietal cortex	1 (2%)		

** $p < 0.05$; ** $p < 0.01$*

stroke sample consisted of fifty post-stroke patients, 66% of the post-stroke sample was male, the mean age was 60.14 (SD = 14.66), and the level of education in years was 10.26 (SD = 3.83). Of the fifty post-stroke patients, 32 (64%) had an ischemic stroke and 8 (16%) an hemorrhagic stroke. Moreover, 5 (10%) patients had a neoplastic lesion, 3 (6%) a vasculopathy lesion and 2 (4%) an head injury. With respect to side of lesion, 34 (68%) patients had a right hemisphere lesion and 14 (28%) a left hemisphere lesion. Finally, 2 (4%) patients had a bilateral lesion. Regarding the location of lesion, 13 (26%) patients had an internal/pons/capsule lesion, 10 (20%) patients a frontal-parietal lesion, 9 (18%) a frontal lobe lesion, 5 (10%) a temporal lobe lesion, 4 (8%) a fronto-temporal cortex lesion, 4 (8%) parietal lobe lesion, 3 (6%) a cerebellar lesion, 1 (2%) a parieto-occipital cortex, and 1 (2%) a temporal-parietal cortex.

The control sample consisted of fifty orthopaedic patients, 56% was male, the mean age was 55.04 (SD = 17.07), and the level of education in years was 10.26 (SD = 4.31). No differences were found between post-stroke sample and control sample for the mean age and level of education.

TABLE II. *Results of t-test for independent samples for post-stroke sample at subacute phase (T1) and after 2 months (T2) and control sample of HRSA and HRSD.*

Variable	Post-stroke sample (n = 50) M (SD)	Control sample (n = 50) M (SD)	Mean difference	Std. error difference	t (df = 98)	d
HAM-A T1	22.96 (1.77)	12.64 (3.98)	10.32	0.62	16.76**	3.35
HAM-D T1	22.20 (2.67)	7.84 (4.64)	14.36	0.76	18.98**	3.79
HAM-A T2	18.20 (2.13)	10.16 (2.57)	8.04	0.47	17.02**	3.40
HAM-D T2	18.20 (2.52)	6.88 (4.07)	11.32	0.68	16.70**	3.42

*Notes: * p < 0.05**; p < 0.01; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale*

Comparisons between post-stroke sample and control sample at subacute phase and after 2 months

Table II shows the mean scores and results of the t-test for two independent samples. Results showed significant differences (with Bonferroni correction for four comparisons, the new critical alpha levels was 0.01) between post-stroke during subacute phase (T1) and control samples (p = 0.001). In addition the mean effect size between the two samples was large for anxiety and depression (respectively, d = 3.35 and d = 3.79).

As shown in Table II there were significant differences for the two samples after two months with post-stroke patients scoring higher than controls (p = 0.001). Moreover the mean effect size between the two samples was large both for anxiety and depression (respectively, d = 3.40 and d = 3.42).

Hence, post-stroke patients showed higher levels of anxiety and depression than control sample both at T1 and T2.

Efficacy of neuropsychological and behavioural treatment for post-stroke sample

Table III shows results of the paired t-test, the correlation coefficients and the effect size for post-stroke sample among the subacute phase and after two months. Results of paired t-test (with Bonferroni correction for 7 comparisons, the new critical alpha level was 0.007) showed significant differences for all the variables considered. The post-stroke patients showed higher scores on cognitive functioning after two months of treatment. On the other hand, the anxiety and depression levels decreased after the treatment.

These results were confirmed by the mean effect size between the two evaluations for post-stroke sample. The largest effect size was for anxiety (d = 2.431) and the smallest for the MMSE score (d = -0.901). However all the variables considered showed large effect size.

Moreover the results showed high correlation coefficients between the subacute phase and after two months of treatment. The higher coefficient was for the MMSE (r = 0.70; p < 0.01) and the lowest was for the Prose Memory task (r = 0.35; p < 0.01). The anxiety and depression scores showed large correlation coefficients between the subacute phase and two months after stroke (respectively, r = 0.41, p < 0.01 and r = 0.51, p < 0.01).

Table III also shows correlation coefficients between the baseline evaluation and the changes after the neuropsychological intervention. All the evaluated variables at baseline were negatively correlated with the change over the time. Specifically, the higher coefficient was for the MMSE (r = -0.71; p < 0.01) and the lowest was for the Prose Memory task (r = -0.38; p < 0.01).

Discussion

Depression and anxiety after stroke are associated with poorer quality of life and compliance to the rehabilitation. In fact, PSD and PSA are relevant symptoms in patients after stroke that can worse the functional outcome. Past studies have deeply examined PSD and the impact on rehabilitation (Robinson, 2003). Recently some researchers have also investigated PSA but there are still not clearly evidence about treatments. The first aim of this study was to examine the PSD and PSA levels in a sample of patients following a stroke. The first evaluation was made in the subacute phase comparing post-stroke patients with a control sample of orthopaedic patients. Results have shown that post-stroke patients have higher scores for both anxiety and depression comparing with control subjects. These results were confirmed at two months evaluation with post-stroke patients scoring higher than controls. In a previous study similar results were found, even if anxiety level was higher than depression level [15]. These results can be explained by the characteristics of the two sample influencing PSD and PSA. Nonetheless, PSD and PSA represent a relevant problem that must be addressed in the rehabilitation. A limit of the past studies was to consider separately anxiety and depression. Another limit of the scientific literature regards the presence of few studies

TABLE III. *Results of t-test, correlations at subacute phase of stroke (T1) and after two months (T2), and T1-T2 change of neuropsychological functioning, anxiety, and depression in post-stroke sample (n = 50).*

Variable	T1 M (SD)	T2 M (SD)	Mean difference	Std. error difference	R	R T1-T2 change	t (df = 49)	d
MMSE	23.68 (4.27)	27.00 (2.99)	-3.32	0.43	0.70**	-0.71**	-7.69**	-0.901
RCPM	21.82 (7.16)	28.24 (5.39)	-6.42	0.90	0.52**	-0.69**	-7.15**	-1.013
CORSI	1.66 (0.69)	2.48 (0.61)	-0.82	0.10	0.44**	-0.60**	-8.39**	-1.259
VERBAL SPAN	1.76 (0.71)	2.46 (0.68)	-0.70	0.10	0.53**	-0.53**	-7.30**	-1.007
PROSE MEMORY	1.42 (0.54)	2.44 (0.73)	-1.02	0.11	0.35**	-0.38**	-9.72**	-1.589
HAM-A	22.96 (1.77)	18.20 (2.13)	4.76	0.30	0.41**	-0.42**	15.70**	2.431
HAM-D	22.20 (2.67)	18.20 (2.52)	4.00	0.36	0.51**	-0.54**	11.00**	1.541

*Notes: * p < 0.05**; p < 0.01; MMSE: Mini-Mental State Examination; RCPM: Raven's Colored Progressive Matrix Task; CORSI: Corsi block-tapping task; VERBAL SPAN: Verbal Span subtest; PROSE MEMORY: Prose Memory task; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale*

on the efficacy of intervention. For this reason, the second aim of this was to evaluate the efficacy of a two months early neuropsychological and behavioral intervention to decrease anxiety and depression levels and to enhance cognitive functioning. The neuropsychological part of the treatment was aimed to develop compensating skills, awareness of limits and improvement of cognitive deficits. The behavioral part of the treatment was aimed to teach appropriate behaviors and prepare social reintegration. Results showed that the early intervention was efficacy to reduce PSA and PSD at two months evaluation. Results also showed that there was a significant improvement of the cognitive deficits evaluating at subacute phase. Moreover, the baseline evaluation of the variables is negatively correlated with the changes after the neuropsychological and behavioral intervention. At this regard the role of the values at baseline to predict the outcome should be investigated by the future research. Anyway the evaluation of cognitive functioning and emotional distress is needed for each patient following a stroke. As stated there are only few guidelines available for treatment of post-stroke patients with the most of patients that are not adequately treated [7]. Results of this study suggest that early neuropsychological and behavioral treatment could be useful to improve the rehabilitation outcome. However interventions of this kind must be considered only a part of a multidisciplinary rehabilitation program for post-stroke patients. If confirmed by future research, the results of this study could have implications in clinical practice. A supportive and time-limited group intervention [27-28] could helpful to decrease negative emotions and fostering mentalisation [29] after the early stages after stroke. Moreover time auxiliary therapies should be considered to enhance efficacy of multidisciplinary intervention [30].

In addition, future research must be addressed to examine psychological factors that can influence anxiety and depression levels after stroke. Findings from other fields of research have shown that metacognition is strictly associated with anxiety and depression and that can be considered as a vulnerability factor that pre-exist emotional disorders in patients [31-33], their caregivers [34], and clinicians [35]. The results of this study may be affected by a number of limitations that should be addressed by future research. First, the sample was small and all patients were consecutively recruited in a rehabilitation center. Hence the sample may not be representative of the clinical population of post-stroke patients. Second, the sample was heterogeneous for medical variables. We did not evaluate the influence of such variables as type and location of cerebral lesion. Third, there are some additional variables whose role we did not consider, such as social and family support, personality factors. For these reasons, this study needs replication to address the role of other variables and longitudinal data to examine the nature of the relationships found in this study.

Conflict of interest

The Authors declare to have no conflict of interest.

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Quantum neurobiological view to mental health problems and biological psychiatry

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Without exception, what we call schizophrenia is a strategy devised to live in a situation where life is unlivable. Mystics and schizophrenics are in the same ocean, but where mystics float, schizophrenics sink… Madness need not always be understood as a collapse of personality. It can also be thought of as a great step forward. As much as captivity and existential death, it can carry the seeds of liberation and rebirth…

Ronald D. Laing
(1927-1989) Psychiatrist

Summary

Psychopathology is the state of the normality of daily life being affected by a deviation from what is considered normal. The most important of these are measurements of statistical deviation from normal, disruption in coping with social relationships, disruption in the perception of reality, and sleeplessness. Their importance is not in that they occur sporadically or rarely, but in their persistence and the diagnosis of psychopathology. With this approach, more average behavior is accepted as ideal. With a more systematized diagnosis, a psychiatric condition, in order to be called pathological, must show deviance from the ideals of feeling, emotion and behavior, it must be related to negative feelings, it must disrupt daily functions, and it must constitute a danger to the persons themselves or to those around them. In the biological approach, psychopathologies are reduced to neurons, neural nets, synaptic pathologies and neurotransmitters. However, the basis of psychopathologies can today also be demonstrated at much deeper levels. When these deep structures are considered, a new viewpoint emerges, which can be called super reductionism or a quantum psychopathological approach. In this article, information on quantum psychopathology, which is still in its infancy, will be reviewed, and psychopathologies will be considered with the somewhat speculative quantum physical approach.

Key words
Psychopathology • Quantum physics • Psychiatric diseases • Mood disorders • Schizophrenia

Introduction

Engel proposed the bio-psycho-social model of psychopathology starting from classical physical analogies [1]. The popularity of this idea slowly grew and became more established when the theory of nerve cell nets came to prominence. According to this, abnormal communication between nerve cells in the brain are the cause of psychiatric illness. For example, Hoffman connected schizophrenia in this way to a parasitic attractors [2]. Hoffman's paper marks beginning of the neural modelling of schizophrenia. Some other researchers have connected indirect brain dynamics with the nerve cell nets theory and, connecting it to the excessive effects of dopamine, have proposed a model to explain schizophrenia [3]. In this way, each synaptic connection causes a chemical disruption, and schizophrenia is reduced to an increase in dopamine or a reduction in glutamate in spe-

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cific areas of the brain. However, this clinical picture, reduced to nerve communications, does not improve in all directions and in all patients [4]. In fact, it is unclear whether the proposed synaptic imbalance is an epiphenomenon of the clinical picture or whether it is the cause of the illness [5]. However, the diagnosis of psychopathology is different from the viewpoint of psychodynamic, behavioral and cognitive psychology. Whereas from a psychodynamic point of view subconscious conflicts form between basic desires and limitations (libidinal balance and hydraulics), from the point of view of behaviorism, certain formal behaviors come about as a result of reinforcement and penalization. From the point of view of cognitive psychology, negative beliefs about individuals themselves and others and the outside world lead to negative behavior and feelings.

So far until today, the disease model valid for psychiatric illnesses has been reduced to the basis of a disruption in brain chemistry. From this chemical disruption emerge disruptions to differing extents in feelings, thoughts and behaviors. It is accepted that with a trend arising for genetic reasons, added to environmental reasons, illness caused by vulnerability in a person brings out the clinical phenotype. Another model of the appearance of illness is the diathesis-stress model, according to which illness occurs when a threshold is passed and a pressure system breaks down.

Quantum psychiatry and psychopathology: a short history

The term quantum psychopathology (QPP) was first used by Donald Mender, of Yale University. In June 2008 he planned an international meeting under the name of *Quantum Paradigms of Psychopathology*, and recommended discussion on whether quantum physics and brain theories provided a new viewpoint on psychiatric illnesses such as schizophrenia, bipolar disorder or hallucination, and the possible relation to psychopathologies. Later, following the Fano (Italy) conference in March 2012, and the third *Quantum Paradigms of Psychopathology* meeting in Palermo, in Sicily, Italy in April 2013, and the Palermo Declaration was published. New scholarly papers opening up fresh perspectives on the potentially key role of quantum neurodynamics in mental illness have been generated in the wake of interchanges in Fano (Italy). All these developments herald a bright future for the QPP initiative. On April 27, 2013 a core international group of investigators, offering expertise in the fields of psychiatry, biochemistry, physics, computational neuroscience, mathematics, philosophy and theology, gathered in Palermo, Sicily under the auspices of the global QPP initiative with the aim of assessing the potential relevance of quantum physics and quantum chemistry to the mapping of mind-brain relations in normal and abnormal states of consciousness applicable to humans and non-human animals. Positions taken by members of the Palermo Group have argued that [6]: recent progress of a restricted kind in mainstream consciousness research has proceeded rapidly due to dramatic technical improvements in relevant empirical research tools. Classical biophysics, which provides the paradigmatic foundation of mainstream consciousness research, has offered bountiful correlations between subjective reports of qualitative human experience and quantitative measurements of objective physical processes. However, these merely correlative advances have not at all addressed what David Chalmers has termed the “Hard Problem” of mind-brain relations by bridging what Joseph Levine has called the “Explanatory Gap” between qualitatively subjective phenomenal experience and quantifiably objective physical events [7]. So far no explanatory bridge between consciousness and corporeal neural tissue has issued from the classical biophysics of mind and brain in *Homo sapiens*, and, in research on non-human subjects precluding self-reports via human language abilities, even correlations have remained substantially elusive [8]. Quantum approaches may offer greater latitude in addressing these classical deficiencies, to the extent that at least some latent links formally exist between the qualitative dimensionality and quantitative measurability of canonically conjugate quantum observables, whereas no such formal links are required with reference to the possessed observables of classical physics [9]. Moreover, at least one interpretation of quantum measurement as formulated by John Von Neumann casts the measuring agency itself as subjectively conscious per se, in contrast to an absence of any such classical notion [10].

Quantum generalization of classical biophysics opens up the possibility that relevant brain processes may reach both beneath the scale and beyond the boundaries of discrete neurons separated by synaptic clefts. Quantum-germane structures and dynamics within the brain may include superposed dimeric tubulin conformations in the microtubular cytoskeleton spanning both intraneuronal and interneuronal spaces, ordered water in relation to cytoskeletal proteins, membrane channels and lipids together with their second messenger pipe lines to neuronal interstices, and solitons communicating along cytoskeletal routes between classical and quantum aspects of brain function. Max Tegmark’s objections [11] to the thermodynamic feasibility of such quantum structures and processes surviving thermal decoherence at biological temperatures entailing orders of magnitude comparable to those within the human skull have been thrown into doubt by the recent work which has demonstrated non-trivial quantum com-

putation in photosynthesis. The ubiquity of water, cytoskeletal tubulin, membrane lipids, and second messengers in non-human life suggests that a new biophysics, accounting for quantum-generalized processes in living tissue, may lead to future predictions about consciousness not only in human beings but also in organisms lacking any semblance of human brain architecture at the level of organized neuronal networks or "higher" [12].
The quantum wetware outlined above is more compatible with these formalistic findings than is any classical model of neural biophysics. Both quantum-logical and quantum-physical cartographies of mind and brain also promise to generate avenues for improved comprehension of neurophysics in psychopathology. Explanatory and even psychotherapeutic opportunities may emerge from considerations of superpositional logic and malattunement in primary process thinking by schizophrenic patients, of Everett's quantum ontology in the "alternate/many worlds" of psychotic perception, and of membrane and second-messenger interfaces between serotonin biochemistry and quantum-microtubular nanowire dysfunction in mood disorders. Aberrations of scale-dependent emergence in quantum thermofield phase transitions and problematic barriers to Bohmian holism may be important in multiple forms of mental illness. *We declare the following:*

Even the absence of highly complex synaptic connections among neurons does not preclude the presence of at least rudimentary phenomenal experience in organisms endowed with superposed microtubular dimers, ordered water, membrane ion channels, and/or crucial lipid raft assemblies connected to selected second messenger systems. In addition, quantum-biophysical aspects of these and/or other yet unmapped structures and related processes may prove to be potent factors in the deeper etiologies and improved treatments of psychiatric disorders.

This is the official history, but in fact an inquiry article had been published in 2000, before a name had been given to the subject [13]. Articles continue to be published considering topics such as depression, schizophrenia, bipolar disorder, hallucination, anorexia nervosa and decision-making disorders with a quantum psychopathology approach.

Why quantum psychopathology?

Until today, the brain pathology of all psychiatric illnesses has been reduced by the trend towards biological psychiatry to networks between nerve cells, to nerve cells and to synaptic imbalances in the communication between cells. However, if this is so, the end-point of nerve networks and inter-cell communication and relations is not synapses but may extend to ion canals, ions, electrons and even to a quantum field giving temporary forms to subatomic particles. Looked at this way, even if quantum psychopathology is regarded as super-reductionism, when quantum field theory and quantum physics are considered, this type of reductionism can lead to a more holistic point of view [14]. Another aspect is that quantum physics with its one-century history is relatively new compared to the three centuries of classical physics. This new quality brings a new language with it, and this has had a jarring effect on classical ways of thought. It is forcing us to change from the language and thought patterns to which we are accustomed to new forms. For example, the binary system of 0 and 1 which we have always used in the decision processes of classical physics has given way to the quantum bit or Qbit, as also in computer processing and symbolic logic, and we have found that the choices are not only between 0 and 1, but 0, 1 and both 0 and 1 at the same time. This quantum bit is known as a Qbit, and is represented as $|0\rangle$, $|1\rangle$. Unlike the classical bit or C-bit, which takes the value 0 or 1, the Qbit can take other states in addition to these two classical states – the states of $|0\rangle$, $|1\rangle$, and both differently superposed – that is, it can be in the states of both $|0\rangle$ and $|1\rangle$ at the same time [15].
Thus, Qbits show two basic states: $|0\rangle$ and $|1\rangle$. Classically, they can occur only in one of these two states, but for Qbits the possibilities are infinite. Any state can form a superposition, and the total wave function is $|\psi\rangle = a|0\rangle + b|1\rangle$, and is $|a|^2+|b|^2=1$ here. Both *a* and *b* are complex numbers. All states of a Qbit carry the structure of two-dimensional Hilbert space. If we measure whether the system is in a state of $|0\rangle$ or $|1\rangle$, the superposition collapses. The state, with probabilities of $|a|^2$ and $|b|^2$, is reduced from the basic states of $|0\rangle$ and $|1\rangle$ to one of them. Therefore, any measurement of $|\psi\rangle$ represents much more than it represents in a classic understanding. Quantum probability is a better model for human cognitive functions than classic Bayesian probability theories. The classic approach is inadequate for many subjective and behavioral states. In particular, the existence of the state of quantum superposition (in addition to the state of 0, 1, the state of 01) can provide new points of view from the angle of cognitive functions. The result of Qbits is still classic.
New analogies both in language and in quantum physics can help us to understand psychiatric illnesses. The understanding that classic physics imposes, that we are observers of everything outside of ourselves, forces us to consider the question of whether we are part of the universe. An example in quantum physics is where unobserved matter behaves as a wave, but when observed displays the behavior of a particle. In this way, quantum physics makes our understanding of the reality of the universe disappear in a puff of smoke. In the 1960s, new particles kept on being discovered; in the

1970s it was understood that these particles were energy or energy fields, and since the 1980s energy is gone and everything has become information. In this process some quantum physicists have openly doubted the reality of the universe, and have shared their ideas in books and articles.

One very strange and amazing term is entanglement. Quantum entanglement is a state in which objects are separate from each other but are still in communication. There is nothing like this in classical physics [16]. An observation or measurement which we make of one object independently affects another which may be related to it at a distance. This effect is simultaneous and the communication between them is faster than the speed of light. In general, if the quantum level is thought of as the level of small-scale particles, the concept of small does not in fact indicate a physical dimension. Quantum results have an effect over distances of meters and even light years. This phenomenon has been proven by experiment so that there is no room for argument, and there is not the least doubt of its reality. From the point of view of quantum psychopathology, entanglement may exist not only at the level of subatomic particles but also between brains [17] [18]. That is, people's feelings and thoughts may be affected not only by the network of nerve cells in their own brains but also by a bigger network of brains. This kind of an interaction may help to explain conditions such as hallucinations and thought intrusion which are seen in psychiatric illnesses.

Another concept which was long thought fictional but which has assumed an important place in academic physics publications, the multiple or parallel universes model, has shaken up our understanding of a single reality. When it is thought that there may be a small possibility of communication between the other selves in the universes which are formed whenever a choice is made, just as our viewpoint of "our self alone" will change, so our outlook on its pathologies will change. The model of multiple minds or multiple universes may help to understand "self" disorders and conflicts and indecisive selves.

Another reason for the necessity of quantum psychopathology is that quantum brain theories are becoming better understood and that it can explain higher cognitive functions such as memory, recall, consciousness, decision making and mind content. In the past three decade, quantum brain theories have been increasingly developed, and some of them have now reached the mature stage where they can be tested experimentally or falsified. If in healthy brains higher cognitive functions can be connected to a base of quantum mechanics, a natural consequence of this is that psychopathological conditions must have a place in this normal. That is, it will be a scientific approach which will fit the *zeitgeist* [19].

Quantum brain theories and psychopathology

There are many quantum brain theories which attempt to explain how normal cognitive functions appear in the physical brain. The oldest of these theories are Umezawa's quantum field theory relating to corticons in the brain [20] [21], quantum brain dynamics developed from this theory by Jibu and Yasue [22], and Vitiello's thermofield brain dynamics [23]. Another important theory besides this is Walker's quantum synaptic tunneling [24]. Another theory closely related to this one is Eccles and Beck's dendron-psychon synaptic tunneling, taking place in the dendrons [25] [26].

Stapp's quantum interactive dualism [27] and Bernroider's ion canal entanglement [28] are other theories proposed for the functioning of the normal brain. Also, one of the most written-about and discussed theories is the microtubules consciousness theory of Penrose and Hameroff [29] [30]. Even if these theories seem to be separate, looking at the details, it can be seen that they are closely related to one another, and need to be so. For example, Eccles and Beck's synaptic tunneling is not very different from that of Walker, and Eccles' interaction of brain dendrons with psychons, the basic units of consciousness, Bohm's implicate order and Umezawa's corticons are not very different basic concepts. Penrose and Hameroff's microtubular brain theory appears to be basically related to microtubules, and broad field communication between cells in the brain occurs by tunneling in gap junction areas. For Jibu and Yasue's quantum brain dynamics, the areas under the membrane in the microtubule theory is the fundamental area. As will be seen, although quantum brain theories have been proposed by different people at different times, at a basic level all these theories are in some way related to one another. However, not all theories are able to account for psychopathology, and so particular attention will be given to evidence of psychopathology which may arise from microtubular quantum brain theory [31].

The cause of many neurological diseases has been shown to be microtubule-associated protein-tau (MAP-tau) and microtubule damage. The job of a normal MAP-tau protein is to protect the structure and with it the functioning of MTs, to maintain the integrity of the inside of the cell and to form a relationship like a network with other cellular skeletons. The short function of MAP is to stick the parts of the cell together like a glue. In the brains of adult people, there are six types of MAP-tau protein, and in many devastating brain diseases it is damaged by combining with phosphorus. It loses its functioning as a result of this damage, and breaks down into a hard and indissoluble material inside the nerve cells. In this way, both with the loss of function and the breakdown, nerve cells lose their function and their integrity. Some of these degenerative brain diseases

have even begun to be examined under the name of tauopathies because of these disease-causing mechanisms. Among these MAP and MT-related degenerative diseases, which are neurological but often have a neuropsychiatric element, can be counted Alzheimer's disease, Niemann-Pick disease, fronto-temporal dementia, progressive supranuclear paralysis, Parkinson's disease, Lewy body dementia, Huntington's disease, Creutzfeld-Jacob disease, corticobasal ganglionic degeneration (CBGD) and Down's syndrome [32].

In Alzheimer's disease, in which intermittent fluctuations in consciousness and in particular short periods of memory loss and reduced attention are seen, abnormalities have been found in MAP-tau proteins. The genes coding the MAP-tau protein is on chromosome 17. These proteins are normally located on MTs and are attached to them. In this normal condition, there is a union of MAP-tau proteins and MTs. MAP-tau proteins preserve the structural integrity of MTs. Also, apoprotein E (ApoE) has the function of carrying serum cholesterol in the blood. The gene coding ApoEs is located on chromosome 19. It has different sub-units: apo-E2, E3 and E4. Apo-E2 and E-3 protect the MAP-tau proteins attached to MTs, and excess phosphorus, disrupting the functioning of MAP-tau, prevents bonding (*hyperphosphorylation*). Working in the other direction, ApoE-4 causes phosphorus to bind to phosphorus-adding enzymes and as a result of this addition separates MAP-tau proteins from MT [33]. The separated tau proteins bind with other tau proteins which are free in the environment or which have become separated, and form paired helixes. There are different types with different names according to the dominance of their clinical characteristics. Their clinical appearance is different, and they can have positive (hallucination, thought disturbance) or negative (blunted affect, social withdrawal) symptoms.

Auditory hallucinations are often seen in schizophrenia (SCZ). These are generally religious and warning. Some are in the form of commands. Males generally hear them as commands, while females hear them as criticism [34]. External voices are sometimes heard by 30% of normal people, but these are not insistent. Visual hallucinations are also often observed. Thoughts occur which are contrary to logic and common sense [35]. Thoughts must accord with syntax, semantics, logic and emotional rules. SCZ patients in the early stages try to exert control over their thoughts and for this reason their thought processes slow as they try to impose conscious control over their subconscious thoughts.

SCZ was classically described as split personality. However, the splitting or break-up is not only of the person's own personality, but also of the relationship between this personality and the outside world or objects. People with SCZ feel that they themselves and the reality of the world are different, confusing, uncertain or foreign. The characteristics of objects in the outside world cannot be defined or connected to each other. Because they have lost all of their internal locations, they also lose the defined meanings which they carried for cognitive life. SCZ patients have abnormal and different experiences of the outside world. Hallucinations arise from the different evaluation of internally formed experiences such as thoughts and external reality. Therefore, it is suggested that this disease involves a disorder of "self-monitoring". Once our mental states in daily life are formed, they do not remain there: the state of our mental self in the "now" is a continuation of a previous mental state, and our current self is the precursor to states of self which will form later. This continual stimulation awakens in us a feeling of wholeness and continuity, and at the same time gives us a sense of the flow of time. Mental events are in constant interaction with visual, auditory, tactile, deep sensory and olfactory stimuli coming from the outside world. In this way, internal mental states combine with bodily sensations and produce a localization of self in the body. When I have the intention to move my hand or arm, the combination of my internal mental state and the deep sensation that results at the time of my arm movement with my mental processes creates the feeling of the self in my body.

SCZ is evaluated by some people as "disorders of self or disorders of the boundaries of self". However, the self here and the "ego" of psychoanalysis are not the same thing. As described above, "self" relates to the internally and externally formed selves in the body. It is suggested that in sensory breakdowns or irregularities in time category, boundary breakdowns in irregularities in the category of object, and breakdowns in causality, SCZ psychoses must be mentioned. For example, SCZ patients often talk about problems with their "selves": "I feel that this thought is not my own, it's not me thinking my thoughts, there's a close relationship between these objects and me, my thoughts can affect objects and it's like that because I thought it, I myself am not real, there's a glass wall between me and everything else, time has disappeared…" etc.

Mental life exists primarily as awareness of present time. This awareness of now is not experienced as arising from mental processes which are not of the present moment but of the past. Awareness of the present continues without attachment to the past and without being affected, or only weakly, by what will happen later. This disintegration in internal time causes experiences described by many SCZ patients as an "extended or broadened present". Because of the disintegration of the connection between body and self, a SCZ patient's actions are experienced as produced only to a small

extent by the person himself and more often by others. Therefore, SCZ is not only the breakup of self and personality, but also the separation of self and the reality of the outside world. Integrated unity breaks down. It is for this reason that the term "lack of wholeness" has been proposed for SCZ. It is for this reason that some patients have a fixed idea that their thoughts are controlled by others. The feeling of being controlled by others weakens the self [36].

Perception is founded on three components: sensory input, the internal product of concepts and experience or censorship. There is a mutual interaction between these three and in SCZ the balance between them is upset. Rather than a breakdown of the censorship which protects the brain from the outside world, internal conceptualization appears with the breakdown of internal correction mechanisms interacting with sensory data coming from the outside world.

Quantum neuropathology in schizophrenia: microtubules

There is a high genetic disposition for SCZ and bipolar disorder: the concordance with monozygotic twins is 40%. However, the phenotype of the disease, that is its clinical appearance, varies. The change from genotype to phenotype with polygenetic factors (SNP, single nucleotide polymorphism) is not deterministic, and is quantum probabilistic [37]. When searching for a relationship between the two, at least genetic relationships can be looked at as a common point relating both SCZ and MT. Many genes have been found to be related to SCZ. These can be grouped as the genetically related structures DISC-1 (disrupted-schizophrenia-1), NR-1 (neuroreguline 1-SNP), DYSB-1 (dysbindin-1) and STOP (Stable Tubule Only Peptide).

DISC-1 has important functions particularly in protein-protein interactions. It has an effect on the cellular skeleton by way of dynein. Dynein performs the function of transport over MTs, and functions in cell migration, the growth of cell extensions and the formation of axons. DISC-1 has functions at critical stages in brain development, in important nerve cell differentiation, proliferation and network formation in the mother's womb. It is found in large amounts in the brain in the dentate gyrus and the hippocampus. The DISC-1 gene is a risk factor for SCZ, BPB and recurring major depression. It normally allows neural development, plasticity, dynein movement along the MT, migration, proliferation and actin filament configuration [38]. The structure of the MT matrix and the inside of the cells is directly connected by actin filaments to the nerve cell membrane. The actin filaments fill spiny dendritic projections and the positive ends of MT2s extend to these regions [39]. The actin filaments, especially the dendritic spines, are very elastic and play an important role in learning and memory functions. MT tubulin expression is disrupted in SCZ by DISC-1 gene variations (beta-3 and delta-1) [40]. In knockout rats, neural migration and dendritic branching are reduced [41].

Six abnormalities in the Neuroregulin-1 gene have been reported in SCZ. They all have functions relating to the cellular skeleton. It enables cell proliferation, migration, neurite growth, synaptogenesis, maturation and myelinization [42].

The Dysbindin-1 gene (*DYSB-1*) increases the risk of SCZ. It is related to MT, and is found in the terminations of axons, which are the extensions of nerve cells. It regulates the secretion of the neurotransmitter GLU. It is connected with NR-1. It functions in neural development and plasticity, and a deficiency disrupts cellular structure [43].

The STOP (Stable Tubule Only Peptide) gene has been found to appear predominantly in animals with intercellular synaptic dysfunctions and behavioral problems similar to SCZ. It ensures the structural integrity of *microtubule*-associated proteins (MAPs). It is one of the best models of SCZ, and regulates antipsychotic treatment and behavioral problems. When STOP is present, it binds to MT, and prevents the tubulins from breaking up. When this gene is removed, atypical behaviors occur and this is accepted as a successful animal model of SCZ. In rats without the STOP gene, deterioration occurs in recognition and long-term memory. This resembles memory deterioration in SCZ [44]. At the same time, as glutamate levels fall as a neurotransmitter in their brains, there is an increase in dopamine [45]. When MT stabilizing drugs and antipsychotics are given to rats without this gene, they show a better pattern of behavior [46].

In schizophrenia patients, disruptions in the concentrations in the brain of MT and MAP have been found. In SCZ, a reduction in MT in the anterior limbic system has been shown, and MAP-2 is reduced in SCZ in the prefrontal, subiculum and entorhinal cortex [47]. Another developmental thought is that neurons have not been able to properly form the proliferation area of the cortex and the formation of further cortical layers. In the frontal cortex and the subcortical white matter, they detected an increase in the NADPH-diaphorase-positive nerve cell density. This study is in accordance with the observation of an increase MAP in the white matter of the front brain [48].

Antipsychotics, which are frequently used in SCZ, are effective over MT and MAP. It has been shown that antipsychotics increase the production of MAP [49], they protect the neuroskeletal structure from oxidative stress [50], they prevent MT swelling in cell cultures [51], and that haloperidol and clozapine perform synaptic reorganization in MTs [52 53].

Quantum neuropathology in mood disorders

A reduction of serotonin in the brain causes a clear reduction in MAP-2. In rats, when levels of MAP-2 and alpha-tubulin levels fall in the hippocampal neurons, social isolation and recognition deficiencies occur [54]. In SCZ also, defects in social interaction and the perception of social clues are an important characteristic of the disease. Plasticity decreases in animals in which shock-learned unhappiness or depression forms a similar picture. MAP-2 is reduced and this reduction is partly reversed by antidepressant treatment [55]. In animals subjected to chronic unexpected stress (depression), acetyl tubulin increases (it makes stabilized MT) and tyrosine MT and phosphoryl MT decrease (that is, they become unstable and their tendency to break down increases). These skeletal changes are reduced by the antidepressant fluoxetine [56 57].

G-protein dynamics in G-proteins and cell membrane fat layers are in a close relationship with MT and intracellular skeletal structure [58]. Fatty acids have a direct dynamic relationship to MT and the cellular skeleton [59]. G-protein dynamics on the cell membrane are important in depression and suicide attempts [60]. The same applies to thrombocytes in the blood [61]. With suicide, a rapid change takes place in GS-alpha protein. This is known as “the slide towards suicide”. In depressive patients with a tendency to suicide, there is a higher level of GS-alpha protein in nerve cell membranes [62]. In connection with this, there is an increase in arachidonic acid in the brain and the reuptake of serotonin to the nerve cells is reduced with an increase in nerve cell membrane familiarization [63].

In Bipolar Disorder, valproic acid and lithium are generally used as a long-term treatment. Abnormalities have been detected in 34 genetic areas in bipolar disorder, and these genes are related to 18 tubulin proteins. In particular, a change occurs in beta isoform, and MT loses its structure and function [64]. It has been shown that valproic acid inhibits tubulin polymerization in MTs and binds to MAP [65]. It has been shown that lithium and VPA increase neurogenesis and increase beta-tubulin [66]. It has been suggested that colchicine binding to tubulins in rats disrupts learning [67]. It has been shown that hallucinogenic substances such as LSD and phenyl ethylamine damage the structure of the neural skeleton in humans [68].

In anxiety disorder, a protein called stathmin is found in the lateral nucleus of the amygdala and in the thalamus-cortical regions. The lateral nucleus has a function in fear and learning [69]. When stathmin-producing genes are knocked out, rats are less aware of danger and their fears relating to the amygdala are reduced [70]. They show less tendency to avoid dangers which they should avoid. Stathmin is found in very large concentrations in nerve cells, and is an MT destabilizer, increasing its breakdown [71]. It is important for the reconstruction of the neural skeleton. Excessive production prevents the growth of dendrites. That is, balanced stathmin is a key factor in dendritic MT dynamics [72].

Perception of reality and subject-object relationship

The understanding of the objective and real world occupies the minds of the members of three professions: quantum physicists, mathematicians and psychiatrists. The totally real understanding to the outside world almost disappeared a short time after the appearance of quantum physics, at least among some quantum physicists [73]. To a quantum physicist, only what is measurable and observable is real. Until it is observed, reality stays in the realm of probability. We cannot fully know results, and all that we have is probability. For a mathematician, ‘real’ and ‘correct’ are equivalent in meaning [74]. The way of working of mathematics is in fact simple. For example, let us take a real part of the world. This real world which we want to describe scientifically is the actual problem. First of all, a symbolic metaphor is developed. A mathematical model is constructed for the part of the real world which is being studied, and a part of the real world becomes an abstract copy in the mathematical world. The process of bringing about this mathematical model is this process of abstraction. Mathematics is at base divided into two: pure and applied mathematics. Pure mathematics is a game played in the mind. It mostly consists of symbols and equations set out on paper. At his stage, new ideational objects are created. Initial axioms move away from the reality of what is accepted. Pure mathematics is mathematics for its own sake and has no practical use in the world. The other branch of mathematics is applied mathematics, and is performed for “something else”. That something else is always an aspect of reality and objectivity. Thus for mathematicians, there are two different worlds. One is the real world or the world of sensory experience. The second is the mathematical world or the world of ideas. This world is composed of imaginary mathematical objects like numbers, analytical functions, matrices, differential equations, series, and topological spaces. The mathematical world exists in the mathematician’s head, while the real world is outside.

An object is a thing which can be perceived by at least one of the senses, has concrete existence in space-time, can be distinguished and recognized by the consciousness, and which is thought of by a thinking subject. In fact, the whole universe facing a subject is composed of objects. Because of the act of thinking, a subject can temporarily become an object in any condition which

the subject imagines for itself. Being objective and being real are different from one another. There are different forms of objects. *1. An ideal object:* one found in the consciousness as a result of pure thought, and having no existence without thought. *2. A real object:* an object existing in the outside world independent of a subject, thought or consciousness, and which would exist even if we did not. *3. An abstract object:* these are numbers and geometrical figures, which do not occupy space-time. Maurice Marleau-Ponty states that a distinction must be made between subject and object, and says that "everything which there is exists either as a thing or as consciousness, and a third state other than these or even a mid-point is out of the question" [75].

For a psychiatrist who meets a schizophrenic patient, the understanding of the objective world is confusing. Objectivity in general psychiatry is paramount, but the interest of the psychiatrist is the mental and internal life of the other person. Karl Jaspers, in his *General Psychopathology*, defined delusions as "beliefs which can neither be proven or disproven", and this statement is the cornerstone of the diagnosis of psychosis [76]. A diagnosis is a reflection of classical Newtonian physics, is founded on an acceptance of a "single objective external reality". This single and objective reality is the source of all internal experiences. In 1913, the year in which Jaspers' book was published, the quantum physicist Niels Bohr published the quantum theory of the hydrogen atom, and made the confusing proposal that there might not be a single objective accepted reality, but that it came into being by observation. This was later accepted by many quantum physicists as a result of experimental research. For example, in a double slit experiment, if you observe subatomic particles behaving as particles, when you do not observe them, the same particles show wave behavior. In this situation, a reality forms which changes according to the observer, implying that there is no single objective reality. This being so, how can a diagnosis of psychosis be made based on the concept of a single reality [77].

Many-worlds, multiverse and multimind

The idea of parallel universes has recently taken an important place in popular culture, and has figured in films and many books. Parallel universes are not just science fiction but may be a characteristic of the universe. The idea of parallel or multiple universes may seem like a fantasy, but when participants at an international physics meeting in 1997 were asked which view they favored as a solution to the measurement problem, the Copenhagen interpretation came first and the Many-Worlds Interpretation (MWI) second [78]. Stephen Hawking (1942-2018), Murray Gell-Mann and Richard Feynman (1918-1988) all responded to the MWI by saying they thought it was real. Only Roger Penrose did not accept it. More than three hundred published articles are to be found on the topic in the relevant physics archives. Just as there may be other dimensions in the universe in which we are located, there may also be other universes beyond the horizon of our universe. However, the subject is still at a theoretical level, and is far from being tested experimentally.

The MWI was proposed in Hugh Everett's doctoral thesis [79], and is one of the solutions to the problem of the measurement problem in quantum mechanics. It has also been called the many minds interpretation. In this theory, each of all possible states can be found in reality in different universes. According to Everett, everything possible is to be found in a huge universe as small probability universes. There are people observing each one of the states of probability in many sub-universes. However, these people or their minds are not aware of each other. Thus for example, if you have a choice in front of you of tea, coffee or fruit juice to drink and you choose the coffee, copies of you will separate into as many different universes as there are choices. That is, there will be a copy of you in one universe that chooses tea, and one in another universe that chooses fruit juice. They continue with their lives, and it is because you chose coffee that all the events take place in this objective world [80].

Considering the quantum measurement problem, for the condition of every cat in our universe for which the possibility has not collapsed, there is a cat in another universe for all possible results. A universe forms for the observer who sees the dead cat and the dead cat itself, and another for the person who sees the cat as alive and for the living cat. These two universes are inside a larger universe. Given that the state of consciousness and the mind of each observer "splits into two", each observer will exist twice, and will have different experiences in each existence. The whole universe in which the observer lives splits into two or more multiple or parallel universes at each "measurement". As a result, the "branches" of the universe spread out unbelievably. In fact, the choice of each possibility will exist at one point. Can relations or communications be established between divided multiple parallel worlds? According to MWI, each division is thermodynamically irreversible. Events in our minds are also irreversible. Normally, this division would not be noticeable to us. In order to choose and be aware, we need to have a reversible mind. According to general belief, we can detect other worlds with a reversible mind. If worlds are dividing, where are the other worlds? Why are we not aware of them? Why do we only ever experience a single world? The answer to these questions is not very clear. In his book *Other Worlds* (1997), the physicist Paul Davies wrote this about Everett's multiple universes:

…we don't even know if they are suitable for life. In Everett's theory, all these other worlds really exist alongside us. According to a more traditional theory, these are potential worlds which have most likely not come into existence, but nevertheless may exist in the far future or in another part of the universe. Maybe our tiny, extremely regular world is just a small hospitable bubble in this mainly chaotic cosmos, and the reason why it is seen only by us is that our existence is connected to the mild conditions here.

Fred Alan Wolf discusses the possible existence of people in parallel universes:

In a parallel universe there are not only other people, at the same time these people may be copies of us, and are only connected to us though mechanisms which can be understood by using the principles of quantum physics [81].

Also, in an interesting view, he draws attention to the possible relationship between the closeness of parallel universes and conditions of psychiatric disease:

If the parallel universes of relativity are the same as those in quantum theory, it is possible that parallel universes may be very close to us: this proximity may be only at atomic scales, or it may be at an astronomical scale. Modern neurosciences show, with research which has been conducted on states of altered awareness, schizophrenia and dreaming, that parallel worlds may be close to us.

Hallucinations and thought insertion

The most noticeable characteristics of schizophrenia patients are auditory or visual hallucinations, obsessions which cannot be proven or disproven (delusions), and impairment of thought content (thought intrusion, insertion, monitoring, broadcasting). Bleuler in 1911 used the term schizophrenia, meaning "splitting of the mind", but in fact there is nothing like that. In schizophrenia patients, there is an inability to distinguish the real from the unreal [82]. In thought intrusion, a thought occurs, but is not perceived as being the person's own thought. Rather, it is perceived as being someone else's thought, but at the same time it is a very clear thought [83] [84].

Hallucination is defined in DSM-IIIR (p. 398) as "a sensory perception occurring without external stimulation of the relevant sensory organ." Being in a hallucinatory state has been defined as "… a person who believes he/she has perceived something when there is nothing in the sensory field which could cause such a sensation" [85]. About 30% of the normal healthy population has experienced a hallucination at least one time. Approximately 16-70% of schizophrenia patients have visual hallucinations. In people who experience hallucinations, their clinical situation is slow and poor. Visual hallucinations can be very variable, but many have much in common, and can be in the form of spirits, dead people, prophets, devils, God, sages, or sometimes space aliens. The type of hallucination is generally closely related to the social and cultural environment in which the person grew up. In places where religious factors or tendencies are strong, visual hallucinations have a religious basis. More than seeing things which are not there, schizophrenia patients have a greater tendency to hear imagined sounds: nearly 63% of patients hear such sounds. These sounds come in the form of voices speaking, voices speaking their own thoughts, and voices giving warnings or making threats. A person is talking about himself and listening. In fact, he doesn't know the source, but ascribes it to the TV or another source. It can be in the form of orders or comments. It may be wrong to call these "voices". Some, as with the visual hallucinations, hear the voice of spirits or of God, and others state that they can hear the voices of dead people, prophets, or devils. Various mechanisms have been proposed for the occurrence of hallucinations. These include defects of neural sensory mechanisms, revival of previous memory remnants, and perceptual liberation.

Along with hallucinations, schizophrenia patients also have delusions [86]. These come in many forms, and can include feelings that their minds are being read, that harm is about to done to them or that they are being poisoned, that their thoughts are being broadcast and are known to everyone, or that others can affect their thoughts from a distance. There is also a delusional feeling of being in love, which is seen in 6% of these patients. There are also mystical delusions, such as of dying and coming back to life, or that the world has ended and will be destroyed.

In thought insertion/intrusion, there is an outside agency which is like a guest in the person's mind. The thoughts of this agent are added to the patient's own, and it is different from thoughts being controlled from outside. In this situation, two people are thinking in the person's self and brain. One of these is the familiar self, while the other is a stranger or a thought other than the person himself. The person is consciously aware of his own thoughts and at the same time someone else's thoughts. Even though there is unity of consciousness, the agency is separate. It is not the person himself, it is like another/multiple or parallel thought. Where is the source of this second personality? The subconscious? Is it a separate delayed function of the brain? Is it the work of the left hemisphere of the brain, distinguishing what is itself and not itself? Is it thoughts coming from another universe? Is it the confusing effect of other personalities in other

universes? Some of these are fictional, and some beyond fiction. Nevertheless, these are questions which must be considered.

Seen from the point of view of quantum brain theory, all of a person's mental structure relating to thermo-field brain dynamics arise from the relationship between sensory input, memory traces and self-tuning. The origins of thermofield brain dynamics go back to the quantum brain dynamics of Umezawa and coworkers [87]. Vitiello greatly extended quantum brain dynamics to a thermofield brain dynamics by bringing in dissipation [88]. It was recognized that symmetry-breaking in the ground state of the brain-the vacuum state of a water electric dipole field-offers a mechanism for memory. Sensory inputs fall into the ground after dissipating their energy and break the dipole symmetry. The broken symmetry is preserved by boson condensation (Nambu-Goldstone condensates). When the sensory input is repeated, the condensate-trace is excited from the vacuum state and becomes conscious. Thought intrusion arises from disorders in the inadequacy of response and the flow of information. Seen from the point of view of covered or hidden order, which is another quantum brain theory, behind the real universe which we see and the objective world, there is a hidden structure which shapes it, and a hidden structure in the form of a quantum field is connected to the brain. Affecting the brain, it provides thoughts, beliefs, feelings, perceptions, emotions and desires. Hallucinations may be interference caused by a hidden order in the brain [89].

Health is the whole of the state of mental and bodily wellbeing. According to David Bohm (1917-1992), mental health is basically related to the whole hidden below, and to flowing consciousness. Disruption of the whole occurs with mental disorder. Quantal information in Bohm's *implicate order* determines effect and particle behavior [90]. For example, when we see a snake, a perception of danger occurs and fear develops. How does the mental side affect the brain in this situation? Quantum field information causes the particles to dance and affects the chemistry and physics of the physical brain. Bohm called this pass effect "soma significance", and the effect on brain physics "signa-somatic". In this situation, the human mind and consciousness are sometimes subtle. That is, it is a non-physical structure. It is probable that information experienced in consciousness is like a volatile invisible quantum field. Objectivity, mind content (qualia), and the experience of consciousness take place here. This typically affects downwards and accompanies behaviors. However, it is more important how this subtle field affects the brain, and this is probably done with a quantum field. A quantum field carries active information, and continuously provides a condition of creation (consciousness, thought…) by having an effect on particles. This is one of the best explanations of the mind-brain model since Descartes [91].

In Bohm's quantum field theory, the non-material consciousness may enter into relations with the material brain through the effect on tubulin dimers in the MTs [92]. Changes in the quantum field in the environment of the related MTs changes the behavior and position of electrons. As a result, large-scale neural behavior appears with MT tubulin changes which occur successively in a domino effect (alpha-beta). This leads to kinetic or emotional results. The effect of quantum force on nerve cells is the spread of desire or intention. There is a mutual two-way effect, and this is an effect which is also not dead material. This interaction is completely under the control of "active information". The quantum field carries information on the environment of the particle and as John Wheeler said, "reality is information". The field turns into a quantum potential, and affects particles, determining their behavior. This is not a mechanical effect. Its appearance in mental illnesses happens with the effect of information of discordant and disturbing thoughts. These are perceptions which are unwanted but which we become aware of (*mind-popping or mind wandering*). Bohmian theory may also be connected with Eccles' psychons (the smallest cognitive units) and dendrons (the smallest units of the physical brain). Dendrons are places of intense synaptic joining, and at the same time are suitable places for Walker's electron quantum tunneling. Also, these regions are areas of dense MT.

The question arises as to whether hallucinations, delusions, thought intrusions and indecisiveness (ambivalent thoughts) in schizophrenia patients may be a result of setting up interference connections in minds in this universe with these parallel universes, collective consciousness/mind in the hidden order, or with our other minds making decisions. According to the physicist David Bohm (1917-1992), the universe consists of two basic structures. Behind the objective, what we call real, universe, is another potential, hidden world which gives it form and which contains all the entities of this universe. This deeper level of reality is called "implicate order", and the level or existence in which we are located is called "explicate order". Seen in another way, electrons and all other particles are no more than the temporary form taken by water bubbling from a spring. These are supported by a constant flow coming from the implicate order, and when we see what looks like a particle disappearing, it does not in fact disappear. In this situation, the particle has merely returned from its structure to the order in the depths from which it emerged [93].

The quantum information in Bohm's implicate order has the effect of determining particle behavior. For example,

when we see a snake a feeling of danger arises and fear develops. How does the cognitive side affect the brain in this situation? The quantum field information causes the particles to dance and affects the brain's chemistry and physics. Bohm called this crossover effect *the emergent effect in the body*. In this situation, the human mind and its information are carried by a subtle structure, that is, a non-material structure. It is probable that knowledge experienced in the consciousness, visible or subtle, is like an invisible quantum field. Objectivity, that is individual mind content and conscious experience, is located here. This typically affects downwards and accompanies behaviors. However, the way this *zahir* field affects the brain is more important, and it probably does this by means of a quantum field. A quantum field, like a'yân thâbita, carries active information, and produces a state of continuous creation with its effect on particles. This continuous creation in the outer world brings subatomic particles into existence in the objective world, while the same process in the brain causes mental images and momentary thoughts. How do our perceptions and thoughts affect our physical brains? This, according to Bohm's approach, happens by a route called the "reverse effect". That is, the effect happens from the field to the particles. The material brain, that is the physical brain composed of particles, affects the accompanying super-quantum field (a kind which is covered or implicate). In the opposite way, thoughts resulting in movement or speech (kinetic output) appear with the effect on particles of super quanta.

Bohm's theory is in some ways similar to the thoughts of Ibn Arabi [94]. The relation of the *bâtın* (inward, hidden, internal) to the *zahir* (outward, visible, external) and the formation of what is *kesif* (coarse) from what is *latif* (refined, subtle) of Ibn Arabi's view of the universe are the same, with small differences. Ibn Arabi gives the name a'yân thâbita (fixed entities, archetypes) to the implicate order, and this is the field of imagination in the divine consciousness if God. The a'yân thâbita are the "fixed prototypes" or "latent realities of things". The fixed entities are not the "archetypes" of the existent entities but are rather identical ('ayn) with them; nor are they "essences", if by this is meant anything other than the entities' specific whatness. The original copies there take on a dull existence, including space and time, in this universe of Einstein's. a'yân thâbita is a field which has no actual existence, just like a universal quantum probability wave. It contains potentially within it all the possibilities of existence. It has not yet come to reality and has not manifested itself.

Even if this model is accepted as one of the best consciousness-brain explanation models put forward since Rene Descartes (1596-1650), it is true that Ibn Arabi (1165-1240) had done this some 700 years before. The quantum universal field potential is like a kind of implicate and explicate order, a Noosphere, Gaia, universal subconscious, biologist Rupert Sheldrake's morphic fields, neuroscientist John Carew Eccles' (1903-1997) quantum psychons, psychiatrist Carl Gustav Jung's (1871-1961) archetype, mystic Ibn Arabi's a'yân thâbita *and levh-i mahfuz*, philosopher Karl Popper's (1902-1994) cognitive worlds, or Plato's world of ideas. All these names are labels proposed by different people for the place where the original structure is stored which provides a common consciousness-mind or a coming into existence.

In Bohm's quantum field theory, the non-material consciousness may enter into a relationship with the material living brain by influence on the tubulins which form the skeleton in the nerve cells. Changes in the quantum field around this cellular skeleton change the behavior and position of electrons in the material structure. As a result, tubulin changes (alpha-beta conversions) in the cellular structure following each other in a domino effect produce observed behavior spreading to the large-scale nerve cell net. This leads to movement or speaking, or has sensory results. The effect of quantum force on nerve cells is the spread of desire or intention. Here, there is a reciprocal, which is two-way, interaction between the mind and the brain. The reciprocal interaction is an effect which is not in dead material. This interaction is completely under the control of "active information". The quantum field carries information about the environment of the particle and as the physicist John Wheeler said is "reality information". In other words, the quantum field changes to a quantum potential, it has an effect on particles at the cellular level, and particle effects in total act on the material structure in the nerve cell and determine its ultimate behavior. The same mechanism may be thought of for the quantum field effect on Eccles' dendrons and Umezawa's corticons. This is not a mechanical effect. With all this information we may reach this conclusion: the appearance of mental illnesses occurs with a reflection on the brain of the information of incongruous and disruptive thoughts. These are perceptions which we become involuntarily aware of, like mental hiccups, mental wandering or random thoughts.

Sudden thoughts coming out of nowhere

These are words, images or music that suddenly pop into our consciousness seemingly out of nowhere. They take the form of sudden information or music, and have been called mental hiccups or mind-pops. Very often, these uninvited thoughts have nothing to do with what our minds are currently occupied with. According to some scientists, these sudden thoughts are not entirely random but are connected to our knowledge and experience of the world. Some people often have mental hic-

cups, and these contribute to their creativity. They make problem solving easier. They generally appear 90% of the time when the person is alone and when performing routine work, and they appear without mental effort. These mental wanderings appear of their own accord and unbidden, and so cannot be controlled. They can come to mind while we are brushing our teeth or tying our shoelaces. That is, they appear when the mind is free and when we are not concentrating on anything. The most important sign of a mental hiccup is that the thought has no relation to what is going on in the mind at that moment. In some circumstances, the triggers for the mental hiccups can be identified, and these are subliminal. Sometimes connections may be formed with events which happened a few hours or a day previously. That is, the thoughts did not come entirely of their own accord or by chance, but were connected to previous mental states. In terms of their content, these verbal, visual and musical mind-pops are different from several other involuntary phenomena described in the literature [95].

These mental hiccups may be the source of thought intrusions and hallucinations. In persons with diseases like schizophrenia, harmless mental hiccups may turn into hallucinations. When schizophrenia patients and normal individuals were examined with regard to these mental hiccups, interesting findings appeared. In particular, it was found that they appeared in great variety to the schizophrenia patients, and with a frequency of about 3-4 times a week, whereas they happened 3-4 times a year in the normal people and 1-2 times a month to the depressive patients [96]. It can be seen from this that in the case of a mental illness such as schizophrenia, mental hiccups are very frequent. However, it is not scientifically possible to make a connection between these sudden thoughts of unknown origin and hallucinations.

Wandering thoughts

This condition, like mental hiccups, means thoughts which are unrelated to what the person is doing at that moment. It may be called mind wandering, daydreaming, or being lost in thought, and it generally happens while doing something which does not require attention, such as while reading or driving [97 98]. The person is occupied with his thoughts, and it makes little difference what is going on around him. Daydreaming may even be a gift of evolution: it may stimulate creativity and keep the mind active. A person may be aware of mental wandering, or partially unaware. In general, people are unaware one third of the time. Thus, when a person studies for an hour, his mind may be elsewhere for twenty minutes. For example, when a person is reading a book, he may be unaware that he has left off reading and that his thoughts have gone elsewhere until someone alerts him. “What are you doing? Oh, er, my thoughts had drifted off…” [99].

Conclusions

Many quantum psychopathology hypotheses may not be testable. Quantum mechanical analogies may provide a better understanding of patients. The use of quantum insight – used heuristically by experienced psychiatrists – provides better clinical results [100]. Although there have been different *Diagnostic and Statistical Manual of Mental Disorders* (DSMs) at different times, there has been a general trend towards pathology. DSM-I (1952), DSM-II (1968, 1974), DSM-III (1980, revision-1987), DSM-IV (1994, revision-2000) and DSM-V (May 2013) are basically not very different from each other. If we add the accumulation of symptoms of 1980, the multi-axis system of 2000 and the dimensional variables of 2013 to the DSMs, there are many psychiatrists who are not satisfied. DSM-V has been criticized as being a possible cause of medicalization, with the excessive and unnecessary use of drugs. For example, normal grief may now be taken as pathological. A diagnosis is traditionally given with scientific clinical findings, and these diagnostic measurements may take shape under the influence of *American Psychological Association* subcommittee dynamics, pharmaceutical companies, the press and media organs, and patients’ rights groups. There is no effect of quantum physics in DSM-V, and it is affected by classical physics. Knowledge advances in its normal phase [101]. DSM has not yet made that leap, and can be seen to be advancing in slow steps. To repeat Karl Jaspers’ words: *Having excluded all theories regarding the mind, we must find a way to develop theories to be used in describing the minds of other people, (1963). The purpose of psychopathology is to create clear theoretical awareness of what is known, of how it is known, and of what is not known (1957, p. 19).*

Conflict of interest

The Author declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Inter-rater reliability and psychometric characteristics of the Italian version of the Cognitive Assessment Interview (CAI)

Summary

Objectives

Cognitive impairment in people with schizophrenia is a core feature of the disorder. It is increasingly regarded as an important target of both pharmacological and rehabilitation treatments. The Cognitive Assessment Interview (CAI), developed as part of the "Measurement and Treatment Research to Improve Cognition in Schizophrenia" (MATRICS) initiative, is an interview-based measures of cognition. In this paper, we report on the inter-rater reliability and psychometric properties of the CAI Italian translation.

Methods

One psychiatrist, one psychologist and one trainee in psychiatry translated the CAI from English to Italian. The author of the original version, Josef Ventura (JV), evaluated the resulting Italian version to ensure the absence of translation or interpretation errors. The three translators examined the modifications suggested by JV and applied them when deemed appropriate or re-discussed the suggestions with him, until they reached an agreement. JV trained the three translators and two additional persons (one psychiatrist and one trainee in psychiatry) in the use of the interview. When they reached a satisfactory degree of experience with the instrument became trainers of other raters. The intraclass correlation coefficients (ICCs) and the Cronbach's alpha coefficients provided, respectively, a measure of the reliability and internal consistency of the Italian version of the CAI.

Results

For the three considered scores (patient, informant and composite scores) of each item of the CAI, as well as for the score on Global Assessment of Functioning-Cognition in Schizophrenia, the ICCs ranged from 0.69 to 0.91. Cronbach's alpha coefficients for the CAI patient, informant e composite scores were respectively 0.90, 0.93 and 0.93.

Conclusions

The Italian version of the CAI revealed good to excellent reliability and excellent internal consistency. The availability of such a suitable tool may help clinicians to assess cognitive impairment and its impact on daily functioning in patients with schizophrenia.

Key words

Schizophrenia • Cognition • Interview-based evaluations • Co-primary measures • Cognitive Assessment Interview – Italian version

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Introduction

An impairment of several cognitive domains has been reported in patients with schizophrenia [1-5]. It is regarded as a core feature of schizophrenia and not just a consequence of other factors, such as symptoms, pharmacological treatments or chronicity. Evidence supporting this view include the presence of cognitive deficits in patients with schizophrenia at their first episode of illness [6 7], before illness onset [8], and in first degree unaffected relatives of patients with schizophrenia [9-13], and the persistence of

cognitive impairment after clinical remission [14 15]. Cognitive deficits in patients with schizophrenia are associated with poor functional outcome [12 16-18] and quality of life [19] and have a greater impact on social functioning than positive and negative symptoms [12 20-23]. For these reasons, cognition is increasingly considered an important target for schizophrenia treatment, and for research on both pharmacological and rehabilitation treatments.
In 2006, in the US, the National Institute of Mental Health (NIMH), together with the Food and Drug Administration (FDA), pharmaceutical industry and academia [24] supported a project aimed to identify a consensus test battery, suitable to assess performance of cognitive domains more frequently impaired in people with schizophrenia. The output of the project was the "Measurement and Treatment Research to Improve Cognition in Schizophrenia" (MATRICS) Consensus Cognitive Battery (MCCB), now regarded as the 'state-of-the-art' neuropsychological battery for research purposes in schizophrenia and other severe psychiatric disorders. It provides a valid and reliable assessment of seven distinct cognitive domains: processing speed, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, social cognition. It has proven sensitive to changes induced by pharmacological treatments [25 26].
Within the MATRICS initiative, the FDA indicated the need to integrate primary measures of cognitive changes, carried out by assessing performance to neuropsychological tests, with co-primary measures [27], such as interview-based evaluations. In a separate set of guidelines for the pharmaceutical industry, the FDA also indicated as important for the development of new cognitive enhancing medications Patient-Reported Outcome (PRO) measures (PROMs) (FDA, February, 2006), as some of the effects of treatment can be perceived subjectively, and therefore reported exclusively by the patient. Interview-based cognitive assessment has several advantages. Clinicians find it easier to use in clinical contexts than neuropsychological test batteries [28-30]. In addition, it can be used to provide a self-evaluation of cognition by patients, as well as an evaluation by caregivers, and this may increase motivation of both to adhere to cognitive rehabilitation programs. Similarly, the assessment of cognition carried out by clinicians may increase their motivation to prescribe cognitive rehabilitation programs. Furthermore, a subjective assessment may enable the identification of cognitive deficits not evidenced by objective evaluations, such as the perception of memory impairment interfering with real-life functioning, in spite of a good performance on neuropsychological tests exploring memory.
The Cognitive Assessment Interview (CAI), developed as part of the MATRICS initiative [31], is one of such interview-based measures of cognition. In the paper we provide a description of this interview, as well as of the procedures followed to translate and validate its Italian version.

Description of the Cognitive Assessment Interview

The CAI is a semi-structured interview developed by shortening and modifying two previous scales: the Clinical Global Impression of Cognition in Schizophrenia (CGI-CogS [30]) and the Schizophrenia Cognition Rating Scale (SCoRS [32]). The development of a shorter version to facilitate repeated use in clinical trials was stimulated by the results of the Item-response theory analysis of the original scales, indicating that only 10 to 12 items were necessary to achieve accurate estimate of the neuropsychological deficits [29].
The CAI differs from traditional psychopathological rating scales, which focus on areas such as consistency of speech, thought content, hallucinations, delusions, mood, emotions and sleep/appetite. Although these areas are important in schizophrenia, these symptoms are well assessed by other rating scales and their inclusion may distract the clinician from an independent assessment of cognitive functioning.
The CAI includes a manual providing definitions of cognitive domains and rating instructions, as well as supplemental guidelines for the administration, providing suggested additional questions to explore each cognitive domain. It also includes a scoresheet divided into 3 different sections: 1) General information; 2) Interview, and 3) Global Assessment of Functioning.
Section 1. The "General Information" section is aimed to collect information not specifically evaluated by the interview, but may modify or explain the scores obtained in the investigated cognitive domains (e.g. presence of a systemic illness causing a transient reduction of functioning). This section is divided into two parts: the first one, specific for the patient, investigates adherence to treatment and patient orientation in time and space; the second, for the patient and the informant, investigates the anamnestic and demographic aspects.
Section 2. The interview section should be administered to both patient and informant (e.g., a caregiver or someone who knows patient's daily functioning, such as her/his physician). It includes 10 items that investigate 6 cognitive domains derived from the "MATRICS" project (working memory, attention/vigilance, verbal learning and memory, reasoning and problem solving, processing speed, and social cognition). Each item includes several questions to investigate the cognitive domain; however, further investigation besides the provided questions is suggested. In fact, the interviewer is encouraged to modify the suggested questions and/or to add new ones to improve the flow of the interview and

obtain more information. For each item, a score is assigned from 1 to 7, with higher scores reflecting greater impairment. It is also possible to make a rating of "N/A" for "not applicable" or "not available" (for example, if the participant interrupts the interview or if only few information is available). To assign the score, the clinician must consider how much the cognitive dysfunctions impact on functioning expected in the workplace, school or social environment. Two separate sets of scores are obtained from the two interviews (patient and informant). Patient's assessment should reflect the judgment of the clinician exclusively based on patient's interview. The assessment of the informant's interview should only reflect the clinical judgment based on the patient's deficit reported during the informant's interview. Finally, the clinician can define a composite score that reflects his judgment by integrating all sources of information. Generally, the duration of the CAI interview ranges from a minimum of 15 to a maximum of 30 minutes.

Section 3. The global assessment of functioning section assesses global severity of cognitive impairment. The score must be attributed at the end of each interview. The interviewer must assess the cognitive impairment of each individual domain investigated by the CAI and apply a global severity score for the patient interview, the informant interview and a composite score based on both sources of information. The score does not have to be an average of the scores on the different CAI domains, but a weighted evaluation of the impact of patient's cognitive impairment on her/his functioning. For example, a patient can show a dysfunction only in one cognitive domain, but the impairment is severe affects patient functioning in real-life. In this case, a high score on global severity is required. This section of the CAI also provides an additional assessment of global cognitive functioning using the Global Assessment of Functioning – Cognition in Schizophrenia (GAF – CogS). The GAF-CogS is used as an integration to the CAI score, and is similar to the DSM-IV GAF. GAF-CogS scores are placed on a continuum from 1 to 100, where the lowest score indicates a greater dysfunction. The score should be based on the information collected during the interview, using all available information about the cognitive function of the patient.

Several studies have demonstrated good psychometric characteristics of the CAI [33-36]. In particular, a good internal consistency was found for the evaluations of patient, informant and rater, although higher correlations were observed between scores of raters with those of patients and informants, while a lower correlation was reported between patient and informant scores [33]. Test-retest reliability has been reported from good to excellent [33]. Other studies showed significant relationships between the CAI scores with the total score of the MCCB, a scale that objectively measures cognitive functioning [34-36]. A moderate-strong relationship emerged between single CAI domains and the related MCCB domains, except for the domain of social cognition [36]. CAI scores are also largely related to functional capacity test scores and functioning in real life [33-35].

Overall, the CAI seems to respond to the needs for which it was conceived: a brief and reliable interview for the assessment of cognitive functions and their impact on day-to-day functioning.

The Italian translation of the Cognitive Assessment Interview

The Italian version of the CAI was developed using the translation-backtranslation method. All materials (manual, supplemental guidelines and scoresheet) were translated into Italian by a psychiatrist (AM), a psychologist and a trainee in psychiatry. The translated version was then back-translated into English by an English teacher. The back-translated version was reviewed by Joseph Ventura (JV), the author of the original version, in order to ensure the absence of translation errors or misinterpretations. The changes suggested by JV were examined by the persons who made the first translation, applied when considered appropriate, or re-discussed with JV until an agreement was reached.

The Italian version is attached: Appendix 1 includes the manual, Appendix 2 the supplemental guidelines, and Appendix 3 the scoresheet.

Inter-rater reliability and internal consistency

The assessment of the reliability and internal consistency of the Italian version of the CAI was carried out as part of the project "Factors influencing real-life functioning of people with a diagnosis of schizophrenia: a four-year follow-up multicenter study", a multicenter study of the Italian Network for Research on Psychoses coordinated by our Center. The study was approved by the Ethics Committee of the University of Campania Luigi Vanvitelli Hospital.

The Inter-Rater Reliability (IRR) and internal consistency of the instrument was assessed on the data of the coordinating center. Five evaluators (2 expert psychiatrists, two trainees in psychiatry and 1 psychologist) of the University of Campania "Luigi Vanvitelli" participated in the CAI training. It was a three-week training conducted by JV by weekly meetings held via Skype. During the first meeting, the CAI was explained in detail by its author who also answered queries and clarified doubts. Subsequently, the 5 Italian evaluators gave an independent rating on two videos showing the CAI interview administered by JV to 2 patients affected by schizophrenia and to their informants. Scoring of the two interviews

TABLE I. *Inter-rater reliability for the Cognitive Assessment Interview (CAI).*

CAI item	ICC patient	ICC informant	ICC composite
Working memory - Item 1	0.887	0.856	0.865
Working memory - Item 2	0.890	0.911	0.870
Attention/vigilance - Item 3	0.903	0.799	0.851
Attention/vigilance - Item 4	0.823	0.796	0.847
Verbal memory and learning - Item 5	0.802	0.737	0.745
Verbal memory and learning - Item 6	0.784	0.782	0.772
Reasoning and problem solving - Item 7	0.793	0.775	0.763
Reasoning and problem solving - Item 8	0.694	0.753	0.727
Speed of processing - Item 9	0.808	0.689	0.712
Social cognition – Item 10	0.856	0.844	0.816
Global severity	0.788	0.818	0.745
GAF – CogS	0.763	0.732	0.733

Note. ICC: Intraclass Correlation Coefficient; GAF – CogS: Global Assessment of Functioning - Cognition in Schizophrenia.

were discussed during the other two meetings with JV. Through this training phase, participants familiarized with the CAI and learnt how to set a correct score for the different degrees of cognitive impairment severity. The training was completed only when the group of Italian raters was able to administer the instrument and to perform a correct evaluation, in line with that of JV.

In order to analyze the IRR three videos were recorded. In each video the CAI was administered by the senior psychiatrist AM to an outpatient of the Department of Psychiatry of the University of Campania affected by schizophrenia and her/his informant Subsequently, the three videos were assessed individually by the other 4 Italian evaluators. The Intraclass Correlation Coefficient (ICC) was calculated for each item and for the GAF – CogS score. For each item of the CAI, the ICC was assessed separately for the score based on the patient or informant interview, as well as for the composite score. The ICC values ranged from .689 to .911, therefore the IRR resulted good to excellent. The values of ICC for each item are reported in Table I.

In order to calculate the internal consistency, the CAI was administered to 30 outpatients with a diagnosis of schizophrenia according to the DSM-IV and their respective informants. Psychopathological characterization of patients was carried out by using the Positive and Negative Syndrome Scale (PANSS); scores for the dimensions “positive symptoms”, “negative symptoms” and “disorganization” were calculated based on the consensus 5-factor solution proposed by Wallwork et al. [37]. Demographic and clinical characteristics of patients’ sample are reported in Table II. The coefficient alpha for the CAI patient and informant interview scores and for the composite scores resulted very high (from .897 to .932; Table III) indicating an excellent internal consistency of the tool.

TABLE II. *Patients’ demographic and clinical characteristics.*

Males (%)	50
Age (years, mean ± SD)	41.3 ± 7.9
Education (years, mean ± SD)	12.6 ± 2.9
CAI patient global score (mean ± SD)	3.0 ± 1.2
CAI informant global score (mean ± SD)	3.0 ± 1.2
CAI composite global score (mean ± SD)	3.2 ± 1.3
PANSS positive simptoms (mean ± SD)	8.5 ± 4.2
PANSS negative symptoms (mean ± SD)	13.6 ± 6.9
PANSS disorganization (mean ± SD)	7.7 ± 3.6

Note. CAI: Cognitive Assessment Interview; PANSS: Positive and Negative Syndrome Scale.

TABLE III. *Cognitive Assessment Interview (CAI) Internal Consistency.*

10-item CAI	Cronbach’s alpha
CAI patient	.897
CAI informant	.926
CAI composite	.932

Note. CAI: Cognitive Assessment Interview.

Conclusions

The present paper reports on the Italian version of the CAI and demonstrates that a good to excellent inter-rater reliability can be achieved for this tool even after a relatively brief training. The possibility of using a short and validated interview may help Italian researchers and clinicians in the assessment of cognitive impairment in patients affected by schizophrenia in clinical trials. Moreover, the use of this tool may help to overcome some practical limitations of the cognitive assessment during clinical routine care, such as difficulties in training the staff for the administration of neurocognitive batteries, as well as their high cost and long duration of administration. Furthermore, it will give an assessment of the insight concerning cognitive deficits in subjects with schizophrenia and possibly help to motivate them to engage in cognitive rehabilitation programs contributing to improve functional outcome.

Conflict of interest

The Authors declare to have no conflict of interest.

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Cognitive Assessment Interview

(CAI)

Intervista per la valutazione cognitiva

2° Versione

MANUALE DELL'INTERVISTATORE: Linee guida per le definizioni e l'attribuzione del punteggio

18-01-08

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Cognitive Assessment Interview (CAI): RAZIONALE

La CAI è stata ideata per offrire ai clinici un metodo per la valutazione delle funzioni cognitive dei pazienti affetti da schizofrenia, indipendente dalle valutazioni psicometriche formali. La ricerca recente ha mostrato che i deficit cognitivi nella schizofrenia sono spesso severi e pervasivi, e che probabilmente essi sono correlati al funzionamento dell'individuo più di quanto lo siano i sintomi psichiatrici del disturbo tradizionalmente valutati. Nuovi trattamenti sono in corso di valutazione per definire la loro efficacia nel migliorare le funzioni cognitive nella schizofrenia, il che rende sempre più importante per i clinici valutare le funzioni cognitive dei loro pazienti. Purtroppo, può non essere sempre possibile ottenere valutazioni neurocognitive formali. Inoltre, la valutazione clinica delle funzioni cognitive può considerare aspetti più ampi che non vengono affrontati in modo completo da più specifici test neurocognitivi. La CAI è stata ideata per essere utilizzata da clinici esperti allo scopo di ottenere una valutazione della severità e delle variazioni dei deficit cognitivi, e di quanto essi possano incidere sulle attività della vita quotidiana. La CAI potrebbe diventare un utile contributo per i clinici per valutare l'efficacia dei trattamenti che possono migliorare le disfunzioni cognitive nella schizofrenia e nei disturbi ad essa correlati.

Contesto scientifico

La CAI è un'intervista semistrutturata sviluppata a partire dal CGI CogS (Bilder et al., 2003) e dalla SCoRS (Keefe et al., 2006) usando i classici metodi della Test Theory e approcci statistici quali l'Item Response Theory (IRT), l'analisi bifattoriale e il Computer Adaptive Testing simulation (CAT). Tutti i 10 item della CAI sono presi dal CGI-CogS che si basa, in parte, sullo strumento Alzheimer's Disease Collaborative Study (ADCS) Clinical Global Impression of Change (CGIC) e sulle successive modifiche delle scale che si trovano nella Clinician Interview Based Impression of Severity (CIBIS) e nella Clinician Interview Based Impression of Change (CIBIC), con le informazioni del caregiver (CIBIC+). Tuttavia, ci sono numerose differenze tra la CAI e la CIBIS/CIBIC+, incluse differenze nel formato e nel contenuto specifico. Alcune differenze rilevanti includono i punti riportati di seguito.

1. Al fine di ottenere informazioni il più possibile accurate per la valutazione delle funzioni cognitive, e poiché una valutazione affidabile del cambiamento trae vantaggio dall'avere informazioni analoghe in momenti diversi, è stato ritenuto importante includere le informazioni sia del paziente che dell'informatore, sia per le valutazioni in condizioni di base che per quelle successive (la CIBIS include esclusivamente l'intervista al paziente in condizioni di base).
   Se le sole informazioni ottenute dal paziente forniscano una valutazione sufficientemente affidabile e valida delle funzioni cognitive nella schizofrenia, è una questione ancora aperta. Si spera che la ricerca possa far luce sulla questione utilizzando questo ed altri strumenti simili.
2. La CIBIS/CIBIC+ comprende una categoria per la valutazione del "Comportamento" che include la valutazione del contenuto del pensiero, di deliri/allucinazioni e dell'umore. Poiché la CAI è stata ideata specificamente per ottenere una valutazione delle funzioni cognitive indipendente da tali aspetti, per i quali esistono invece scale ad hoc (ad esempio PANSS, BPRS, SAPS, SANS), questa categoria è stata eliminata. Infatti, è importante per i valutatori che utilizzano la CAI separare il più possibile la valutazione dei deficit cognitivi dalla valutazione dei sintomi positivi, negativi e disorganizzativi della sindrome. La ricerca ha

mostrato solo una modesta correlazione tra i deficit cognitivi e questi altri sintomi. Le istruzioni per valutare gli item della CAI (per ulteriori informazioni vedere di seguito) sono state ideate per aiutare l'intervistatore a condurre tale valutazione indipendentemente dai sintomi osservati.

3. Il miglioramento degli item esistenti e delle aree indagate, e l'aggiunta di nuovi item e aree indagate, sono stati messi a punto considerando le caratteristiche di diverse altre scale, comprendenti: la Independent Living Scale (Ashley, Persel, and Clark 2001); la Quality of Life Scale (Heinrichs 1984); la Global Assessment of Functioning (GAF) Scale of DSM IV (APA, 1994); e la Schizophrenia Cognition Rating Scale (Richard S.E. Keefe, Duke University Medical Center, 2001). Ulteriori influenze sul contenuto degli item e delle aree indagate derivano dalle attuali revisioni della letteratura sul funzionamento cognitivo nella schizofrenia, sugli effetti del trattamento sulla cognizione nella schizofrenia, sulle relazioni tra i deficit cognitivi ed i deficit del funzionamento dell'individuo e sul ruolo della cognizione sociale come mediatore dell'esito funzionale. Infine, uno studio pilota condotto su pazienti ed informatori, in cui è stata utilizzata una versione precedente di questo strumento, ha prodotto numerosi cambiamenti del contenuto e della sequenza degli item oltre che del contenuto di un'area di indagine.
4. La CIBIS/CIBIC+ ha 6 domini all'interno della categoria "Stato Mentale/Cognitivo". Questi domini comprendono diverse aree (Orientamento, Linguaggio/Discorso e Prassia) che possono essere maggiormente rilevanti nello studio della demenza che della schizofrenia. La CAI identifica sei domini neurocognitivi derivati dal progetto "MATRICS" (un'iniziativa dell'NIMH nata per favorire lo sviluppo di un consenso sui metodi per il trattamento della schizofrenia in base alle indicazioni che derivano dalle valutazioni cognitive; per ulteriori informazioni: www.matrics.ucla.edu).
   La selezione degli item e delle aree indagate nei diversi domini per la valutazione della neurocognizione ha esaminato ulteriormente le richieste cognitive di specifici test psicometrici, considerati nella MATRICS come misure dei costrutti di tali domini. In contrasto con il focus delle definizioni psicometriche di tali costrutti, tuttavia, la CAI enfatizza le plausibili manifestazioni cliniche (osservabili) dei deficit presenti in questi costrutti.

Le valutazioni finali della CAI sono state ideate per ottenere il punto di vista di un clinico esperto sulle funzioni cognitive degli individui affetti da schizofrenia, come queste si manifestano nella vita quotidiana. La struttura generale della CAI, infatti, è stata ideata per consentire ai clinici esperti di raccogliere informazioni mediante l'intervista ad un paziente affetto da schizofrenia e mediante l'intervista ad un informatore; è stata ideata inoltre per ottenere impressioni globali affidabili sulla severità della compromissione cognitiva del paziente ed i cambiamenti del funzionamento cognitivo che possono manifestarsi con il passare del tempo o con un trattamento.

STRUTTURA DELLA CAI E ISTRUZIONI PER L'INTERVISTATORE

La CAI utilizza tutte le fonti d'informazione ed il punteggio è ottenuto in base allo stato delle funzioni neurocognitive del paziente ed in base a come esso incida sul suo funzionamento quotidiano. La CAI differisce dalle scale di valutazione tradizionali il cui focus è su aree come la coerenza del discorso, il tipo di contenuto di pensiero, le allucinazioni ed i deliri, umore e affettività e sonno/appetito.
Sebbene queste aree siano rilevanti nella schizofrenia, tali sintomi sono già ben valutati da altre scale di valutazione ed una loro analisi potrebbe distrarre il clinico da una valutazione indipendente del funzionamento cognitivo. Per la valutazione CAI è di principale importanza

che l'intervistatore provi a fornire un punteggio basato sull'impressione circa il funzionamento cognitivo del paziente evitando l'influenza indesiderata della severità/cambiamento degli altri sintomi del disturbo.
Numerosi studi hanno mostrato una bassa correlazione tra i sintomi caratteristici della schizofrenia, il livello di funzionamento cognitivo ed altri esiti sul funzionamento nella vita reale. Le valutazioni CAI sono basate, quanto più possibile, unicamente sul funzionamento cognitivo e adattivo.

Nella sezione "Informazioni Generali" l'intervistatore annota le informazioni generali che non sono specificamente valutate, ma che potrebbero modificare o aiutare a spiegare i punteggi ottenuti in altre categorie o domini. Se l'intervista rivela che un paziente ha avuto una malattia sistemica transitoria che ha danneggiato temporaneamente il suo funzionamento, è importante che l'intervistatore consideri ciò quando procede alla valutazione degli altri domini. Poiché l'obiettivo della CAI è di consentire una valutazione globale della compromissione cognitiva e delle modifiche della cognizione che possono essere dovute al trattamento, l'effetto di fattori situazionali transitori potrebbe non essere tenuto in considerazione[1].
La parte "Generale" dell'intervista è ideata per ottenere dal paziente e dall'informatore maggiore chiarezza sulle circostanze associate con i casi di comportamento insolito del paziente, e per aiutare l'intervistatore a porre domande che possano fornire esempi più caratteristici del comportamento del paziente nell'intervallo di tempo che interessa la valutazione (più in basso ulteriori informazioni circa tale intervallo di tempo).

Le valutazioni delle funzioni neurocognitive ottenute mediante la CAI si basano su sei domini del funzionamento cognitivo. Questi sono sei dei sette domini definiti, dal consenso tra esperti, come importanti per gli studi clinici sulle sostanze pro-cognizione nella schizofrenia (MATRICS Project; per ulteriori informazioni http://www.matrics.ucla.edu/). La struttura generale dei livelli di punteggio degli item in ciascun dominio della CAI e dei punteggi globali è illustrata in modo schematico in Figura 1.

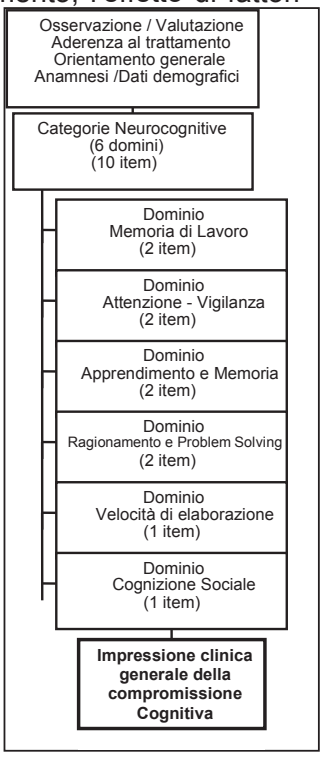

Figura 1. CAI Categoria Globale, Domini e struttura degli items.

Ciascun dominio cognitivo contiene uno o due item per la valutazione delle funzioni neurocognitive rilevanti per il dominio stesso, e per ogni item sono suggerite ulteriori indagini. L'intervistatore è incoraggiato a modificare tali domande e/o includerne di proprie, a seconda della necessità, per migliorare lo scorrimento dell'intervista ed i suoi ambiti d'interesse. L'intervistatore dovrebbe essere a conoscenza del fatto che le diverse aree di indagine sono proposte per facilitare il procedere dell'intervista e che tale procedere è utile ad orientare l'intervistatore verso specifiche aree di

[1]Ad esempio, si consideri un paziente che ha già avuto una prima valutazione ed è poi intervistato nuovamente dopo 3 mesi per un follow-up. Si supponga che questo paziente ha fatto passi avanti significativi nel funzionamento cognitivo ma, 2 settimane prima dell'intervista di follow-up, ha avuto un attacco influenzale che lo ha reso inabile per qualche giorno, con un persistente malessere che si è protratto per il resto della settimana; dopo ciò il paziente si è ristabilito ed è tornato ai livelli prestazionali pre-influenzali che mostravano un miglioramento dalla prima intervista. In questa circostanza, l'intervistatore dovrebbe considerare lo schema generale delle performance cognitiva, non considerando i deficit transitori che sono emersi durante il periodo influenzale.

interesse da indagare ulteriormente. I punteggi finali per ogni item delle funzioni neurocognitive e per la valutazione globale del funzionamento dipende dalle domande poste proprio dall'intervistatore e dalle impressioni acquisite durante l'intervista. Le istruzioni per l'attribuzione del punteggio a ciascun item della CAI e per la valutazione globale sono fornite nella sezione successiva. La quantità di tempo richiesta per l'intervista è variabile. E' stimato che potrebbero essere necessari circa 15 minuti per ciascuna intervista al paziente ed altri 15 minuti per l'intervista all'informatore. La conduzione di interviste durante la fase di formazione potrebbe richiedere più tempo.

La scelta dell'informatore da intervistare è guidata da determinati principi. E' generalmente consigliato intervistare un individuo che abbia maggiore familiarità con il funzionamento del paziente per un lungo periodo. Membri della famiglia che sono regolarmente in contatto con il paziente, lo staff di una casa di cura, gli infermieri o altro staff clinico che regolarmente interagisce con il paziente in regime ambulatoriale o di ricovero potrebbero essere tutti candidati appropriati all'intervista. La sezione "Generale" richiede informazioni sulla natura della relazione ed una stima del tempo totale speso settimanalmente dall'informatore con il paziente discutendo del paziente con altri. Per esempio, un familiare potrebbe passare solo un'ora di tempo a settimana direttamente con il paziente, ma passare ancora un'ora a parlare del paziente con altri membri della famiglia che gli fanno visita regolarmente, un'ora ancora parlando del paziente con lo staff della casa di cura, ed un'altra ora parlando del paziente con i suoi medici. In questo caso andrebbero considerate 4 ore totali settimanali.

La CAI implica che vengano dati punteggi separati all'intervista al paziente, all'intervista all'informatore, ed alla Severità Globale della Compromissione Cognitiva. La valutazione del paziente dovrebbe rispecchiare il giudizio qualificato del clinico basato esclusivamente sull'intervista al paziente, l'intervista all'informatore dovrebbe rispecchiare il giudizio del clinico basato esclusivamente sull'intervista all'informatore, infine il punteggio composito dovrebbe rispecchiare il giudizio del clinico ottenuto facendo riferimento a tutte le fonti di informazioni disponibili, combinando le informazioni ottenute dall'intervista al paziente e all'informatore e, quando disponibili, da altre fonti di informazioni (ad esempio la cartella clinica o altre informazioni sul paziente). Andrebbero riportate, nella sezione Note del libricino dei punteggi dell'intervistatore, le fonti di informazione risultate disponibili.

Istruzioni per la Valutazione della Severità alla prima intervista ed al Follow-up

Il punteggio a ciascun item per le funzioni neurocognitive e il punteggio globale dovrebbero essere attribuiti usando una scala di valutazione a 7 punti (da 1 a 7) dove un punteggio più elevato rispecchia una maggiore compromissione. È possibile anche attribuire un punteggio "N/A" ovvero "non applicabile" o "non disponibile", ma la nostra esperienza ci suggerisce che in poche circostanze il punteggio "N/A" è necessario (ad esempio, se il partecipante avesse terminato l'intervista precocemente, o se solo poche informazioni fossero disponibili, allora sarebbe consigliabile inserire questo tipo di valutazione).

<u>Punteggi di ancoraggio per i Domini Cognitivi</u>

I punteggi d'ancoraggio per gli item delle funzioni neurocognitive si focalizzano sul grado di compromissione e su quanto il deficit influenzi il funzionamento quotidiano. Bisogna considerare quanto il deficit dello stato neurocognitivo impedisca al paziente il raggiungimento di un certo livello di funzionamento atteso in ambito lavorativo, scolastico o nel proprio

ambiente sociale. Si ricordi di confrontare il livello del paziente con i suoi coetanei di pari istruzione. Poiché molti pazienti vivono e lavorano in contesti che rispecchiano un peggioramento rispetto alle aspettative basate sull'età e sulla scolarità, è importate che le valutazioni riflettano i deficit rispetto ai livelli di funzionamento "normali" piuttosto che un livello di funzionamento individuale interno ad un ristretto ambiente di supporto[2]. Si potrebbe sostenere che un individuo che vive in un ambiente di supporto meriterebbe sempre un punteggio di "6" perché i deficit "mettono a rischio l'autonomia". I valutatori dovrebbero allenarsi per ottenere giudizi da esperti così da determinare il punto fino a cui lo specifico deficit cognitivo contribuisce all'attuale situazione lavorativa e di vita del paziente, e riconoscere che una collocazione individuale del paziente in un contesto specifico potrebbe essere dovuta ad altri fattori (tra cui la mancanza di contesti alternativi).

Punteggi di ancoraggio per gli item delle funzioni neurocognitive: tutti i domini cognitivi
Per ogni item nei domini di stato neurocognitivo, consideri i seguenti punteggi d'ancoraggio nella sua valutazione, e consideri i punteggi numerici per il dominio di stato neurocognitivo finale valutato su tutti gli item all'interno del dominio stesso:
N/A = Punteggio non applicabile, o informazioni insufficienti
1. Normale, assenza di compromissione
2. Deficit cognitivi minimi ma funzionamento generalmente conservato
3. Deficit cognitivi lievi con alcuni significativi effetti sul funzionamento
4. Deficit cognitivi moderati con chiari e consisatenti effetti sul funzionamento
5. Deficit cognitivi gravi che interferiscono con il funzionamento quotidiano, incluse le attività della vita quotidiana
6. Deficit cognitivi severi che mettono a rischio l'autonomia
7. Deficit cognitivi così severi da causare pericoli a sé o agli altri

Poiché i punteggi d'ancoraggio cambiano tra i domini, gli "ancoraggi" corretti da applicare ad ogni dominio sono disponibili in fondo ad ogni pagina del libricino dei punteggi.

Item delle funzioni neurocognitive e Valutazioni globali.

La CAI prevede punteggi separati tra gli item delle funzioni neurocognitive ed il livello di severità globale. I punteggi di severità globale vanno attribuiti al termine di ogni intervista completa.

Gli intervistatori non dovrebbero calcolare la media dei singoli item per inserire i punteggi di Dominio, né la media dei punteggi di Dominio per inserire i punteggi di Categoria, né la media dei punteggi di Categoria per inserire i punteggi del livello Globale. Ogni punteggio, sia per gli item che per il livello globale, dovrebbe essere ottenuto basandosi sull'opinione esperta del valutatore sul singolo dominio cognitivo, considerando tutte le informazioni ottenute a quel livello.

I punteggi dell'intervista al paziente ed all'informatore dovrebbero essere inseriti immediatamente dopo ciascuna intervista. I punteggi compositi dovrebbero essere inseriti in seguito ad entrambe le interviste (in pratica, i punteggi compositi possono essere inseriti simultaneamente alla seconda intervista, sia che questa fosse al paziente che all'informatore). I punteggi compositi sono stati ideati per riflettere la migliore stima possibile da parte del valutatore delle reali capacità/limiti funzionali del paziente, sulla base di tutte le informazioni disponibili. Il punteggio composito non deve rispecchiare necessariamente una "media" dei

[2] Ad esempio, un uomo di 42 anni che ha frequentato per 3 anni l'università potrebbe funzionare bene in un lavoro di supporto in officina, ma i deficit cognitivi potrebbero impedirgli di ottenere un impiego competitivo che ci si aspetterebbe se non avesse tali deficit.

punteggi alle interviste al paziente ed all'informatore, ma deve piuttosto riflettere la stima complessiva del valutatore. Tale stima è ottenuta basandosi sia su entrambe le interviste sia su qualsiasi informazione aggiuntiva sul funzionamento del paziente, ottenuta ad esempio dalla revisione della cartella clinica o da altre fonti disponibili. Tali fonti dovrebbero essere annotate nella sezione "Informazioni di base" del libricino dei punteggi dell'intervistatore. In tale sezione è anche importante registrare l'ordine delle interviste. L'intervistatore tenga presente che è anche importante registrare l'ordine delle interviste nella sezione "Informazioni generali" dell'intervista.
Ci sono diversi punti da considerare nell'attribuire i punteggi di severità a ciascun livello della CAI: i punteggi hanno l'obiettivo di considerare specificamente l'impatto dei deficit cognitivi sulle limitazioni funzionali, quindi gli intervistatori devono fare del loro meglio per escludere tutte le fonti non-cognitive di limitazione.
I punteggi più bassi (punteggio di "1") fanno riferimento ad individui sani di età e livello di scolarità simile al paziente, non ad altre persone affette da schizofrenia o altri disturbi mentali o che assumono farmaci psicotropi.
I punteggi medi ("2", "3", "4" e "5") sono graduati in base alla rilevanza dei deficit, a quanto siano evidenti e a quanto pervasivo sia il loro impatto sul funzionamento quotidiano.
I deficit che corrispondono a punteggi bassi (punteggio "2") interferiscono di rado con il funzionamento quotidiano (emergono solo pochi esempi concreti) e, in generale, non si nota alcun effetto su di esso.
I deficit che corrispondono a punteggi lievi (punteggio "3") hanno un abituale impatto quotidiano sul funzionamento, ma le persone potrebbero non notarlo senza delle specifiche domande.
I deficit che corrispondono a punteggi moderati (punteggio "4") sono generalmente notati con chiarezza nella quotidianità; la maggioranza delle persone si accorgerebbero del problema.
I deficit che corrispondono a punteggi gravi (punteggio "5") fanno riferimento a deficit cognitivi che risultano evidenti alla maggioranza delle persone che incontrano il paziente ed hanno un impatto evidente sul funzionamento.
I deficit che corrispondono a punteggi molto gravi ("6" o "7") vanno applicati ad individui che hanno deficit cognitivi così gravi da essere evidenti a chiunque.
Poiché molti pazienti affetti da schizofrenia hanno difficoltà nella vita autonoma (ad esempio vivono in alloggi di supporto), il punteggio "6" è riservato ai casi in cui "le abilità di base per vivere autonomamente" come nutrirsi, prendersi cura di sé e orientarsi sono compromesse a causa dei deficit cognitivi.
L'ultima categoria ("7") va applicata nei casi in cui il deficit cognitivo è così profondo, e le attività della cura di sé tanto compromesse, da esserci evidenti rischi per la sopravvivenza.

La CAI fornisce inoltre una valutazione aggiuntiva del funzionamento cognitivo globale per mezzo della Global Assessment of Functioning – Cognition in Schizophrenia (GAF – CogS), che riporta un punteggio su una scala a 100 punti. La GAF-CogS è utilizzata come intregrazione al punteggio CAI di Severità Globale, ed è simile alla DSM-IV GAF. I punteggi di ancoraggio elencati in basso per la valutazione corrispondono grossomodo ai punteggi della GAF-CogS, con la severità dei punteggi tra 1 e 7 sistematicamente correlata ai punteggi da 100 a 1 della GAF-CogS. Si raccomanda di ottenere il punteggio basandosi sulle informazioni raccolte durante le interviste al paziente ed all'informatore, utilizzando tutte le possibili informazioni circa le funzioni cognitive del paziente.

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Punteggi d'ancoraggio per la Valutazione della Severità del Deficit Cognitivo su una scala a 7 punti, e relativo confronto con la GAF-CogS (Global Assessment of Functioning – Cognition in Schizophrenia)		
Punteggio di Severità Globale CAI	GAF-CogS	Descrizione (vedere anche le descrizioni della GAF-CogS)
NA	NA	Punteggio non applicabile, o informazioni insufficienti
1	100-88	Normale, assenza di compromissione
2	87-74	Deficit cognitivi minimi ma funzionamento generalmente conservato
3	73-59	Deficit cognitivi lievi con alcuni effetti costanti sul funzionamento
4	58-43	Deficit cognitivi moderati con chiari effetti sul funzionamento
5	42-28	Seri deficit cognitivi che interferiscono con il funzionamento quotidiano
6	27-14	Deficit cognitivi severi che mettono a rischio l'autonomia
7	13-1	Deficit cognitivi così severi da causare pericolo per sé o per gli altri

I Domini non necessitano di essere valutati in un ordine definito. È comunque essenziale che ogni Dominio sia esaminato e che le osservazioni siano annotate con dettagli sufficienti per facilitare la valutazione dei cambiamenti dopo un periodo di 1-6 mesi (l'intervallo effettivo è su scelta del clinico o dello studio in cui si sta utilizzando la CAI).

Sono previsti spazi per riportare brevi note per evidenziare osservazioni che supportano la valutazione del funzionamento per ciascun dominio. È importante documentare separatamente i contributi del paziente e del rispettivo informatore, poiché devono essere applicati punteggi differenti per ciascuno. È riconosciuto che può risultare difficile separare le informazioni ottenute dal paziente da quelle dell'informatore, in particolare durante la seconda intervista dopo che una data informazione è stata già riportata in precedenza da un intervistato o dall'altro. Il valutatore è incoraggiato a far uso del proprio giudizio da esperto per inserire un corretto punteggio basato sulle informazioni ottenute dall'intervistato, anche se il punteggio stesso è influenzato dalle informazioni ottenute dall'altro intervistato (ad esempio, se un intervistato ha fornito informazioni circa le limitazioni in particolari compiti o abilità, l'intervistatore dovrebbe usare queste informazioni nell'intervista all'altro intervistato).

Il periodo da indagare per la valutazione è il mese che precede l'intervista, a meno che non sia indicato diversamente per gli scopi di uno specifico protocollo di ricerca. Ciò significa che l'intervistatore dovrebbe principalmente provare ad ottenere informazioni sulla condizione del paziente nell'ultimo mese. Potrebbero essere riportati esempi di particolari deficit cognitivi risalenti ad un periodo antecedente al mese indagato: in questi casi è compito dell'intervistatore determinare se tali esempi sono rappresentativi dell'abilità attuale del paziente.

Istruzioni per la valutazione delle funzioni cognitive al follow-up

La struttura complessiva dell'intervista di follow-up è molto simile alla struttura della prima intervista. In ogni caso, per la categoria Generale, l'enfasi è posta sull'annotazione di eventi che potrebbero essere accaduti a partire dalla data dell'intervista precedente. Tutti gli altri aspetti dei punteggi individuali nell'ambito di ciascun dominio dovrebbero continuare ad avere il focus sul grado di severità dei deficit e dovrebbero utilizzare lo stesso criterio di ancoraggio della prima valutazione.
I punteggi dei singoli domini devono essere compilati separatamente a seguito delle interviste al paziente e dell'informatore, basandosi sulle informazioni delle rispettive interviste. La valutazione composita del cambiamento deve essere compilata basandosi sulle informazioni ottenute sia dall'intervista al paziente che all'informatore.

Linee guida per le valutazioni degli item per le Funzioni Neurocognitive

Lo scopo della valutazione CAI è di ottenere un giudizio qualificato sia per gli item delle funzioni neurocognitive che per il livello Globale, basandosi sull'intervista al paziente ed al suo informatore. Le indagini suggerite sono proposte per aiutare gli intervistatori ad orientarsi, ma sta all'intervistatore adattare le domande allo specifico paziente ed informatore intervistati. Dovrebbe anche essere evidente che le aree indagate sono maggiormente appropriate per l'intervista al paziente, quindi il valutatore deve riformularle in maniera da ottenere notizie dall'informatore circa la sua impressione sul funzionamento del paziente e le sue abilità in ciascuna area. Per ottenere i punteggi degli item di "osservazione diretta" dell'area "Informatore" (ad esempio, nel dominio Velocità di elaborazione, alcuni punteggi sono basati sulle impressioni dell'intervistatore sulla velocità dell'eloquio e di movimento del paziente), all'informatore possono essere chieste le sue osservazioni dirette sul paziente.

Le seguenti linee guida sono fornite per aiutare a chiarire la distinzione tra i domini e gli item delle funzioni neurocognitive. Alcune distinzioni possono risultare arbitrarie, mentre altre sono basate su una teoria che può risultare difficile da convertire in osservazioni oggettive di ogni singolo caso. Per tale motivo è particolarmente importate che i valutatori esaminino attentamente queste linee guida e tentino di risolvere i propri dubbi durante la fase di training.

Dominio: Memoria di lavoro

Gli elementi essenziali di tale dominio consistono nell'abilità di tenere brevemente in mente l'informazione, per un periodo di circa 20 secondi, e di "fare qualcosa" (ad esempio, "agire" o compiere qualche operazione mentale) con quella informazione. È importante distinguere questa abilità dal dominio di Apprendimento Verbale e Memoria, che consiste nell'abilità di apprendere e ricordare delle informazioni per lunghi periodi, e particolarmente dopo alcune attività intercorrenti. Per esempio, l'abilità di ricordare un numero di telefono abbastanza a lungo per annotarlo o digitarlo, immediatamente dopo averlo ascoltato, andrebbe considerata come Memoria di Lavoro. Al contrario, l'abilità di ricordare un numero telefonico, dopo averlo ripetuto più volte, sarebbe da considerarsi come Apprendimento Verbale e Memoria.
I due item si focalizzano su due abilità:

Item 1. Difficoltà a ritenere le informazioni apprese di recente per periodi brevi (lunghi a sufficienza per usarle)?

Il focus qui è sulla ritenzione, ovvero l'abilità di conservare l'informazione in mente, a prescindere dal fatto che questa serva realmente o meno per mettere in atto un'azione.

Item 2. Difficoltà a fare rapidamente calcoli a mente o elaborazioni mentali?

Il focus qui è sull'elaborazione delle informazioni che devono essere memorizzate, ad esempio i calcoli eseguiti a mente sono un ottimo esempio.

Le aree di indagine per questi item si concentrano sulla memoria di lavoro verbale, soprattutto perché gli esempi di vita quotidiana per la memoria di lavoro spaziale sono difficili da ottenere. In ogni caso l'esaminatore dovrebbe considerare se altre informazioni, acquisite in qualsiasi situazione, dove appare chiaro che la memoria di lavoro è deficitaria, possono essere rilevanti per la valutazione di questi due item. Ad esempio, se ad una biglietteria un paziente si trova a guardare la lista delle partenze degli autobus o i titoli dei film ma non è capace di conservare questa informazione abbastanza a lungo per informare il bigliettaio della propria scelta; o, ad esempio, se vede un segnale che indica diverse direzioni ma non è in grado di mantenere questa informazione in mente abbastanza a lungo per intraprendere la giusta azione (segnato sull'item 1 di Memoria di Lavoro). Altre forme di elaborazione mentale che comprendono materiali che necessitano di essere tenuti a mente, dovrebbero essere segnate nell'item 2 del dominio Memoria di Lavoro. Per esempio, in un compito di assemblaggio un paziente potrebbe non essere in grado di convertire un'informazione ottenuta da uno schema di istruzioni al compito effettivo. Mentre potrebbe sembrare che ciò rispecchi un problema primario dell'abilità visuospaziale, la difficoltà potrebbe essere dovuta all'incapacità di conservare l'informazione nella memoria di lavoro visiva. Il compito dell'intervistatore è di determinare se un determinato esempio possa meglio riflettere un problema di:

a) Elaborazione dell'informazione (che dovrebbe essere valutata come problema di "memoria di lavoro");
b) Un problema di apprendimento visivo e memoria (che dovrebbe essere valutata come deficit di apprendimento visivo e memoria se l'informazione andasse applicata dopo un intervallo di tempo più lungo);
c) Una difficoltà di Ragionamento e Problem Solving (che dovrebbe essere valutata in questo dominio se la difficoltà sembrasse far parte di un deficit più generale nell'applicare informazioni preesistenti a nuovi problemi);
d) Altri problemi non valutati dalla CAI

Dominio: Attenzione/Vigilanza

Gli elementi essenziali di tale dominio sono la capacità di concentrarsi in maniera efficace, di selezionare da un ambiente complesso gli elementi che richiedono attenzione e l'abilità di scartare una miriade di stimoli distrattivi che potrebbero disturbare l'elaborazione dei compiti cognitivi quotidiani. Questa è una delle aree più impegnative per la valutazione dei singoli item dato che necessita di sottili distinzioni e possibili interconnessioni. Abbiamo diviso "Attenzione/Vigilanza" in 3 ampi item, teoricamente rispecchianti l'attenzione sostenuta, l'attenzione selettiva, e la capacità di non distrarsi.

Item 3. Problemi a mantenere la concentrazione nel tempo (senza distrazioni)?

Questo item pone il focus sulla "vigilanza", è dunque importante ottenere informazioni su

quanto a lungo il paziente è in grado di mantenere l'attenzione durante una particolare attività. L'indagine potrebbe esser condotta ponendo domande di ordine generale (ad esempio, " Ha problemi di concentrazione?" che spesso porta a risposte di rilievo), e domande più specifiche (ad esempio, durante una lettura riesce a sostenere l'attenzione abbastanza a lungo per finire un capitolo?) Di fatto non è concettualizzato un periodo di tempo durante il quale un individuo dovrebbe essere in grado di mantenere l'attenzione, infatti l'obiettivo è di determinare esclusivamente se questa abilità è funzionale per il paziente. Se la capacità di sostenere l'attenzione fosse compromessa solo in presenza di distrazioni, allora questa limitazione andrebbe considerata sotto questa voce.

Item 4. Difficoltà a focalizzarsi su specifiche informazioni (in assenza di evidenti distrazioni)?

Questo item fa riferimento all'abilità di selezionare dettagli specifici in ambienti complessi e focalizzarsi sugli stessi. Virtualmente in qualsiasi attività gli individui hanno bisogno di focalizzarsi su aspetti e dettagli specifici che sono rilevanti in una data situazione, hanno bisogno quindi di ignorarne altri, o necessitano di scegliere di quale "aspetto" occuparsi astenendosi da considerazioni generali. Le aree indagate suggerite offrono esempi di situazioni di vita quotidiana in cui può risultare impegnativo restringere il focus attentivo su elementi rilevanti inseriti in un contesto piuttosto complesso.

Dominio: Apprendimento Verbale e Memoria

Le caratteristiche essenziali di questo dominio consistono nell'abilità di apprendere e ricordare nuove informazioni verbali, sia mediante l'ascolto che la lettura. I problemi di apprendimento e di memoria sono tra le compromissioni più frequenti dei pazienti che giungono ad una valutazione neuropsicologica, e i deficit cognitivi in questo dominio sono stati considerati i più gravi in numerosi studi. Per una buona valutazione dei deficit di apprendimento e di memoria la difficoltà maggiore consta nel distinguere i possibili effetti di altri deficit che hanno un impatto sul processo di apprendimento. Ad esempio, problemi di attenzione potrebbero rendere difficile acquisire qualsiasi nuova informazione, problemi relativi alla memoria di lavoro potrebbero rendere difficile il ritenere abbastanza a lungo informazioni in modo da codificarle per un utilizzo a lungo termine, e problemi di ragionamento e problem solving potrebbero sottendere problemi nell'acquisire nuove abilità. Ai valutatori non è richiesto di fornire un'analisi accurata del ruolo che le altre funzioni cognitive giocano nella compromissione dei processi di apprendimento e di memoria, ma è loro richiesto uno sforzo per ottenere degli esempi su informazioni relative alle funzioni di apprendimento/memoria che vanno comprese e/o ripetute. Come sarà evidenziato successivamente, la distinzione di tale dominio dalla memoria di lavoro è facilitata se si determina l'intervallo di tempo tra il momento dell'apprendimento ed il tentativo di richiamare a mente l'informazione. Se questo intervallo è inferiore a un minuto, l'esempio è probabilmente riferibile alla memoria di lavoro. Se l'intervallo è maggiore di qualche minuto, e ancor di più se durante tale periodo è intercorsa un'attività, allora l'esempio è tendenzialmente riferibile all'apprendimento verbale e memoria.

Item 5. Difficoltà ad apprendere e ricordare informazioni?

Questo item si riferisce alle capacità di apprendimento in memoria di nuove informazioni verbali, ascoltate o lette. È importante distinguere tale abilità dalla memoria di lavoro, che è l'abilità di ricordare qualcosa abbastanza a lungo per poi utilizzarla (solitamente per un periodo

fino a circa 20 secondi). Diversamente, questo item fa riferimento all'abilità di apprendere mediante la lettura o l'ascolto, e di ricordare le nuove informazioni apprese per un certo periodo di tempo durante il quale sono intercorsi altri compiti o attività. Ad esempio, ricordarsi il nome di qualcuno *immediatamente* dopo averlo ascoltato (abbastanza a lungo da utilizzarlo per una risposta immediata) dovrebbe essere preferibilmente riferito al dominio di memoria di lavoro, ma la difficoltà di ricordarsi il nome di qualcuno 20 minuti dopo, dopo averlo ascoltato e ripetuto in una conversazione, e dopo aver parlato con qualcun altro, andrebbe valutato sotto questa voce.

Item 6. Difficoltà nel richiamare alla memoria eventi recenti?

Questo item si concentra sull'abilità di richiamare alla mente eventi specifici (ovvero la memoria episodica) che sono stati esperiti personalmente dall'individuo, ed alle conoscenze dell'individuo su notizie di l'attualità del mese scorso o giù di lì. La compilazione dei punteggi su "eventi di attualità" dovrebbe considerare il livello di esposizione ai media dell'individuo o di altre persone che potrebbero condividere tali informazioni.

Dominio: Ragionamento e Problem Solving

Gli aspetti essenziali di questo dominio sono la capacità di sviluppare piani d'azione ed iniziare a metterli in atto, principalmente quando si interrompe una routine, e la capacità di eseguire questi piani nonostante vari ostacoli e conflitti di priorità. Questo dominio appare simile al dominio cognitivo definito "funzioni esecutive", ma è di portata più ampia. È uno dei più complessi ed onnicomprensivi tra i domini del funzionamento, spesso coinvolge molte abilità, ed è tra i domini considerati maggiormente compromessi nelle persone affette da schizofrenia. Si è tentato di dividere il dominio in due aree chiave, comprendenti flessibilità e giudizio in situazioni nuove.

Item 7. Perdita della flessibilità nel generare piani alternativi quando necessario?

L'item si concentra sulla capacità del paziente di generare soluzioni alternative quando è interrotta la sua routine. Le aree indagate suggerite si riferiscono a diverse attività giornaliere che sono soggette a modifiche che necessitano di un pensiero flessibile (ad esempio, utilizzare i trasporti, fare compere); l'intervista CAI nella sezione "Informazioni Generali" in merito alle attività di vita quotidiana potrebbe suggerire indagini alternative. Particolari sforzi devono essere fatti per distinguere la valutazione di questo item da quelli che si concentrano maggiormente sulle iniziative generali di problem solving piuttosto che di flessibilità di pensiero.

Item 8. Difficoltà in situazioni che richiedono una decisione?

Questo item si riferisce alla capacità di esercitare un giudizio sensato nel processo decisionale, particolarmente quando non ci può essere una soluzione ovvia e diretta. Le aree indagate suggerite offrono diversi esempi di problemi quotidiani, se un paziente risponde con una soluzione diretta e sensibile l'intervistatore potrebbe continuare l'intervista complicando ancor di più la situazione (ad esempio, se è stato chiesto "che cosa farebbe se saltasse la corrente?" e il paziente rispondesse "chiamerei il portiere…" l'intervistatore potrebbe continuare e chiedere: "Bene, ipotizziamo che il portiere sia irraggiungibile, allora lei che cosa

farebbe?"). Lo scopo del valutatore è di giudicare le risposte di problem solving del paziente nei termini di rilevanza ed adeguatezza rispetto alla soluzione del compito.

Dominio: Velocità di elaborazione

Tale dominio ha lo scopo principale di fornire valutazioni su come il paziente svolge i compiti, parla e si muove. La velocità di elaborazione è risultata in molti studi di analisi fattoriale del funzionamento neurocognitivo come una dimensione chiave tra le abilità in cui le persone affette da schizofrenia presentano deficit. Sebbene la base di questi deficit rimanga poco chiara, e verosimilmente sono coinvolti più sistemi nel determinarli, la lentezza generale delle prestazioni sia su compiti motori semplici che su compiti cognitivi complessi appare spesso evidente. Questo item si focalizza su più attività complementari ed è valutato mediante l'osservazione obiettiva da parte del valutatore dell'eloquio e dei movimenti del paziente durante l'intervista. Per quel che concerne l'osservazione diretta, nessuna area di indagine specifica o domanda aggiuntiva è necessaria.

Item 9. Lentezza nell'eseguire i compiti?

Questo item mira a determinare quanto lentamente il paziente svolge compiti relativamente complessi che richiedono abilità cognitive, come ad esempio cucinare o fare compere. I valutatori dovrebbero tentare di chiarire se il tempo totale per il completamento dei compiti complessi è dovuto ad un rallentamento generalizzato, o se è meglio spiegato da altri deficit cognitivi, come ad esempio i deficit di attenzione (ad esempio, la distraibilità può in effetti condurre un paziente a spendere un po' più di tempo su un compito agevole) o il ragionamento ed il problem solving (ad esempio, se un paziente neanche inizia un tentativo di completare un compito, allora di certo non lo completerà rapidamente).

Dominio: Cognizione Sociale

Gli aspetti essenziali di questo dominio si riferiscono all'abilità di percepire segnali sociali, di cogliere il punto di vista altrui nelle situazioni sociali, e di partecipare efficacemente alle interazioni sociali. Il progetto MATRICS ha scelto il subtest Managing Emotions dal Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) per valutare questo dominio. Citando gli editori di questo test, riportiamo che "l'intelligenza emotiva implica l'abilità di percepire accuratamente, valutare, ed esprimere emozioni; l'abilità di avere accesso e/o di generare sentimenti quando essi facilitano il pensiero; l'abilità di comprendere le emozioni e la coscienza emotiva; e l'abilità di regolare le emozioni per promuovere lo sviluppo emotivo ed intellettuale". Dunque, gli item selezionati per la valutazione di questo dominio comprendono diverse aree come ad esempio la percezione delle emozioni, il comprendere le intenzioni degli altri (anche definita come "teoria della mente"), la comprensione di significati sottesi, ed altre osservazioni dirette delle interazioni sociali durante l'intervista.

10. Difficoltà nel comprendere le intenzioni o il punto di vista di un'altra persona?

Questo item fa riferimento all'abilità del paziente di considerare la prospettiva di un'altra persona, o la capacità di giudicare mediante comunicazioni non chiare ed indirette che emozione sta provando un'altra persona, che cosa intende dire/fare o cosa desidera.
Le aree indagate prevedono sia domande dirette "Ha problemi nel comprendere il punto di

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vista degli altri (se non è d'accordo con loro; anche se non lo dicono espressamente)?" e domande relativamente indirette ("Se sta parlando con qualcuno e questa persona guarda l'orologio quali crede siano le sue emozioni e i suoi pensieri?") per elicitare informazioni utili a questa valutazione.

Questa versione della CAI (2° Versione; 18 Gennaio, 2008) è stata progettata per essere utilizzata dagli autori per studi di affidabilità e validità. Si prevede che, nelle prossime versioni dello strumento, potrebbero esserci modifiche alla struttura, al contenuto degli item e delle aree indagate e ai punteggi di ancoraggio. Le valutazioni raccolte in questo lavoro preliminare permetteranno la stima delle proprietà psicometriche di item che potrebbero essere eliminati nelle successive versioni della CAI. Per l'uso della scala in trials clinici, c'è un punteggio di base da utilizzare come punteggio finale che è il GLOBAL SEVERITY OF COGNITIVE IMPAIRMENT – RATER COMPOSITE IMPRESSION. La Global Assessment of Function – Cognition in Schizophrenia (GAF-CogS) potrebbe essere utilizzata in analisi statistiche per valutare le interazioni tra il funzionamento alla valutazione iniziale ed i cambiamenti, o in modo descrittivo, ad esempio "Il trattamento X è risultato associato con un miglioramento significativo come mostrato dalla Global Impression of Change in Cognitive Function, ma i pazienti continuavano a mostrare un livello di disfunzione cognitiva da lieve a moderato al termine del trial, come evidenziato dalla Global Assessment of Cognitive Function". Saranno necessari studi empirici per determinare se la somma totale dei punteggi degli items neurocognitivi vs. punteggi di severità globale, offra una migliore misurazione del costrutto generale che questo strumento ha lo scopo di misurare.

Appendix 2. Supplemental Guidelines

Linee Guida supplementari per la somministrazione della Cognitive Assessment Interview (CAI)

Principi base della valutazione della cognizione tramite intervista: l'intervistatore CAI è in grado di fornire un giudizio qualificato sul funzionamento cognitivo del paziente che non è unicamente basato sull'autovalutazione o sulla percezione del paziente del proprio funzionamento cognitivo. L'intervistatore cerca di collegare il funzionamento cognitivo del paziente con le attività quotidiane come le prestazioni scolastiche, i successi lavorativi e le interazioni sociali. Quando possibile, si tenta di separare l'influenza dei sintomi positivi e negativi o depressivi sul funzionamento nelle attività quotidiane dagli effetti dovuti alla compromissione cognitiva. I pazienti per i quali la sintomatologia sembra avere un ruolo primario sull'esito funzionale hanno un punteggio CAI inferiore per i deficit cognitivi rispetto ai pazienti per i quali appare più evidente l'associazione tra i deficit cognitivi e la compromissione funzionale. Sebbene il periodo di tempo su cui soffermarsi per la valutazione CAI è l'ultimo mese, l'intervistatore avrà spesso la necessità di ampliare tale periodo di indagine per includere gli eventi passati in cui il paziente aveva un'occupazione lavorativa, frequentava la scuola o aveva un'elevata frequenza di interazioni sociali.

Linee guida per condurre un'intervista:

1) Innanzitutto nel processo di valutazione bisogna effettuare un collegamento tra il funzionamento cognitivo del paziente ed il funzionamento lavorativo, le prestazioni scolastiche, le attività domestiche o altre attività che richiedono capacità cognitive. Non bisogna aspettarsi di comprendere la totalità di questa relazione immediatamente perché parte della valutazione CAI comporta l'educare il paziente a comprendere la relazione tra le abilità di pensiero ed il funzionamento. Se il paziente attualmente non frequenta la scuola né lavora né socializza, bisogna chiedergli di fornire informazioni circa le ultime occasioni in cui erano richieste abilità di pensiero per lo svolgimento di determinate attività o gli si può chiedere di supporre le sue abilità attuali in queste prestazioni.

2) Chiedere al paziente di immaginare una connessione tra il funzionamento cognitivo e circostanze di vita quotidiana è un metodo utile per ottenere informazioni, ad esempio quando gli si chiede perché non lavora o non va a scuola. Se il paziente riconosce che non gli è possibile frequentare la scuola o lavorare perché ha un deficit di memoria o concentrazione, queste informazioni possono essere usate per ottenere un punteggio. Un altro esempio di come l'intervistatore può determinare l'abilità della memoria di lavoro è chiedere al paziente se è in grado di ricordare un numero telefonico da poco appreso. Se il paziente risponde che ha l'abitudine di annotare sempre un numero di telefono, si può chiedere se si ritiene in grado di ricordare un numero di telefono nel caso in cui non abbia la possibilità di annotarlo.

3) Quando si somministrano gli item che richiedono al paziente di descrivere quale comportamento sarebbe appropriato in determinate circostanze richiedenti abilità di problem-solving, bisogna valutare attentamente la risposta del paziente. Bisogna chiedere un chiarimento se il fondamento razionale di un comportamento risulta ambiguo, ad esempio nel caso di una risposta come la seguente: "se resto chiuso fuori casa, andrei a casa del vicino". L'intervistatore dovrebbe chiedere "perché andresti a casa di un vicino"? Presumibilmente il paziente risponderà che userà il telefono per chiamare un familiare oppure che attenderà lì che una persona con le chiavi rientri a casa. Se durante qualsiasi momento della CAI il paziente da una risposta che sembra stereotipata, bisogna stimolarlo a

spiegare il razionale del comportamento e valutarla di conseguenza, ad esempio “non mi sono mai perso, conosco l’intera città dopo che ho vissuto qui per 18 anni”. A questo paziente si dovrebbe chiedere “che cosa farebbe se fosse in una città a lei poco familiare, userebbe una mappa per trovare la strada giusta”?

4) Nel momento in cui l’intervistatore indaga i vari domini del funzionamento cognitivo, bisognerebbe fare uno sforzo per definire ogni singolo dominio cognitivo mediante termini conosciuti, ad esempio la memoria di lavoro è definita come “la memoria a breve termine” e l’attenzione/vigilanza è definita come “concentrazione”.

Domande generali supplementari: sono qui suggerite una serie di domande ed indagini di approfondimento che possono essere utilizzate per ottenere informazioni aggiuntive sulle prestazioni cognitive del paziente nella vita quotidiana. Generalmente, le indagini di base della CAI partono dall’analisi di alti livelli di deficit cognitivi perciò, considerando che la maggioranza dei pazienti non sono eccessivamente compromessi, esse dovrebbero essere integrate con altre domande più impegnative per un’accurata valutazione del funzionamento cognitivo.

Valutazione del contesto
Ha avuto modifiche nella terapia farmacologica o ha subito infortuni? Il motivo per cui le chiedo ciò è perché vorrei capire se questi cambiamenti possano aver influenzato in qualche modo le sue abilità di pensiero. Infatti, questa intervista riguarda le sue capacità di pensiero.

Dominio: Memoria di lavoro

1. Difficoltà a ritenere le informazioni apprese di recente

Se partecipa ad una festa e conosce 5 persone, quanti nomi sarebbe in grado di ricordare nei momenti immediatamente successivi all’ascolto? Se meno di 4 o 5: quante volte avrebbe bisogno di ascoltare i loro nomi prima di essere in grado di ricordarli? Se avesse chiamato il servizio informazione per avere il numero di telefono di una pizzeria e non avesse con sé una matita né una penna per segnarsi il numero, sarebbe in grado di ricordarlo?

2. Difficoltà a fare rapidamente calcoli a mente o elaborazioni mentali

Si ricorda che in questo item di “memoria di lavoro” l’intervistatore chiede al paziente se è in grado di ricordare una serie di cifre a mente mentre è impegnato a pagare le bollette. Se il paziente non ha il compito di pagare le proprie bollette bisogna chiedergli “perché non lo fa?”. Se il paziente riporta che il motivo non è in relazione alle sue abilità cognitive, ad esempio “mia madre si prende cura di tutte le questioni finanziarie di casa”, bisogna allora chiedere al paziente se si ritiene in grado di ricordare le cifre a mente in modo da pagare le bollette nel caso in cui sua madre fosse impossibilitata a farlo.

Dominio: Attenzione/Vigilanza

3. Difficoltà a mantenere la concentrazione nel tempo (senza distrazioni)

Indagine di approfondimento suggerita: dopo aver letto un articolo o guardato un film, sarebbe in grado di ricordare che cosa ha appena letto o di discutere con un’altra persona su cosa ha imparato o

di raccontare la trama del film? Ha la tendenza a dimenticare che cosa ha appena letto o ha problemi a mantenere il filo delle informazioni di un articolo, di uno spettacolo televisivo o di un film?

4. Difficoltà a focalizzarsi su specifiche informazioni (in assenza di evidenti distrazioni)

Se dopo aver posto la domanda: "Ha difficoltà a capire il percorso giusto sulla piantina alla fermata dell'autobus"? Il paziente riporta che utilizza un comportamento appreso in modo meccanico per orientarsi per strada, chiedergli se si ritiene in grado di farlo in una situazione nuova come ad esempio in una città sconosciuta.

Dominio: apprendimento verbale e memoria

5. Difficoltà ad apprendere e ricordare informazioni?

Che cosa succederebbe se non scrivesse le istruzioni o le informazioni? Si affiderebbe ad altri perché ciò che annota non è sufficiente?

6. Difficoltà nel richiamare alla memoria eventi recenti?

Chiedere se il paziente è uscito di recente con familiari o amici. Se si, chiedere se è in grado di ricordare qualche dettaglio riguardo le attività come ad esempio il tipo di posto o di evento, ad esempio il nome del film visto al cinema, il luogo dove è sito il cinema, la trama del film, il tipo o la sede del ristorante, il tipo di cibo che è stato ordinato. Se il paziente non ha svolto attività sociali, l'intervistatore può chiedere al paziente cosa ha mangiato per pranzo o cena la sera precedente o due giorni addietro.

Dominio: Ragionamento e problem solving

7. Perdita della flessibilità nel generare piani alternativi quando necessario.

Ricordare che la capacità di generare alternative su che cosa fare nel caso in cui un negozio fosse chiuso è uno dei più semplici problemi di vita quotidiana. Assicurarsi di iniziare la domanda indicando che quell'oggetto è necessario quel giorno, ad esempio un ingrediente è necessario per completare una ricetta o un oggetto è necessario per la casa. Se il paziente dovesse dire che se il negozio è chiuso lui tornerebbe a casa, chiedergli "Perché"? La risposta del paziente potrebbe fare chiarezza se l'incapacità di generare alternative è dovuta ad un "atteggiamento disfattista" o alla sintomatologia negativa.

8. Difficoltà in situazioni che richiedono una decisione

Rispetto alle domande relative ad un'interruzione di corrente, rimanere chiusi fuori casa, all'avere un lavandino otturato, la risposta "chiamerei il portiere o il vicino di casa" dovrebbe essere approfondita con "che cosa farebbe se non fossero reperibili"?

Dominio: Velocità di elaborazione

9. Lentezza nell'eseguire i compiti

Se l'intervistatore ritiene che il paziente abbia scarsa consapevolezza riguardo la propria ridotta velocità di elaborazione, può chiedergli se qualcuno si lamenta che il paziente è stato troppo lento nel portare a termine un compito, ad esempio la madre del paziente o un supervisore.

Domini: Cognizione sociale

10. Difficoltà nel comprendere le intenzioni o il punto di vista di un'altra persona

Questo item misura l'abilità del paziente di astrazione riguardo al fatto che il punto di vista di un'altra persona, diverso dal proprio, potrebbe essere influenzato dalla differenza di età o stato sociale. Chiedere al paziente: "Se stesse parlando con una persona più giovane o più anziana di lei, o proveniente da un'altra parte della nazione o del mondo, avrebbe problemi a comprendere come o perché l'opinione di quella persona differisce dalla sua? Il semplice domandare ad una persona se sia in grado di comprendere il significato di una persona che guarda l'orologio non è molto impegnativo. Altre domande di approfondimento potrebbero includere il chiedere se il paziente comprende le intenzioni o le emozioni degli altri dall'espressione facciale, dal tono della voce o dal comportamento".

Data: _____

Paziente ID: _____

Valutatore: _____

Sessione: _____

CAI

Cognitive Assessment Interview
(Intervista per la valutazione cognitiva)

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Version 2 -- 1/18/08--

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Informazioni Generali		
DOMINI PER IL PAZIENTE		
	Paziente	
Osservazione/Valutazione		
Aspetto – pulizia ed igiene generale, abbigliamento (adeguatezza degli indumenti alla stagione, pulizia, abbinamento colori/fantasie, abiti correttamente abbottonati).	Riportare note:	
Utilizzare tutte le fonti di informazione	Riportare fonti di informazione:	
Aderenza al trattamento		
Assume i farmaci nella dose e all'orario prestabiliti, come da prescrizione?		
Modifiche di terapia		
Orientamento generale		
Tempo (Giorno, Anno, Data), Luogo (Città, Nazione, Clinica), Persona		
Descrivere la situazione di vita del paziente		
Attualmente il paziente ha sintomi psicotici come ad esempio allucinazioni?	Descrivere:	
Mancino o destrimane (mano utilizzata per scrivere)		
Chiedere al paziente di descrivere la relazione con la persona che fornisce le informazioni, ad esempio la madre, l'assistente sociale e il numero di ore trascorse con quella persona in una settimana.	Riportare informazioni:	
DOMINI PER IL PAZIENTE E PER L'INFORMATORE		
	Paziente	**Informatore**
Dati anamnestici rilevanti		
Eventi clinici recenti rilevanti, malattie del paziente, dell'informatore o di altri membri della famiglia, eventi sociali o personali significativi. Oscillazioni significative della condizione clinica. [Per la valutazione di Follow-up: eventi clinici successivi alla prima intervista]		
Dati demografici		
Scolarità (Anni; medie superiori=13)		
Studente / Lavoratore (specificare se tempo pieno o *part-time*)		
Data di nascita:		
Durata dell'intervista:	Indicare in minuti:	Indicare in minuti:
Note:		

CAI - Cognitive Assessment Interview - Page 3

DOMINIO: Memoria di lavoro

1. Difficoltà a ritenere le informazioni apprese di recente per periodi brevi (lunghi a sufficienza per usarle)?

Dimentica facilmente i nomi delle persone che ha appena conosciuto? Ha difficoltà a ricordare i numeri di telefono dopo averli ascoltati? Ha difficoltà a ricordare ciò che il suo medico le ha appena detto durante una visita? Deve spesso scrivere le informazioni per ricordarle?

Esempi del paziente:	Esempi dell'informatore:

Paziente	Informatore	Punteggio composito
N/A 1 2 3 4 5 6 7	N/A 1 2 3 4 5 6 7	N/A 1 2 3 4 5 6 7

2. Difficoltà a fare rapidamente calcoli a mente o elaborazioni mentali?

Ha difficoltà a calcolare quanto resto deve avere quando fa acquisti? Ha difficoltà nel fare i calcoli a mente quando paga dei biglietti o quando legge un estratto conto?

Esempi del paziente:	Esempi dell'informatore:

Paziente	Informatore	Punteggio composito
N/A 1 2 3 4 5 6 7	N/A 1 2 3 4 5 6 7	N/A 1 2 3 4 5 6 7

DOMINIO: Attenzione/Vigilanza

3. Problemi a mantenere la concentrazione nel tempo (senza distrazioni)?

Ha difficoltà a concentrarsi? Ha bisogno di fare spesso delle pause? Ha difficoltà a mantenere la concentrazione quando legge, ascolta la radio o guarda la televisione abbastanza a lungo da leggere/ascoltare/vedere un intero articolo/capitolo/programma?

Esempi del paziente:	Esempi dell'informatore:

Paziente	Informatore	Punteggio composito
N/A 1 2 3 4 5 6 7	N/A 1 2 3 4 5 6 7	N/A 1 2 3 4 5 6 7

4. Difficoltà a focalizzarsi su specifiche informazioni (in assenza di evidenti distrazioni)?

Ha difficoltà a trovare ciò che le serve quando è al supermercato? Ha difficoltà a capire il percorso giusto sulla piantina alla fermata dell'autobus?

Esempi del paziente:	Esempi dell'informatore:

Paziente	Informatore	Punteggio composito
N/A 1 2 3 4 5 6 7	N/A 1 2 3 4 5 6 7	N/A 1 2 3 4 5 6 7

PUNTEGGI DI ANCORAGGIO PER DEFINIRE IL GRADO DI SEVERITA'			
N/A = Punteggio non applicabile, o informazioni insufficienti	**1.** Normale, assenza di compromissione	**2.** Deficit cognitivi minimi ma funzionamento generalmente conservato	**3.** Deficit cognitivi lievi con alcuni effetti significativi sul funzionamento
4. Deficit cognitivi moderati con chiari effetti sul funzionamento	**5.** Seri deficit cognitivi che interferiscono con il funzionamento quotidiano	**6.** Deficit cognitivi severi che mettono a rischio l'autonomia	**7.** Deficit cognitivi così severi da causare pericolo per sé o per gli altri

DOMINIO: Apprendimento verbale e Memoria

5. Difficoltà ad apprendere e ricordare informazioni verbali?

Ha difficoltà ad apprendere e ricordare istruzioni o altre informazioni importanti (ad esempio nomi dei farmaci)? Ha difficoltà a ricordare successivamente i nomi delle persone che incontra? Ha bisogno di avere con sé degli appunti per aiutarsi a ricordare le cose?

Esempi del paziente:	Esempi dell'informatore:

Paziente	Informatore	Punteggio composito
N/A 1 2 3 4 5 6 7	N/A 1 2 3 4 5 6 7	N/A 1 2 3 4 5 6 7

6. Difficoltà nel richiamare alla memoria eventi recenti?

Le succede di avere la necessità che qualcuno le ricordi le cose che sono successe di recente? Ricorda cosa ha mangiato ieri sera a cena? Quali sono le notizie sentite al telegiornale o scritte sui giornali recentemente*?*

Esempi del paziente:	Esempi dell'informatore:

Paziente	Informatore	Punteggio composito
N/A 1 2 3 4 5 6 7	N/A 1 2 3 4 5 6 7	N/A 1 2 3 4 5 6 7

DOMINIO: Ragionamento e Problem-Solving

7. Perdita della <u>flessibilità</u> nel generare piani alternativi quando necessario

Ha difficoltà ad immaginare piani alternativi quando i suoi programmi subiscono una variazione (per esempio se i mezzi di trasporto che usa abitualmente non fossero disponibili o il negozio dove di solito fa la spesa fosse chiuso)?

Esempi del paziente:	Esempi dell'informatore:

Paziente	Informatore	Punteggio composito
N/A 1 2 3 4 5 6 7	N/A 1 2 3 4 5 6 7	N/A 1 2 3 4 5 6 7

8. Difficoltà in situazioni che richiedono una <u>decisione</u>?

Cosa farebbe se… (saltasse la corrente …restasse chiuso furi casa… il suo unico lavandino fosse otturato… una lampadina si fulminasse)?

Esempi del paziente:	Esempi dell'informatore:

Paziente	Informatore	Punteggio composito
N/A 1 2 3 4 5 6 7	N/A 1 2 3 4 5 6 7	N/A 1 2 3 4 5 6 7

PUNTEGGI DI ANCORAGGIO PER DEFINIRE IL GRADO DI SEVERITA'			
N/A = Punteggio non applicabile, o informazioni insufficienti	**1.** Normale, assenza di compromissione	**2.** Deficit cognitivi minimi ma funzionamento generalmente conservato	**3.** Deficit cognitivi lievi con alcuni effetti significativi sul funzionamento
4. Deficit cognitivi moderati con chiari effetti sul funzionamento	**5.** Seri deficit cognitivi che interferiscono con il funzionamento quotidiano	**6.** Deficit cognitivi severi che mettono a rischio l'autonomia	**7.** Deficit cognitivi così severi da causare pericolo per sé o per gli altri

DOMINIO: Velocità di elaborazione

9. Lentezza nell'eseguire i compiti?

Nota che lo svolgimento di un compito è per lei più lungo di quanto dovrebbe (per esempio cucinare o fare la spesa, assemblare materiali, leggere delle istruzioni)?

Esempi del paziente:	Esempi dell'informatore:

Paziente	Informatore	Punteggio composito
N/A 1 2 3 4 5 6 7	N/A 1 2 3 4 5 6 7	N/A 1 2 3 4 5 6 7

DOMINIO: Cognizione sociale

10. Difficoltà nel comprendere le intenzioni o il punto di vista di un'altra persona?

Ha difficoltà nel comprendere il punto di vista di un'altra persona (se è in disaccordo anche quando non lo dica in modo diretto)? Se sta parlando con qualcuno e questa persona guarda l'orologio quali crede siano le sue emozioni e i suoi pensieri?

Esempi del paziente:	Esempi dell'informatore:

Paziente	Informatore	Punteggio composito
N/A 1 2 3 4 5 6 7	N/A 1 2 3 4 5 6 7	N/A 1 2 3 4 5 6 7

IMPRESSIONE CLINICA GENERALE DELLA COMPROMISSIONE COGNITIVA

Considerando tutte le fonti di informazioni raccolte per questo paziente attribuire un punteggio globale alla severità della compromissione cognitiva, dopo averlo paragonato alla popolazione generale. Quanto è compromessa la cognizione in questa persona? (Cerchiarne uno)

SEVERITÀ GLOBALE DELLA COMPROMISSIONE COGNITIVA – dall'INTERVISTA AL PAZIENTE		
N/A = Non applicabile	4 = Compromissione moderata	Note
1 = Nella norma, nessuna compromissione cognitiva	5 = Compromissione marcata	
2 = Compromissione molto lieve o deficit cognitivi minimi, ai limiti della normalità	6 = Compromissione grave	
3 = Compromissione lieve	7 = Tra i più marcatamente compromessi	
SEVERITÀ GLOBALE DELLA COMPROMISSIONE COGNITIVA – dall'INTERVISTA ALL'INFORMATORE		
N/A = Non applicabile	4 = Compromissione moderata	Note
1 = Nella norma, nessuna compromissione cognitiva	5 = Compromissione marcata	
2 = Compromissione molto lieve o deficit cognitivi minimi, ai limiti della normalità	6 = Compromissione grave	
3 = Compromissione lieve	7 = Tra i più marcatamente compromessi	
SEVERITÀ GLOBALE DELLA COMPROMISSIONE COGNITIVA – PUNTEGGIO COMPOSITO		
N/A = Non applicabile	4 = Compromissione moderata	Note
1 = Nella norma, nessuna compromissione cognitiva	5 = Compromissione marcata	
2 = Compromissione molto lieve o deficit cognitivi minimi, ai limiti della normalità	6 = Compromissione grave	
3 = Compromissione lieve	7 = Tra i più marcatamente compromessi	

PUNTEGGI DI ANCORAGGIO PER DEFINIRE IL GRADO DI SEVERITA'			
N/A = Punteggio non applicabile, o informazioni insufficienti	**1.** Normale, assenza di compromissione	**2.** Deficit cognitivi minimi ma funzionamento generalmente conservato	**3.** Deficit cognitivi lievi con alcuni effetti significativi sul funzionamento
4. Deficit cognitivi moderati con chiari effetti sul funzionamento	**5.** Seri deficit cognitivi che interferiscono con il funzionamento quotidiano	**6.** Deficit cognitivi severi che mettono a rischio l'autonomia	**7.** Deficit cognitivi così severi da causare pericolo per sé o per gli altri

Global Assessment of Function – Cognition in Schizophrenia (GAF-CogS)	
100 91	Funzionamento cognitivo superiore alla norma in un ampio spettro di attività, è richiesto per lavorare su complessi problemi cognitivi, sostiene un funzionamento cognitivo superiore alla norma in una professione impegnativa sotto il profilo cognitivo.
90 81	Deficit cognitivi assenti o minimi (vuoti di memoria occasionali o difficoltà nel trovare le parole), buon funzionamento in tutti i domini cognitivi, impegnato ed efficace nello svolgere compiti cognitivi, nessun problema o preoccupazione oltre a quelli della vita quotidiana circa le prestazioni cognitive.
80 71	Se i deficit cognitivi sono presenti , essi rappresentano reazioni transitorie e attendibili a stimoli stressanti (ad es., difficoltà a concentrarsi dopo una discussione familiare); lievissima alterazione del funzionamento sociale, lavorativo e scolastico dovuto a deficit cognitivi.
70 61	Alcuni sintomi cognitivi lievi (ad es., difficoltà a concentrarsi o vuoti di memoria) *oppure* alcune difficoltà nel funzionamento sociale, lavorativo o scolastico a causa di problemi cognitivi (ad es., ha dovuto ripetere un esame universitario a causa dei deficit cognitivi).
60 51	Sintomi cognitivi moderati (ad es., problemi costanti come difficoltà a prestare attenzione o nel ricordare eventi programmati) oppure moderata difficoltà nel funzionamento sociale, lavorativo o scolastico dovuto a problemi cognitivi (ad es., è costretto a chiedere molti permessi per assenze scolastiche).
50 41	Problemi cognitivi gravi (ad es., problemi continui di attenzione, memoria e pianificazione) *oppure* qualsiasi grave compromissione nel funzionamento sociale, lavorativo o scolastico dovuta a problemi cognitivi (ad es., problemi familiari causati dai deficit, impossibilità di mantenere un impiego lavorativo).
40 31	Problemi cognitivi gravi che interferiscono con numerosi aspetti della vita sociale, occupazionale e scolastica (ad es., un individuo è impossibilitato a svolgere un lavoro competitivo, ha difficoltà a svolgere un lavoro anche se assistito, e ha difficoltà a svolgere le faccende domestiche).
30 21	I deficit cognitivi sono così pronunciati che interferiscono con tutti gli aspetti del funzionamento, tra cui un'efficace comunicazione e i comportamenti finalizzati (ad es., difficoltà nel sostenere una conversazione, nello svolgere attività di base della quotidianità).
20 11	Qualche pericolo di fare del male a se stesso o agli altri a causa della compromissione cognitiva (evidente compromissione della capacità di giudizio/pianificazione, incapacità nel riconoscere le conseguenze delle azioni, frequentemente disorientato, incoerente, o confuso. ,
10 1	Persistente pericolo di far del male in modo grave a se stesso o agli altri *oppure* persistente incapacità di mantenere l'igiene personale minima a causa dei deficit cognitivi (ad es., assenza di una comunicazione efficace, incapacità persistente nell'avere la minima cura di sé a causa di difficoltà nell'organizzare il proprio comportamento)
0	Informazioni insufficienti

Global Assessment of Function – Cognition in Schizophrenia			
Sessione	**Paziente**	**Informatore**	**Punteggio composito**
Valutazione di base			
Follow-Up			

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The Karolinska Interpersonal Violence Scale, Italian version

Summary

The Karolinska Interpersonal Violence Scale (KIVS) is a semi-structured interview constructed to measure both the experiences of violence perpetration and victimization in childhood and adulthood. The original version was developed in Sweden in a study involving suicide attempters and healthy volunteers. We developed the Italian version of this innovative scale and administered it to one clinical and to one general sample.

Key words
Interpersonal violence • Karolinska Interpersonal Violence Scale • Violence assessment

Introduction

Over the XX and XXI centuries, interpersonal violence increased as a cause of morbidity and mortality and nowadays it is a major public health problem worldwide [1 2]. The dramatic reduction of the incidence and mortality from infectious diseases and the simultaneous growth of homicide and suicide in the rankings of causes of death contributed to this increasing recognition [3]. Death is the most evident outcome, but only the tip of the iceberg of the burden arising from violence. The non-fatal consequences are by far the greatest part of the health burden and include a wide range of unseen consequences, like mental health problems and risky behaviors [4]. Evidence supports the notion that there is a variety of psychological health problems also among perpetrators [5].

According to this perspective, interpersonal violence consists in relational trauma, which is more prone to cause mental distress than natural disasters because it is perceived as a threat to attachment relationships and to our fundamental sense of trust [6 7]. Moreover, it is typically experienced as intentional rather than as "an accident of nature". In fact, the meaning a person assigns to a stressful event is significant in the development of psychological consequences: the meaningless trauma tends to be more disruptive than a trauma with an assigned meaning.

Despite the strong impact of violence on health and social functioning, only few instruments have been developed to measure violent experiences [8]. In 2010, Jokinen and colleagues proposed the innovative Karolinska Interpersonal Violence Scale (KIVS), a semi-structured interview specific for interpersonal violence [9]. It is composed of 4 subscales investigating exposition to violence or the expression of violent behavior in childhood and adulthood. Within each subscale a score from 0 to 5 is assigned. It has been validated with some questionnaires measuring aggression and acts of violence and it showed good psychometric properties. It has been used in several suicide research studies [10-15] and in observational studies within clinical samples [16-19]. The Italian version of the KIVS is herewith presented. A brief description of the instrument is reported. The procedures followed for translation and adaptations of the interview, as well as the training of researchers and the results on its reproducibility are illustrated.

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Description of the Karolinska Interpersonal Violence Scale

The KIVS is specific for interpersonal violence and, compared to other scales, distinguishes aggressive acts from aggressive thoughts or feelings. It was developed by Swedish researchers from the Karolinska Institutet. In their validation study [9], the Buss-Durkee Hostility Inventory, Hostility and Direction of Hostility Questionnaire ("Urge to act out hostility" subscale) and the Early Experiences Questionnaire were used for concurrent validity. A sample of suicide attempters and one of healthy volunteers were recruited, since the original aim of the authors was also to assess the ability of KIVS to predict suicide. Most of the correlations between the instruments were high, the interrater reliability of the KIVS (and the subscales) was high too. It is composed by four rating scales assessing exposure to violence ("victim of violence" subscales) and expressed violence behaviour ("used violence" subscales) in childhood (between 6-14 years of age) and adulthood (from 15 years upwards). Questions consist of concrete examples of violent episodes that occurred during lifetime. The ratings (0-5 for each subscale, in total maximum of 20) are based on a semi-structured interview performed by trained clinicians. Moreover, it allows for use of composite scores of its subscales, such as lifetime "expression of violence" and "exposure to violence" lifetime [17 19], or "violence in childhood" and "violence in adulthood" [18].

Translation and adaptation

In 2016, our research group asked to original authors for authorization to develop the Italian version of the KIVS. The scale was then translated from English to Italian through an initial translation and back translation process. The English version was translated into Italian by a psychiatrist (RR). Then this translation was back translated in English by another physician (DT). Upon completion of this process, the original author compared the English versions of KIVS and confirmed that the variables had the same meaning.

Training of evaluators and assessment of inter-rater reliability

Within the research group, two senior psychiatrists illustrated then the Italian version to three physicians chosen as evaluators and trained them to the administration and scoring of interviews. These trained researches were responsible for the data collection, via a personal interview with each patient. A pilot test was conducted on 15 patients to check if the questions were well understood. To note that these 15 answers were not entered in the final database. An interrater reliability analysis was performed to determine consistency between two raters. They rotated in the conduction of the interview, but all attributed an independent scoring. The interrater reliability for the KIVS subscales ranged from r = 0.89 to r = 0.95 (p < .05). The Italian version of KIVS is attached in the Appendix.

Psychiatric patients and general population

Two samples were recruited in our studies focused on violence: (1) adult patients consecutively admitted in a psychiatric acute ward (n = 210); (2) individuals from the general population (n = 217). The research project and all the procedures were approved by the local review board, and the participants signed informed consent forms. Patients were administered the KIVS during their hospital stay, whereas the general population completed an online questionnaire, including the KIVS as a self-report instrument. All the participants were evaluated also with the Risky Families Questionnaire [20], the Psychological Maltreatment Review [21], the Positive and Negative Affect Schedule [22] and the Social Network Questionnaire [23]. Means and Pearson bivariate correlations were computed where appropriate. Independent t-test and Z score where calculated to test differences between the two samples and gender differences within both samples. Results are shown in the text, in Figure 1, and in tables (Tabs. I-III).

In the clinical sample, there was a statistically significant difference between males and females on Used violence as a child [t (208) = 3.241, p = .001] and Victim of violence in adulthood [t (208) = -2.102, p = .037]. In the general population, a statistically significant difference between males and females was found on Used violence as a child [t (215) = 3.020, p = .003]. No other gender differences were found in the two subject groups for KIVS means scores.

There were no differences of correlation coefficients between KIVS ratings and the other questionnaires of the clinical and the general population (Z score, p > 0.05). In the clinical sample significant inverse correlations were found between the KIVS ratings and age (-0.15 < r < -.32). In the general population, these correlations were nonsignificant.

The correlation coefficients of Lifetime expression of violence with Used violence as a child and Used violence as an adult showed a statistically significant difference between the clinical and the general population, respectively Z score = -2.43, p = 0.01, Z score = -3.64, p = 0.000. No other significant differences were found.

In the clinical sample, gender specific correlations between the KIVS subscales measuring exposure to and expression of violence showed no differences.

Conclusions

As there is an increasing awareness of relevance of the interpersonal violence issue in public health, the proper and economic assessment of this variable is necessary. Interpersonal violence affects multiple outcomes in be-

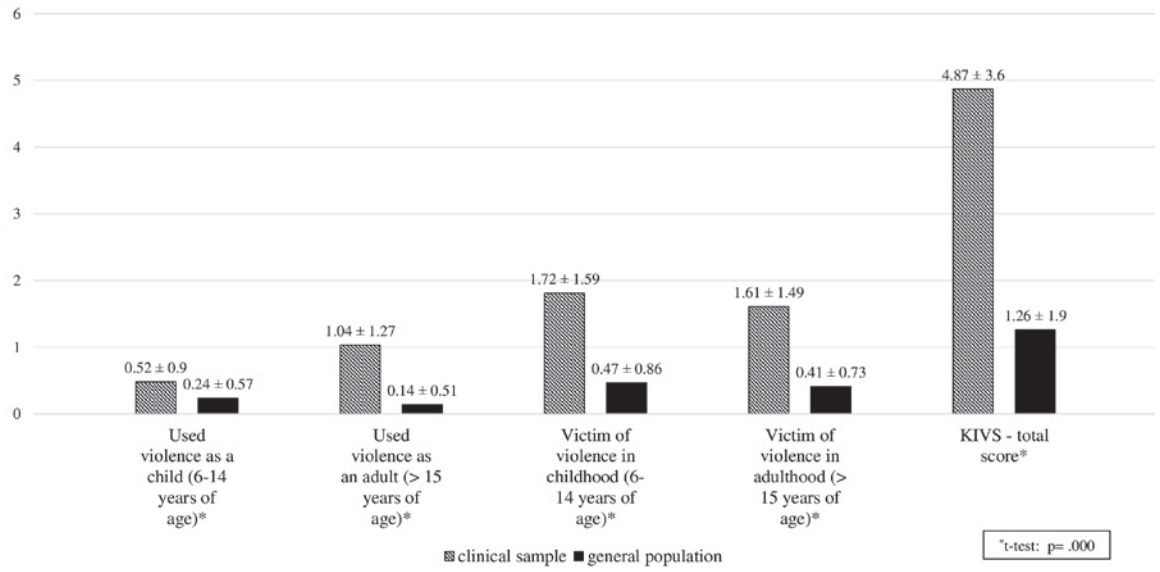

FIGURE 1. *Mean scores on the total Karolinska Interpersonal Violence Scale and each of the subscales were calculated for both samples. The independent samples t-test was used for testing statistically significant differences between means.*

TABLE I. *Correlations between the KIVS subscales and the RFQ, PMR subscales, PANAS subscales and SNQ.*

Scale	KIVS subscale									
	Used violence as a child		Used violence as an adult		Victim of violence in childhood		Victim of violence in adulthood		KIVS Total	
	C‡	G§	C‡	G§	C‡	G§	C‡	G§	C‡	G§
RFQ	0.89	0.20*	0.22*	0.18*	0.43*	0.46*	0.29*	0.35*	0.41*	0.45*
PMR- *M*	0.18*	0.17†	0.26*	0.16†	0.46*	0.50*	0.38*	0.22*	0.50*	0.40*
PMR- *S*	-0.07	-0.13	-0.10	-0.05	-0.15†	-0.20*	-0.16†	-0.4	-0.19*	-0.16†
PANAS- *PA*	0.23*	0.02	0.18†	0.00	-0.1	-0.11	0.05	0.05	0.09	-0.03
PANAS- *NA*	0.07	0.15†	0.03	0.30*	0.23*	0.14†	0.15†	0.23*	0.19*	0.28*
SNQ	-0.03	-0.02	0.01	0.00	-0.17†	-0.12	-0.02	0.00	-0.09	-0.06

**p < .01; †p < .05; ‡clinical sample; §general population*
Note: RFQ: Risky Families Questionnaire; PMR: Psychological Maltreatment Review, M: maltreatment, S: support; PANAS: Positive and Negative Affect Schedule, PA: positive affect, NA: negative affect; SNQ: Social Network Questionnaire; KIVS: Karolinska Interpersonal Violence Scale

TABLE II. *Correlations between the Karolinska Interpersonal Violence Scale (KIVS) subscales measuring exposure to and expression of violence in the clinical sample (n = 210) and in general population (n = 217)*

	1		2		3		4		5	
	C†	G‡	C†	G‡	C†	G‡	C†	G‡	C†	G‡
1. Used violence as a child	-	-								
2. Used violence as an adult	0.32*	0.28*	-	-						
3. Victim of violence in childhood	0.20*	0.28*	0.26*	0.36*	-	-				
4. Victim of violence in adulthood	0.20*	0.26*	0.31*	0.38*	0.40*	0.37*	-	-		
5. Lifetime exposure to violence	0.24*	0.33*	0.34*	0.45*	0.85*	0.86*	0.82*	0.80*	-	-
6. Lifetime expression of violence§	0.74*	0.83*	0.88*	0.77*	0.28*	0.40*	0.32*	0.40*	0.36*	0.48*

** p < .01; †clinical sample; ‡general population; §statistically significant difference between the clinical and the general population of the correlation with Used violence as a child and Used violence as an adult*

TABLE III. *Gender-specific correlations between the Karolinska Interpersonal Violence Scale (KIVS) subscales measuring exposure to and expression of violence in general population (males n = 96; females n =121).*

	1		2		3		4		5	
	M‡	F§	M‡	F§	M‡	F§	M‡	F§	M‡	F§
1. Used violence as a child	-	-								
2. Used violence as an adult	0.22*	0.34**	-	-						
3. Victim of violence in childhood	0.22*	0.32**	0.24*	0.41**	-	-				
4. Victim of violence in adulthood‡‡	0.26*	0.28**	0.61**	0.28**	0.37**	0.37**	-	-		
5. Lifetime exposure to violence	0.29**	0.37**	0.51**	0.43**	0.84**	0.87**	0.81**	0.79**	-	-
6. Lifetime expression of violence**,††	0.88**	0.79**	0.66**	0.84**	0.29**	0.45**	0.50**	0.35**	0.47**	0.49**

** p < .01; † p < .05; ‡males; §females; **Significant gender difference in used violence as a child (Z = 2.19, p = 0.02); ††Significant gender difference in used violence as an adult (Z = -3.08, p = 0.02); ‡‡Significant gender difference in used violence as an adult (Z = 3.03, p = 0.002)*

havioral medicine and mental health, so that a better understanding of its role is needed. KIVS represent a useful tool both in the research and the clinical field.

Conflict of interest

The Authors declare to have no conflict of interest.

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Appendix

KAROLINSKA INTERPERSONAL VIOLENCE SCALE (KIVS)

Versione italiana a cura di Talevi D, Rossi R

NOME e COGNOME _____ **ID**_____

I livelli di questa scala sono definiti da brevi affermazioni riguardanti i comportamenti violenti. Sull'intervista con il soggetto, usare il punteggio più alto quando una o più affermazioni possono essere applicate.

Violenza perpetrata	
Infanzia (6-14 anni)	
0	Nessuna violenza.
1	Sporadiche risse, ma nessun motivo di allarme tra gli adulti della scuola o della famiglia.
2	Spesso coinvolto in risse.
3	Spesso provoca risse. Picchia i compagni che sono stati bullizzati. Continua a picchiare dopo che l'altro si è arreso.
4	Bullizza per primo. Picchia spesso gli altri bambini, con pugni o oggetti.
5	Causa lesioni fisiche gravi. Violento contro uno o più adulti. Il comportamento violento causa l'intervento dei servizi sociali.
Età adulta (≥ 15 anni)	
0	Nessuna violenza
1	Schiaffeggia o sculaccia i figli occasionalmente. Spintona o strattona il partner o un altro adulto.
2	Occasionalmente colpisce il partner o i figli. Partecipa a risse quando è ubriaco.
3	Aggredisce il partner da ubriaco o da sobrio. Ripetute punizioni corporali ai figli. Frequenti risse da ubriaco. Colpisce gli altri da sobrio.
4	Casi di abuso sessuale violento. Ripetuti pestaggi o abusi fisici di figli o partner. Aggredisce gli altri frequentemente, da sobrio o da ubriaco.
5	Ha ucciso o ha causato lesioni personali gravi. Ripetuti casi di violenza sessuale. Condannato per reati violenti.

Vittima di violenza	
Infanzia (6-14 anni)	
0	Nessuna violenza.
1	Sporadici schiaffi. Fa a botte a scuola, ma di non grande significato.
2	Bullizzato occasionalmente per brevi periodi. Occasionalmente esposto a punizioni corporali.
3	Spesso bullizzato. Frequentemente esposto a punizioni corporali. Picchiato da genitori ubriachi.
4	Ha subito bullismo per tutta l'infanzia. Picchiato dai compagni di scuola. Regolarmente picchiato da un genitore o da un adulto. Picchiato con oggetti. Abusato sessualmente.
5	Esposizione ripetuta alla violenza a casa o a scuola, con almeno un grave esito fisico. Abusi sessuali ripetuti, o abusi sessuali che abbiano esitato in una lesione fisica.
Età adulta (≥ 15 anni)	
0	Nessuna violenza
1	Minacciato o soggetto a un basso livello di violenza almeno in un'occasione.
2	Picchiato dal partner occasionalmente. Vittima di scippi. Minacciato con oggetti.
3	Minacciato con un'arma. Rapinato. Picchiato da qualcuno che non sia il partner.
4	Stuprato. Percosso.
5	Stuprato ripetutamente. Percosso ripetutamente. Gravemente percosso, con lesioni fisiche gravi.

This material originally appeared in English as Appendix (the KIVS), page 1032, from J Clin Psychiatry 2010;71:1025-32 (translated with permission of the authors).

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Psychosis exacerbation following group A *Streptococcal pharyngitis*: an immune-mediated phenomenon? A case report

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Summary

According to some theories that postulate an immune involvement in the pathogenesis of Schizophrenia (SCZ), autoimmunity and infections are risk factors for SCZ.

We report the case of a 20-year-old female patient who received a diagnosis of SCZ at the age of 15, in concomitance with having contracted a streptococcal pharyngitis. Interestingly, since then, the patient repeated a number of Group A streptococcal (GAS) infections that, in each case, preceded recurrent significant psychotic exacerbation.

GAS infections are a well-known cause of post-infectious immune-mediated conditions such as Syndeham's corea and PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections), in which a prominent SCZ-like symptomatology has been occasionally reported. The neurobiological basis of the emergence of psychotic symptoms in these cases remains largely elusive. We speculate in this article that psychotic exacerbations following GAS infections are linked to the pathophysiology of the streptococcal pharyngitis.

Key words
Schizophrenia • Streptococcal infections • Basal ganglia

Abbreviations

SCZ: Schizophrenia
GAS: Group A streptococcal
PANDAS: Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections
SC: Syndeham's chorea
CNS: central nervous system

Background

According to literature, infections caused by Streptococcus pyogenes, a beta-hemolytic bacterium also known as the group A streptococcus (GAS), may be related to the onset of neuropsychiatric symptoms. Eygör et al. [1] studied 27 patients with chronic pharyngitis reporting that psychiatric disorders were 6.4 times more frequent in the patient group compared with the healthy population. All the patients involved in the study, received an Axis I DSM-IV TR diagnosis, the most frequent of which were somatization disorder (n = 8, 29.6%) and dysthymic disorder (n = 8). Huang et al. [2] investigated the psychopathological features of 100 pharyngitis patients and found high prevalence of somatization, obsession, interpersonal sensitivity and anxiety. Even if according to these data, psychotic symptoms appear to be less frequent and poorly-defined, they have been occasionally described as associated to the autoimmune processes involved in the post-streptococcal disorders

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Syndeham's chorea (SC) and PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections) [3-5].

Our aim is to report the case of a 20-year-old female patient who received a diagnosis of SCZ at the age of 15, in concomitance with having contracted a streptococcal pharyngitis. Since then the patient repeated a number of GAS infections following which, she always presented recurrent psychotic exacerbations. After pharmacological treatment, based on antipsychotic and beta-lactam antibiotics co-administered for the first psychotic episode and for all psychotic exacerbations, a rapid psychopathological improvement could always be reported, with the patient gaining back the premorbid level of functioning. We speculate in this article that psychotic exacerbations following GAS infections are linked to the pathophysiology of the streptococcal pharyngitis: this clinical case could be conceptualized as an uncommon expression of a pediatric autoimmune neuropsychiatric disorder associated to strep throat infection.

Case presentation

G. came to our observation at the age of 20. The patient had a psychiatric onset at the age of 13 with a mild form of anorexia nervosa that fulfilled the diagnostic criteria. This symptomatology remitted after a few months, although a certain preoccupation about food still persisted. At the age of 15, she had her psychotic onset, preceded by a pharyngeal infection that lasted about 3 weeks. Psychotic symptoms mainly consisted in persecutory delusions accompanied by auditory hallucinations. Because of this psychotic symptomatology the patient was admitted to the hospital for about one week, undergoing treatment with risperidone and beta-lactam antibiotics. After this first psychotic episode, she received pharmacological treatment with antipsychotics (risperidone long acting injectable 25 mg im every two weeks), obtaining a remarkable effect on psychotic symptoms: even if ay significant fear of being judjed by others persisted, hallucinations and persecutory delusions rapidly disappeared. Since then, every single psychotic recrudescence was preceded by a streptococcal infection that presented with or without fever and was treated with a combination therapy based on antipsychotic and beta-lactam antibiotic.

Psychotic exacerbations lasted four to seven days and always occurred in the form of persecutory auditory hallucinations (voices) and delusions. In the latest years, school functioning and social functioning clearly regressed, the patient spends most of her time at home and has recently interrupted school attendance.

Discussion and conclusions

We hereby report the case of a chronic patient with a diagnosis of SCZ who experienced, from the age of 15, multiple episodes of GAS pharyngitis followed by the acute exacerbation of psychiatric symptoms.

Infections, and the resulting immune response, have recently received increased recognition as pathogenic mechanisms for neuropsychiatric disorders [6].

Interestingly, there are numerous descriptions of an association between infection, chronic inflammation of the central nervous system (CNS), and SCZ [7]. An increased level of proinflammatory markers, like cytokines, has been described both in blood and cerebrospinal fluid of patients suffering from SCZ. Animal models have shown that a first hit to the immune system occurring in early life might trigger a lifelong increased immune reactivity. Many epidemiological and clinical studies show the role of various infectious agents as risk factors for SCZ with overlap to other psychoses. A large-scale epidemiological study from Denmark clearly demonstrates severe infections and autoimmune disorders during lifetime to be risk factors for SCZ [8].

SCZ-like symptoms have moreover been described in the autoimmune processes of the post-streptococcal disorders, such as SC and PANDAS [4 5 9 10].

Being SC the most well characterized post-streptococcal syndrome and the most widely recognized post-streptococcal autoimmune disorder, it represents a model for this proposed pathogenesis [6].SC is considered a medical complication of group A beta-hemolytic streptococcal infection and it constitutes one of the major criteria for the diagnosis of Acute Rheumatic Fever [5]. SC, in addiction to chorea, is mainly characterized by psychiatric symptoms such as irritability, obsessions and compulsions, tics, and psychotic symptoms [3]. The link between SC and psychosis is unclear, in recent decades, clinicians and researchers have continued to conduct studies in this field.

Some authors discussed the increased incidence of psychotic symptoms in SC [11]. While retrospective chart reviews suggested that patients with SC present a higher risk of developing SCZ if compared to the general population [11 13]. Nausieda et al. hypothesized an increased potential for aberrant thought processing in a subgroup of Sydenham's patients who demonstrated a significant elevation in the psychotic tetrad of the MMPI and adverse reactions to central stimulants [12].

A dysregulated immune response to GAS infection is hypothesized to be linked to the onset of a process of inflammation that can involve clusters of neurons that principally constitute the basal ganglia, the most vulnerable CNS region in post-streptococcal autoimmune disorders.[14] The resulting dysfunction of the basal ganglia nuclei are hypothesized to be for the constellation

of psychiatric symptoms described in these clinical frames [6].

PANDAS (Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infections) has been proposed as a variant of SC, with which it is hypothesized to share a pathogenic mechanism, despite showing a unique, predominantly psychiatric, symptom profile [6].

PANDAS is defined by the presence of obsessive compulsive disorder and/or a tic disorder, prepubertal symptom onset, sudden or episodic course, temporal association of symptom exacerbation and streptococcal infections and associated neurological abnormalities. An autoimmune process triggered by a streptococcal epitope directed to CNS neurons is thought to be responsible for the characteristic symptom profile and for the course of illness [4].

PANDAS may arise when antibodies directed against the invading bacteria happen to cross-react, such as in SC, with basal ganglia structures.

As most symptoms of SC and PANDAS may be considered the result of a basal ganglia dysfunction determined by autoimmune mechanisms elicited by streptococcal infection [15], we speculate that psychotic symptoms in our clinical case report, may have been determined by the same pathophysiological process.

According to literature, when patients with PANDAS are not treated for long periods, SCZ-like symptoms are an unavoidable manifestation [16]. Thus, it could be assumed that the involvement of the basal ganglia may lower the threshold for the emergence of SCZ-like symptoms. Indeed, evidence from various studies suggest that a basal ganglia disturbance has a role in SCZ and may contribute to the understanding of the pathophysiology of this complex disorder [17-19].

The dopaminergic system of the basal ganglia manifests several anomalies in SCZ [20]. Conversely, prominent psychotic symptoms are often reported in organic disorders with specific involvement of these subcortical nuclei (i.e. Sydenham's chorea, Wilson's disease, Huntington's chorea, Hallervorden-Spatz disease, post-encephalitic psychoses) [21].

The reason why psychosis is not so frequent in post-streptococcal conditions is, however, a matter of debate and the relationship existing between SCZ and post-streptococcal related diseases, specifically PANDAS, has not been completely understood yet.

In conclusion, in this case report we hypothesize the involvement of a basal ganglia dysfunction in the pathogenesis of SCZ, adding interesting and potentially useful information to the international literature related to immune-mediated neuropsychiatric complications following GAS infection.

We presume that our patient suffered from an immune-related post-infectious psychosis triggered by GAS infection that may be an uncommon expression of pediatric autoimmune neuropsychiatric disorder associated with a streptococcal infection.

In spite of the speculative nature of our paper, we have tried to temper our speculations supporting out theory with solid data that have been derived from the scientific international literature.

Conflict of interest

The Authors declare to have no conflict of interest.

Ethics approval and consent to participate

We carefully considered the utility of this case against the likelihood of identification or potential distress.

Consent for publication

The Authors of this article declare to have obtained the written and signed consent from the patient to publish the case report.

Availability of data and materials

Not applicable.

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Author's contributions

All Authors analyzed and interpreted the patient data regarding her psychiatric disorder.

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2. Original articles (which may also include invited articles). The text should be subdivided into the following sections: Introduction, Materials and methods, Results, and Discussion and Conclusions. The manuscript should not exceed 40.000 typewritten characters, including the summary, tables, figures and references (max 35). Summary should be no more than 3000/3500 typewritten characters (please strictly follow the above-mentioned instructions). In the Objective(s) section, the aim (or the aims) of the work must be clearly summarised (i.e., the hypothesis the Authors aim to verify); in the Method(s) section, the Authors must report the context of the study (i.e., general paediatrics, Hospital, Specialist Centre …), the number and the kind of subjects under analysis, the kind of treatment and of statistical analysis used. The Results section should refer to the results of the study and of the statistical analysis. In the Conclusion(s) section should report the significance of the results as related to clinical implications.

3. Brief articles: this space is dedicated to brief communications of clinical and experimental data and to preliminary data of ongoing research of particular interest. The manuscript should not exceed 20.000 typewritten characters, including the summary, tables, figures and references (max 10).

4. Case reports: brief articles (maximum 4000/4500 typewritten characters) in which clinical original experiences from medical practice are described.

5. Assessment and instruments in psychopathology. This section hosts articles on psychological and psychopathological assessment instruments aiming at improving knowledge of psychological functioning of those subjects with mental and behavior disorders in different reference models. The use of such instruments is not limited to clinical population but also includes non-clinical and general population. This section also accepts studies on validation and translation into Italian of instruments, new assessment instruments and competing studies of new assessment instruments with other procedures of assessment than psychopathological constructs. The manuscript should not exceed 40.000 typewritten characters, including the summary, tables, figures and references (max 35).

6. Clinical psychopharmacotherapy: articles reporting the latest developments in the area of drug therapy should be subdivided into the following sections: Introduction, Materials and Methods, Results, and Discussion and Conclusions. The text must not exceed 30.000 typewritten characters including the references, tables, figures, and summary (3000/3500 typewritten characters, excluding figure legends and table captions).

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