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EVIDENCE-BASED PSYCHIATRIC CARE

OFFICIAL JOURNAL OF THE ITALIAN SOCIETY OF PSYCHIATRY

Editors-in-Chief
Emilio Sacchetti, Claudio Mencacci

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Editorial Office
Editors-in-Chief
Emilio Sacchetti - emilio.sacchetti@unibs.it
Claudio Mencacci - claudio.mencacci@gmail.com

Editorial coordinator and secretary
Lucia Castelli - lcastelli@pacinieditore.it
Tel. +39 050 3130224 - Fax +39 050 3130300

Managing Editor
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Publisher
Pacini Editore Srl
via Gherardesca1 - 56121 Pisa, Italy
Tel. +39 050 313011 - Fax +39 050 313000
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HOW TO INTERVENE ON GAMBLING AND RECREATIONAL USE OF CANNABIS: OVERLY DIVERGENT RECIPES FOR RELATED BEHAVIOURS

Emilio Sacchetti
Claudio Mencacci

Editors,
Evidence-Based Psychiatric Care

A large and increasing body of evidence confirms that the similarities between behavioural addictions and substance-related disorders outweigh the differences. It is therefore far from surprising that the American Psychiatric Association decided to include pathologic gambling in the Fifth Edition of the *Diagnostic and Statistical Manual of Mental Disorder s*[1] in the chapter on substance-related disorders.

To date, public and political opinion in various nations, including Italy, has remained ambiguous on a scientific unitary perspective between substance and behaviour addiction. The overly divergent or even opposing recipes proposed for moderating diffusion of gambling and recreational use of cannabis are a good example of this discrepancy. On the one hand, non-medical discussion on the consumption of street cannabis seems to promote light regulation or even largely liberalized access to the substance because of a general cultural trend that minimizes or denies any detrimental effects on human health. On the other hand, the indications concerning modalities of access to gambling are in the direction of a poorly permissive, softly prohibitionist approach, in full agreement with non-medical debate largely inclined to magnify the negative consequences of this addictive behaviour.

The fact that a restrictive approach to gambling has so far largely been directed against slot machines and related electronic game machines (Fig. 1) is easy to understand: players who play on slot and electronic game machines constitute a special population with the highest rate of transition from non-problematic to problematic and pathologic gambling. However, cogency is inevitably coupled with misleading potential: the almost exclusive focus on slot and slot-like machines is at risk of promoting the false idea that other forms of gambling are largely immune from unfavourable transition, with the consequence of making a fair evaluation of the pros and cons of restrictive policies difficult.

A restrictive approach to gambling also conflicts with at least four other important considerations.

1. Many governments have legalized gambling and emphasize the social use of funds related to gaming taxes.
2. Growth of the global village offers previously unimaginable possibilities of advanced gaming technologies making easy control of gambling impossible.
3 In analogy with the use of street cannabis, the choice between re-

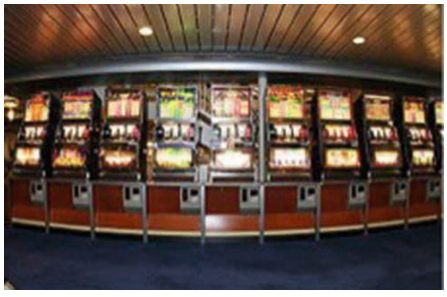

FIGURE 1.
Slot machines on the Norwegian "Kronprinz Harald". Photo by Alexander Blum.

Correspondence

Emilio Sacchetti
emilio.sacchetti@unibs.it

strictive and liberalized policies with regard to gambling is not sufficiently evidence-based.

4. The costs needed for full application and control of extended restrictive measures make systematic application of tough prohibitionist measures complicated; this consideration is especially important nowadays, given the current economic shortages and the probable loss of the tax yield that would reasonably follow.

Therefore, there are good reasons to question whether it is preferable to spend time and money on policies largely based on restrictive interventions or to shift to more versatile and diversified strategies based on a few selected benchmarks. However, it is essential to accept unconditionally that not only is pathologic gambling a definite, often severe, mental disorder but also both problem and pathologic gambling interfere negatively with quality of life, impose a significant burden on families and the wider society, promote unhealthy lifestyles, are associated with abnormally high rates of comorbidities with other mental disorders and numerous medical conditions, consume a surplus of health care resources, and are at special risk for criminal and delinquents acts. It is also important to consider that problem and pathologic gambling are treatable clinical conditions and, at the same time, that only a minority of problem and pathologic gamblers seek and receive help [2]. Furthermore, it is frequently forgotten that if it is true that the large preponderance of the adult population worldwide has experienced gambling at least once, it is also true that "most people who gamble do not develop a gambling problem" because only a small fraction of gamblers "will escalate gradually to larger bets and greater risks" [3]. It is evident that the need for shared interventions also applies to problem and pathologic gambling in full alignment with other health care conditions: the gambler is indeed the ultimate decision maker in choosing if and when to gamble.

These key points clearly call for a public health approach to problem and pathologic gambling that not only *protects* vulnerable groups, *promotes* informed and balanced attitudes, behaviours and policies toward gambling, and *prevents* gambling-related problems [4] but also *publicizes* the idea of problem and pathologic gambling as treatable conditions, *predisposes* facilitated access to treatment, and *privileges* dedicated pre-clinical and clinical research with special interest in the risk factors and their early detection. These 6P goals address the implementation and a strong revision of current educational plans: people continue to be largely unfamiliar with the problems related to gambling; prevention campaigns are in many cases restricted to billboard commercials and flyers; the emerging image of problem and pathologic gambling is that of an almost unpredictable adverse event; and the community is not sufficiently informed about the dimensions of this escalation and the best strategies for preventing this negative situation. On the contrary, educational campaigns of the future should pay special attention to informing about the risk associated with gambling "without overtly disturbing those who gamble in a non-problematic manner" [5] and promoting responsible gambling, offering third-party information about gambling's false myths, the probabilities of winning, the hazards deriving from irresponsible behaviour, and the existence of affordable and effective strategies that can counteract the unfavourable transition from recreational gambling. Of course, correct information requires adequate scientific support and both education and research need robust investment. Toward this aim, it is reasonable to assume that some economic savings would come from parsimonious, almost exclusive use of restrictive policies to protect highly vulnerable groups, such as adolescents and people with severe mental illness. This substantially liberal strategy, however, must be coupled with a firm resolution to apply severe sanctions on those who do not observe the rules. The offer of an "appropriate balance of individual freedom, personal choice and responsibility," must indeed always be balanced with "necessary safeguards and protection strategies to minimize potential harm" [6].

The role of psychiatrists within this scenario is essential, given their involvement in the diagnosis, treatment, and prevention of problem and pathologic gambling and competence in dedicated education and research. Nevertheless, psychiatry has been largely excluded, at least in Italy, from the debate and management of problem and pathologic gambling. The same has applied to the debate on liberalization of recreational cannabis [7]. This bitter evidence could be seen to be a metaphor on the similarities that link substance and behavioural addictions.

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Camilla Callegari
Ivano Caselli
Marta Ielmini
Simone Vender

Department of Clinical
and Experimental Medicine,
Section of Psychiatry,
University of Insubria, Varese, Italy

INFLUENCE OF THE RECOVERY STYLE FROM PSYCHOSIS ON THE DISTRESS IN PSYCHIATRIC PROFESSIONALS: AN OBSERVATIONAL STUDY FOCUSED ON DEPRESSION OF PSYCHOTIC PATIENTS IN A DAY CENTER

Abstract

Objectives: This study aims to analyze the relationship between symptoms – focusing on depression – and the recovery style in a psychiatric day center. Assuming that this relationship affects the burden management, the study has the additional endpoint of evaluate the impact of the interaction between symptoms and recovery style on the distress of the mental health professionals.

Materials and Methods: 45 patients enrolled have been evaluated by the Neuropsychiatric Inventory (NPI - Italian version) and Integration/Sealing Over Scale (ISOS - Italian version), within three months (March-June 2014).

Results: In the sample a statistically significant relationship between integration, depression and nervousness was observed ($p < .001$ and $< .003$). The symptoms which cause a greater distress in the health workers are uninhibition, nervoussess and apathy. Moreover, the results indicate that depression and anxiety cause a greater degree of distress in sealer patients.

Conclusions: Uninhibition, nervousness and apathy were more burdensome for mental health professionals, because they require a greater engagement in the therapeutic relationship. There are some limits: the small size of the sample and the lack of an evaluation of insight, closely related to the construct of recovery style. We are engaged in research to deepen this point, with these goals in mind.

Key words: rehabilitation, recovery style, integration, sealing over, distress

Introduction

In psychiatric rehabilitation, the Day Center is the structure of the Department of Mental Health in which therapeutic/rehabilitation programs and re-socialization activities take place. In this semi-residential setting, the severity is the high presence of the symptoms. The burden is the degree of distress reported by the health professionals in the management of psychotic patients.

McGlashan et al. identified two main recovery styles: “sealing over” in which the subject minimizes and tends to remove the recent psychotic episode, and “integration”, in which there is a continuity between psychotic and pre/post-psychotic experiences [1].

Tait et al. studied how insight, psychotic symptoms and recovery

Correspondence

Camilla Callegari
camilla.callegari@uninsubria.it

style may predict patient's involvement with psychiatric services, recognizing that the tendency to sealing over is associated with a lower service engagement than integration. The same authors recognized as the sealers have attachment difficulties to caregivers [2].

The primary aim of this study is to analyze the relationship between symptoms – focusing on depression – and the recovery style. Secondary, assuming that this relationship affects the burden management, the study has the additional endpoint of evaluate the impact of the interaction between symptoms and recovery style on the distress of the mental health professionals.

Materials and Methods

This study assesses a total of 45 patients in a psychiatric day center, suffering from psychotic disorders and recruited from March to June 2014. Patients had to fulfill the following inclusion criteria: suffer from psychotic disorders (Schizophrenia, Schizoaffective Disorder, Delusional Disorder, according to the criteria of ICD-10); attend the center for at least one year; with a frequency of at least twice a week; sign an informed consent for the participation [3].

The different psychopathological expressions and the degree of distress reported by the health workers were assessed through the Neuropsychiatric Inventory (NPI), semi-structured interview based on twelve questions that enables to evaluate each symptom presented by the patient through the frequency and severity. The recovery style was assessed through Integration/Sealing Over Scale (ISOS). This scale a semi-structured interview administered to caregivers, consisting of 13 items. Each one is expressed by two antithetical hypothesis that respectively refer to integration and sealing over style. This instrument have already been validated and previously used by our working group also within the semi-residential setting [4-7].

Statistical analysis

All collected variables were described by mean and standard deviation or absolute frequencies and percentages, respectively for continuous and categorical variables. The Chi-square test (for categorical variables) and T tests for independent samples, or the corresponding non-parametric Wilcoxon (for continuous variables) were used to compare the two groups. All test were considered significant at 0.05 alpha level. The data were analyzed using SAS (Statistical Analysis Software) version 9.4.

Table I. Socio-demographical and clinical characteristics of the sample.

	Integration	Sealing Over	Test*	p-value
N	23	22	-	-
Age - mean (SD)	51.6 (7.3)	50.2 (9.3)	0.56	0.58
Sex - male (%)	13 (56.5)	12 (54.6)	0.01	0.89
Education attained - high school/graduate (%)	7 (30.4)	7 (31.1)	0.01	0.89
Family caregiving - Yes(%)	13 (56.5)	16 (72.7)	1.29	0.26
Marital Status - Ever married (%)	8(34.8)	4(18.2)	1.58	0.21
Medical History** - Positive (%)	11 (47.8)	8 (36.4)	0.61	0.44
Year frequency - Median§	3	3	1.38	0.16
Weekly frequency - Median§	5	5	-0.63	0.52
Invalidity - complete (%)	15 (65.2)	15 (68.2)	0.04	0.83
Tutor - Yes (%)	2 (8.7)	4 (18.2)	0.87	0.35
Activity - ≥ 4(%)	21 (91.3)	19 (86.4)	0.28	0.60
Use of antipsychotics - %	19 (82.6)	17 (77.3)	0.20	0.65
Use of antidepressants - %	7 (30.4)	4 (18.2)	0.91	0.34
Use of anxiolytics or hypnotics - %	10 (43.5)	16 (72.7)	3.94	0.04
Use of Depot - %	2 (8.7)	4(18.2)	0.88	0.35
Health worker tenure -Median	14	14	-0.42	0.67

** Chi-square (1 df) for qualitative features, t-test (43 df) or Wilcoxon for quantitative features. ** Positive Medical History. § Wilcoxon test was applied due to non-normality distribution.*

Results

Socio-demographic data

Socio-demographic data are reported in Table I. From the analysis of the socio-demographic and clinical characteristics of the sample in comparison with the recovery style there were no statistically significant differences. This fact allows us to perform non adjusted analysis and to feel confident that any significant differences observed are not affected by a different composition of the two groups for socio-demographic and clinical characteristics.

Recovery Style and symptoms

The assessment performed though the filling-in of the ISOS by health workers revealed an overlap for almost all of the sample. Unlike in the previous study which involved the enrollment of inpatients and outpatient structures, where a prevalence of the integration style for females was observed (Vender et al. 2014), in this work the prevalence between the two styles was similar. Furthermore, the overall prevalence of the integration style was observed in the work cited, while the observation targeted to the day center showed an equal distribution of the two types of patients.

This element underlines the importance of being able to formulate therapeutic/rehabilitation programs that take into consideration the different characteristics of both groups of users.

From the analysis of the relationship between symptoms presented (frequency*severity), which correspond to the different items of the NPI, and the recovery style used, no statistically significant differences in the prevalence of symptoms between the two groups were showed. An exception is represented by nervousness, much more present in the sealers (40.9% *vs* 4.4%). Participation in therapeutic/rehabilitation activities can increase the inner tension of the mechanism of denial of the psychotic experience [8]. As we expected, depression was significantly more frequent in the group of integrator patients (100% vs 63.6%) (Table II).

Distress

Figure 1 describes the distress reported by the mental health workers depending on the presence of symptoms in the two different recovery styles. Agitation and nervousness seem to determine a high degree of distress. These symptoms characterize clinical situations of excessive stimulation resulting in an increase of the demand for professional intervention by the mental health workers. Moreover, these symptoms destabilize the emotional climate of the group and represent an exception to the daily program of rehabilitation activities planned with patients. Considering the analysis of the degree of distress related to the recovery style, statistically significant differences were not observed.

In Table III we can find the correlation according to Spearman between distress and symptoms presented (frequency*severity) in both groups of patients and on the total of the sample. We can also find the value of interaction test between severity and recovery style. A significant value indicates that the recovery style for that particular symptom acts as a modifier of the effect on distress.

The Spearman test shows a statistical significance of

Table II. Proportion of subjects with symptoms, appraisal between the recovery style group.

	Integration (N = 23) n (%)	Sealing Over (N = 22) n (%)	Test*	p-value
Delusions	10 (43.5)	11 (50.0)	0.19	0.66
Hallucinations	14 (60.9)	12 (54.6)	0.18	0.67
Agitation	9 (39.1)	10 (45.5)	0.18	0.67
Depression	23 (100.0)	14 (63.6)	10.2	0.001
Euphoria	8 (34.8)	5 (22.7)	0.80	0.37
Aphaty	12 (52.2)	12 (54.6)	0.03	0.87
Anxiety	19 (82.6)	13 (59.1)	3.03	0.08
Uninhibition	4 (17.4)	4 (18.2)	0.005	0.94
Nervousness	1 (4.4)	9 (40.9)	8.7	0.003
Aberrant motor activity	4 (17.4)	5 (22.7)	0.20	0.65
Eating disorders	6 (26.1)	5 (22.7)	0.07	0.79

** Chi-square (1 df). Fisher exact p-value was reported for depression, uninhibition, nervousness and aberrant motor activity.*

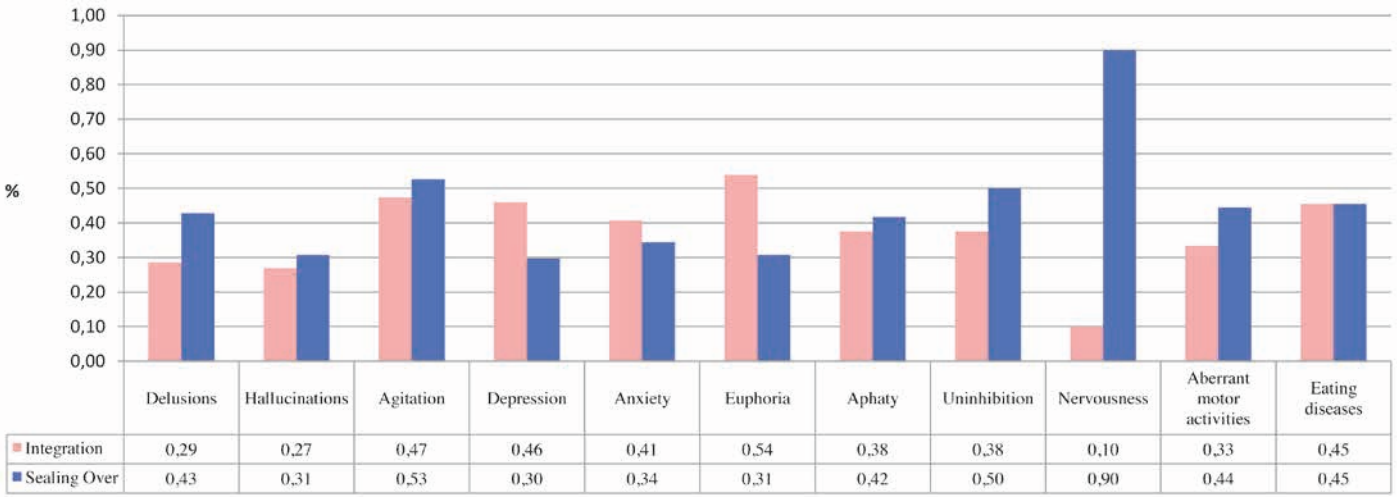

FIGURE 1.
Correlation between distress in the mental health workers and recovery style.

Table III. Correlation between NPI symptoms and distress, differences between recovery style groups.

	N	Overall	Integration	Sealing Over	p-value*
Delusions	21	0.29	0.09	0.68	0.18
Hallucinations	26	0.19	0.30	0.29	0.72
Agitation	19	0.17	-0.10	0.54	0.16
Depression	37	0.32	0.01	0.76	0.01
Euphoria	13	0.01	-0.06	0.00	0.84
Aphaty	24	0.51	0.40	0.64	0.08
Anxiety	32	0.06	-0.27	0.43	0.004
Uninhibition	8	0.86	0.82	0.82	0.49
Nervousness	10	0.56	ne§	0.43	ne
Aberrant motor activity	9	0.27	0.82	-0.18	0.38
Eating disorders	11	0.38	0.57	0.18	0.82

** p-value referred to interaction between recovery style and severity in a regression model. § Only 1 patient in this category. ne: not estimable*

the un-inhibition, on the total of the sample (rho = 0.86, p-value = 0.01). Therefore, it can be considered in an independent way from the recovery style (p-value interaction term = 0.49). As far as nervousness and apathy are concerned, a high correlation was found ($\rho > 0.50$), although not significant. With reference to the recovery style, statistically significant differences were found for depression and anxiety, bearing a greater degree of distress in the management of sealer patients (interaction p-value 0.01 and 0.004, respectively).

These patients can bring the different therapeutic/rehabilitative proposals as bearing excessive inner tension in the mechanism of denial of the psychotic experience. For this reason, symptoms such as anxiety and depression acquire clinical expression that determines a greater degree of tension and psychological stress in mental health professionals.

Discussion and Conclusions

In our sample, equitably represented by integrators and sealers, a significant difference between the recovery style groups for the proportion of subjects with depression and nervousness was observed (p<. 001 and <. 003). Focusing on depression, Drayton found that patients in the sealing over group made significantly more negative self-evaluation than did those in the integration group [9]. Consistent with our findings, Muser found that integrators showed higher levels of depression than sealers [10]. Other authors suggested that a sealing over approach to illness may be a valid and successful coping style for those who adopt it and

that poor insight serves as a protector of self-esteem [11]. Dealing with distress in mental health professionals, symptoms causing a greater distress, in an absolute sense, are uninhibition, nervousness and apathy. These aspects, both for the excess and for the lack of the stimuli caused in the mental health workers, are the least tolerated in the therapeutic relationship. An interesting correlation between depression in sealers and distress of caregivers was observed, although this symptom was more frequently detected in the integrators. It can be assumed that the sealers evoke a greater distress in the mental health professionals because they are less adherent to treatment program [12 13]. The end points were achieved. The limits of the study are the small size of the sample and the lack of an evaluation of insight, closely related to the construct of recovery style. We are engaged in research to deepen this point, with these goals in mind.

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Take home messages for psychiatric care

- Severity is the high presence of the symptoms, the burden is the degree of distress reported by the health professionals in the management of severe patients
- In regard to the recovery style, depression and anxiety cause a greater degree of distress in sealer patients
- The symptoms which cause a greater distress in the health professionals are uninhibition, nervoussess and apathy
- These symptoms are more burdensome for mental health professionals, because they require a greater engagement in the therapeutic relationship
- Further studies are required to depeen an evaluation of insight

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COGNITIVE REMEDIATION IN THE PRODROMAL PHASE OF SCHIZOPHRENIA OR IN SUBJECTS AT-RISK FOR PSYCHOSIS

Stefano Barlati[1]
Cassandra Ariu[1]
Giacomo Deste[1]
Antonio Vita[1,2]

[1] Department of Mental Health, ASST Spedali Civili of Brescia;
[2] Department of Clinical and Experimental Sciences, University of Brescia

Abstract

Objectives: Cognitive impairment is a key feature of schizophrenia with relevant consequences on patients' functioning. Several quantitative reviews and meta-analyses have established that cognitive remediation is effective in reducing cognitive deficits and in improving functional outcome both in chronic schizophrenia and in the early stages of the illness. Current literature underlines that subjects at-risk for psychosis already show an impairment in cognitive domains, that is associated with functional disability and conversion into schizophrenia. Thus, research in primary prevention of schizophrenia should focus its efforts in the improvement of these deficits, before the onset of the illness, with the goal to prevent the conversion to full-blown psychosis. Aim of the present review is to provide an up-to-date overview of current knowledge on the efficacy of cognitive remediation in the prodromal phase of schizophrenia or in subjects at-risk for psychosis, with particular focus on preventing the conversion to psychosis and the deterioration of functional outcome in this population. The secondary aim is the identification of potential areas worth to be investigated, useful for orienting future research.

Materials and Methods: English language and peer-reviewed publications were obtained by electronic searching PubMed/MEDLINE, PsycINFO, Scopus, Embase, and Web of Science database until June 2016, using the following keywords: "schizophrenia", "psychosis", "At-risk Mental State" (ARMS) or "Ultra High Risk" (UHR) or "Clinical High Risk" (CHR) or "prodromal phase" paired with "cognitive remediation", "cognitive training" and "cognitive rehabilitation".

Results: According to our selection criteria, eight studies analyzing the efficacy of cognitive remediation techniques in the prodromal phase of schizophrenia or in subjects at-risk for psychosis were identified. Despite some methodological limitations, the search results provide the first evidence of the feasibility and potential advantages of delivering cognitive remediation at the putative earliest stages of the disease._

Conclusions: Preliminary findings indicate that cognitive remediation should be considered as a key point for early intervention in schizophrenia. Further research on the effectiveness of cognitive remediation applied in the prodromal phases of schizophrenia is needed together with a more rigorous methodological approach.

Key words: schizophrenia, At-Risk Mental State (ARMS), Ultra High Risk (UHR), Clinical High Risk (CHR), prodromal phase, cognitive remediation, cognitive training, cognitive rehabilitation

Introduction

Cognitive impairment is a key feature of schizophrenia with relevant consequences on patients' functioning [1 2]. Evidences support that antipsychotic treatment has a limited influence on this domain and that there is the need of using psychosocial interventions as an integrated approach

Correspondence

Stefano Barlati
stefano.barlati@libero.it

in the management of such impairment [3]. Given the relevant influence of cognitive performance on daily functioning, different cognitive training approaches have been developed to improve cognitive deficits and psychosocial functioning in schizophrenia [4].

Several quantitative reviews have established that cognitive remediation (CR) is effective in reducing cognitive deficits and in improving functional outcome of schizophrenia [5 6]. Furthermore, the available studies support the usefulness of CR when applied both in patients with longer illness duration and with early course schizophrenia [7]. According to the European and international health care policies, on research psychosis of last decades has focused not only on subjects with schizophrenia, but also on help-seeking persons who experience early signs of emerging psychosis, but do not fully meet diagnostic criteria for the disorder [8]. People at heightened risk for psychosis, usually referred to as Clinical High Risk (CHR), Ultra High Risk (UHR), psychosis prodrome or At-risk Mental State (ARMS), meet the following criteria: presence of attenuated psychotic symptoms (APS) and/or a family history of schizophrenia combined with problems in functioning and/or presence of one or more brief limited intermittent psychotic symptoms (BLIPS) such as delusions or hallucinations [9 10]. The ultimate goal of this research approach, focused on people at-risk for psychosis, is to prevent this condition from converting to psychosis. A recent meta-analysis showed that the average 1-year transition rate to psychosis in this UHR group was 22%, increasing to 36% after three years [11].

An alternative set of criteria to detect at-risk patients is given by the so called “basic symptoms” (BS), which consist of subclinical subtle disturbances in stress tolerance, affect, thinking, speech, drive, perception and motor action occurring before the appearance of APS or BLIPS, thus allowing for detection of at-risk patients at an earlier stage [12-14]. The BS approach was developed to detect the risk for psychosis as early as possible, as indicated by the presence of the cognitive-perceptive basic symptoms (COPER) and the cognitive disturbances (COGDIS) criterion [8]. Current literature underlines also that subjects at-risk for psychosis and in the prodromal phase of schizophrenia show an impairment in cognitive domains, especially in verbal executive and memory functions [15]. These cognitive deficits are associated with functional disability and psychosis conversion, suggesting that the presence of cognitive deficits in the prodromal phase of schizophrenia can be considered as a vulnerability predictor [16]. Another possible marker of the liability for psychosis is social cognition, defined through four core domains: emotional perception and processing, social perception and knowledge, Theory of Mind (ToM), and attributional style [17]. Impaired social cognition is considered to result in poor social functioning, a well-established risk factor for transition to psychosis [18]. Impairments in all of these domains have been consistently found in patients with chronic schizophrenia as well as in patients with first episode psychosis (FEP) [19]. Herein, the current scientific literature, emphasizes that the onset of psychosis can be prevented by intervening in the risk phase and treatment in the early stages of schizophrenia is significant to prevent the progression of the disease [20-25]. As for antipsychotic treatment, this is not indicated for the treatment of individuals at CHR, and the use of such medication for this population is controversial also for ethical consideration [26-28]. Because of their unfavorable side effect profiles, pharmacological interventions with antipsychotics should only be applied in individuals at CHR following thorough cost-benefit considerations, after obtaining consent by subject and family, and only for a limited time-period with the primary aim to achieve symptomatic stabilization as a starting point for psychological and psychosocial interventions, but not with the aim to prevent conversion to psychosis [8 29]. On the other hand, several systematic reviews and meta-analyses explored the efficacy of different psychological and psychosocial treatments, such as cognitive behavior therapy (CBT) and family psychoeducation, in the prodromal stages of schizophrenia as early interventions to prevent conversion to psychosis, finding some positive results [28 30-33].

One of the evidence-based psychosocial interventions is CR [3], that improves cognition and daily functioning in schizophrenia [5]. CR can be applied in all the phases of the illness, as highlighted by several meta-analitic studies [5 6 34]. Revell et al., considering 11 studies with 615 partecipants, first reviewed quantitatively the efficacy of CR in early schizophrenia. Results show a significant effect of CR at this stage, with a positive effect on global cognition, especially on verbal learning and memory, and social cognition. Improvements nearing uncorrected significance were also seen in processing speed, working memory and in reasoning and problem solving. Furthermore, CR had a significant effect on symptoms and global functioning [34].

CR has been proposed also as a preventive intervention for at-risk subjects, because a prolonged duration of untreated CHR symptoms can compromise functional outcome [35]. Thus, prevention has two prin-

to evaluate the state of the art of the research in this area of interest.

Objective

The aim of the present review is to provide an up-to-date overview of current knowledge on the efficacy of CR intervention in the prodromal phase of schizophrenia or in subjects at-risk for psychosis, with particular focus on the possibility to prevent the conversion to psychosis and the deterioration of functional outcome in this population. The secondary aim is the identification of potential areas still to investigate, that could be useful for orienting future research. Although there are numerous qualitative and quantitative and meta-analytic reviews on CR in patients with schizophrenia, also at the onset or in the early stage of illness, to our knowledge this is the first qualitative review on this topic in prodromal/high risk subjects.

Material and Methods

Electronic searches were performed on June 2016 PubMed/MEDLINE, PsycINFO, Scopus, Embase, and Web of Science database combining the following search terms (without time limit): [(treatment) OR (therapy) OR (rehabilitation) OR (enhancement)] AND [(neurocognitive) OR (cognitive)] AND [(risk) OR (prodrome)] AND [(psychosis) OR (schizophrenia)]. Two of the authors (SB, CA) independently reviewed the database in order to avoid errors in the selection of articles. In addition, the reference lists of the included articles were carefully hand-searched to further identify other studies of possible interest. Informations taken into account in this review include: study design, duration and setting; sample size and participant demographics; intervention details; outcome measures; follow-up; effect size.

Results

According to our selection criteria, eight studies analyzing the efficacy of CR techniques in the prodromal phase of schizophrenia or in subjects at-risk for psychosis were identified (Table I).

Rauchensteiner et al. performed a pilot, non-controlled, study to examine the differential effects of a computer-based cognitive training programme (Cogpack) in 10 'prodromal' patients compared to 16 patients with fully manifested schizophrenia. Cognitive functioning was assessed by different tests controlling for memory, attention and logical thinking, i.e. Verbal Learning Test (VLMT), Continuous Performance Test, Identical Pairs version (CPT-IP) and a non-verbal attention test. Subjects at-risk for schizophrenia significantly increased their performance in the VLMT ($p < 0.01$), in the CPT-IP ($p < 0.04$) and in five out of eight Cogpack tasks, while patients with schizophrenia did not. The results indicate that prodromal patients can improve their long-term verbal memory, attention and concentration after cognitive training. In two delayed-recall tasks of the VLMT after Cogpack training, prodromal patients were able to memorize significantly more words than at baseline. In the attention and working memory test CPT-IP, the hit rates of prodromal patients in detecting target events among intrusive and distractive numbers or shapes also improved significantly. So, subjects with at-risk mental state could enhance their performance significantly more than patients with schizophrenia. Despite some limitations, this exploratory pilot study of differential cognitive training outcomes in prodromal patients with at-risk mental state for schizophrenia compared to patients with fully manifested schizophrenia can provide a first glance on the effects of preventive non-pharmacological interventions during the prodromal stage of the disease [36].

To investigate short-term outcomes of an 8-week computer assisted cognitive remediation (CACR) in adolescents with psychotic disorders or at high risk for psychosis, 32 adolescents (psychotic, n = 21; at high risk for psychosis, n = 11) were randomised to the treatment condition (CACR) or a control condition (a set of computer games, CG). At the end of the intervention, improvement in visuospatial abilities was significantly greater in the CACR than in CG group ($p = 0.013$), corresponding to a large effect size ($d = 0.62$), with no other significant group differences. Furthermore, results revealed significant differences between baseline and 6-month follow-up in executive functions/inhibition abilities ($p = 0.040$) and reasoning abilities ($p = 0.005$), with better performances found only in the CACR group. A longer duration of CACR sessions was reported to be more effective in improving reasoning abilities ($p = 0.024$). These findings suggest that CACR has specific effects on some of the investigated cognitive capacities, with promising long-term benefits. On the basis of these encouraging preliminary results, authors concluded that studies with larger samples are needed to determine whether the CACR is similarly efficient for adolescents with psychosis and for those at high risk, and whether CACR can prevent the conversion to psychosis in such cases [37 39]. Moreover authors evaluated in the same sample the relationship between mo-

Table I. Studies analyzing the efficacy of cognitive remediation in the prodromal phase of schizophrenia or in subjects at risk for psycosis.

Authors	Type of Study	N	Mean Age (years) (SD)
Rauchensteiner et al., 2011 [36]	Non-controlled pilot study, subjects at risk for schizophrenia vs fully manifested schizophrenia patients	Subjects at risk = 10 Schizophrenia patients = 16	Subjects at risk = 27.2 (5.3) Schizophrenia patients = 30.1 (7.8)
Urben et al., 2012* [37]	A single blinded 8-week RCT, subjects at risk for psychosis and adolescents with psychosis	Cog Rem = 18 Ctrl = 14	Cog Rem = 15.2 (1.3) Ctrl = 16.0 (1.3)
Pihet et al., 2013* [38]	RCT with subjects at high risk of psychosis and adolescent with psychosis	Cog Rem = 15 Ctrl = 13	Mean age = 15.69 (1.3)
Holzer et al., 2014* [39]	A single blinded 8-week RCT, subjects at risk for psychosis and adolescents with psychosis	Cog Rem = 18 Ctrl =14	Cog Rem = 15.4 (1.3) Ctrl = 15.7 (1.4)
Bechdolf et al., 2012 [40]	Multicentre, prospective RCT, young people with EIPS of psychosis	Cog Rem (IPI†) = 63 Ctrl = 65	IPI = 25.2 (5.4) Ctrl = 26.8 (6.2)
Hooker et al., 2014 [41]	An uncontrolled pilot study investigating feasibility and potential behavioral benefits of computer-based TCT in a single group of CHR participant	Cog Rem = 18 Ctrl = 14 (tested at baseline to identify CHR deficits)	Cog Rem = 21.9 (4.2) Ctrl = 24.1 (3.2)
Piskulic et al., 2015 [42]	A single blind, randomized controlled pilot study tested the effectiveness in young people at CHR for psychosis	Cog Rem = 18 Ctrl = 14	Cog Rem = 19.72 (5.71) Ctrl = 17.5 (3.48)
Loewy et al., 2016 [43]	A double-blind RCT in two groups of CHR individuals	Cog Rem = 50 Ctrl = 33	Cog Rem = 17.76 (3.06) Ctrl = 18.73 (4.60)

AT: auditory training; CACR: computer-assisted cognitive remediation; CG: computer games; CHR: clinical high risk; Cog Rem: Cognitive Remediation group; Ctrl: Control group; EIPS: early initial prodromal state; ES: effect size; IPI: Integrated Psychological Intervention; RCT: Randomized Controlled Trial; SD: Standard deviation; TCT: target cognitive treatment; TM: treatment motivation.
** These studies have the same sample; † IPI consists of individual cognitive-behavioural therapy (CBT), modified social skills training (SST), cognitive remediation and multifamily psychoeducation.*

tivation and treatment outcome, showing that a lower treatment motivation (TM) was predicted by more severe symptoms at baseline, and was associated with smaller improvements in symptoms and both cognitive and psychosocial functioning at the end of the intervention. In particular, they found that more severe negative symptoms at baseline were associated with lower TM during the whole intervention, while higher

Cognitive Remediation Program	Duration of Cognitive Remediation	Assessment	Main Findings
Cog Rem: CACR (Cogpack)	10 single sessions (1 h) for 4 weeks	Cognitive and symptoms at baseline and after treatment (4 weeks)	Subjects at risk increased their performance in long-term verbal memory ($p < 0.01$), in attention ($p < 0.04$) and in five out of eight Cogpack tasks, while patients with schizophrenia did not (Effect Size not reported)
Cog Rem: CACR Ctrl: CG	Biweekly single sessions (45 min) for 8 weeks	Cognitive and symptoms at baseline and 6 months after the end of the intervention program	Better performances at follow-up in the CACR group, with significant differences between baseline and follow-up in executive function/inhibition abilities ($p = 0.040$) and reasoning abilities ($p = 0.005$) (Effect Size not reported)
Cog Rem: CACR Ctrl: CG	16 biweekly sessions (30-45 min) for 8 weeks	Cognitive, clinical, functional outcome and TM	Patients with higher TM improved attention and social-occupational functioning, and reported lower general psychopathology Patients with increasing TM over the course of the intervention improve attention and visual-spatial abilities
Cog Rem: CACR Ctrl: CG	Biweekly single sessions (45 min) for 8 weeks	Cognitive, symptoms and functioning at baseline and post-intervention	Visuospatial abilities improved significantly more in CACR than in Ctrl group, with large ES ($d = 0.62$)
Cog Rem: CACR (Cogpack) Ctrl: supportive counselling	12 sessions (12 months)	Symptoms and functioning at baseline, post-treatment (12 months) and at follow-up (24 months post-treatment)	IPI was superior in preventing progression to psychosis at 12-month follow-up ($p = 0.008$) and at 24-month follow-up ($p = 0.019$). (Effect Size not reported)
Cog Rem: online training from home (two programs, one with target on cognition and one with target on social cognition)	Four daily 15 minute sessions (1 h) for 5 days/week (total: 40 h/8 weeks)	Cognitive was assessed pre/post TCT Symptoms and functioning were assessed pre-TCT and one-month post-TCT	Internet based TCT intervention is feasible and has potential cognitive benefits for CHR Processing speed significantly improved after TCT ($p = 0.01$, $d = 0.63$) and predict a larger improvement in role functioning
Cog Rem: auditory processing cognitive remediation therapy Ctrl: CG	1 h sessions for 4 days a week (total: 40 h 10-12 weeks)	Clinical, functioning and cognitive measures at baseline, post-CRT (at 3 months) and at 9 month follow-up	Cog Rem group improved in global functioning between baseline and 9 month follow-up ($P < 0.05$), even though it was not correlated with cognitive functions No other difference was found between the two groups. (Effect Size not reported)
Cog Rem: AT Ctrl: CG	40 hours session (1 h/day, 5 day/week, for 8 week)	Clinical, cognitive and functioning assessment at baseline and post-training	There were significant main effects for global cognition, working memory, visual learning and problem solving (small ES) and verbal memory (medium ES, $d = 0.61$) Both groups improved symptoms and functioning over time.

cipal aims: the accurate identification of the target population and its effective treatment. Nonetheless, research in this field is only preliminary and optimal training parameters, including dose, intensity, and setting, are still unknown. Herein, the authors report a qualitative review of the current scientific literature on CR intervention in the prodromal phase of schizophrenia or in subjects at-risk for psychosis, in order

positive symptoms predicted an increase and then a stabilization of TM and more motivated patients were more likely to show improvement in terms of attention, general psychopathology and social-occupational functioning. The authors concluded that these findings could lead to a significant contribution to the knowledge about determinants, dynamics, and effects of TM in adolescents at-risk or with psychosis within the framework of cognitive remediation [38].

A multicentre, prospective, randomised trial with two parallel groups assigned to alternative out-patient interventions was performed to investigate the effects of integrated psychological intervention (IPI) on the prevention of psychosis in the so-called "early initial prodromal state" (EIPS). Of 168 eligible individuals, 128 help-seeking out-patients in an EIPS were randomized to IPI or supportive counselling. The primary outcome measure was progression to psychosis (incidences of subthreshold psychosis, first-episode psychosis and first-episode schizophrenia) at 12-month (post-treatment) and 24-month follow-up. The cumulative conversion rates to subthreshold psychosis at 12 months were 3.2% for the IPI and 16.9% for the supportive counselling group and 6.3% for IPI and 20% for supportive counselling at 24 months. The time to conversion for the entire study period was significantly shorter for the supportive counselling group than the IPI group (IPI: mean 887.1 days; supportive counselling: mean 784.2 days; p = 0.020). At the 24-month follow-up, significantly fewer patients in the IPI group than in the supportive counselling group had developed psychosis (3.2% vs. 15.4%; p = 0.018) or schizophrenia/schizophreniform disorder (1.6% vs. 12.3%; p = 0.033). In summary, the incidence of and time to conversion to subthreshold psychotic symptoms, psychosis and schizophrenia/schizophreniform disorder during a 12-month treating period were significantly lower for patients who received specially-designed IPI than for those who were treated with supportive counselling. Furthermore, IPI appeared effective in delaying the onset of psychosis over a 24-month period in people with an EIPS. Since IPI covered a variety of psychological strategies, the trial design did not allow assessment of the relative contribution of each intervention, such as cognitive remediation [40].

An uncontrolled pilot study investigated the feasibility and the potential behavioral benefits of a 8-week internet/computer-based targeted cognitive training (TCT) in a single group of 32 individuals at clinical high risk (CHR) for psychosis. Cognitive functions were assessed immediately pre- and post-TCT, while symptoms and functional outcome were assessed pre-TCT and one month post-TCT. Eighteen CHR participants were enrolled. At the end of TCT, CHR participants had a significant improvement in processing speed (p = 0.01, d = 0.63) and a trend improvement in visual learning and memory (p = 0.06, d = 0.54) and in global cognition (p =. 06, d = 0.45). A greater improvement in processing speed predicted greater improvement in role functioning. Despite this is an uncontrolled pilot study, these findings provide evidence that an intensive, internet-based, TCT intervention is feasible and has potential cognitive benefits for CHR, supporting more extensive clinical trials [41].

A recent single-blind, randomized controlled pilot study tested the effectiveness of a 12-weeks auditory processing cognitive remediation therapy (CRT), the Brain Fitness Program (BFP - developed by Posit-Science), in improving cognition in a sample of 32 young people at CHR for psychosis. Participants were randomised to either BFP or a control treatment consisting of commercial computer games (CG) and clinical, functioning and cognitive measures were performed at baseline, post-CRT (at 3 months) and at 9-month follow-up (i.e. 9 months post-baseline or 6 months after post-CRT assessment). The BF group showed a trend of improvement in speed of processing between baseline and 9-month follow-up (P = 0.06) as well as at post-CRT compared to 9 month follow-up (P < 0.05), while the CG group showed a significant improvement in working memory between post-CRT and 9-month follow-up (P < 0.05). Furthermore, in the BF group there was a significant improvement in a global functioning social scale between baseline and 9 month follow-up (P < 0.05), even though this was not correlated with cognitive functions. No other differences were found between the two groups. Despite the small trend of improvement, the study confirms the feasibility of CRT for individuals at CHR and point up the need of additional RCTs, conducted with more attractive cognitive training programs specifically designed for young people [42]. Finally, in a double-blind randomized controlled trial (RCT), 83 adolescents and young adults at CHR for psychosis were assessed as for clinical, cognitive and functional outcome variables at baseline and after 8-week auditory cognitive training (AT) or computer games (CG) application. Participants in the AT group showed, compared to CG group, improvement in global cognition, working memory, visual learning and problem solving with a small effect size and in verbal memory with a medium effect size (ES = 0.61). Symptoms and

functioning improved over time in both groups. The authors concluded that this study could improve the growing research literature on the issue of preventive approaches to psychotic illness, focusing on the identification of effective methods to improve cognitive dysfunctions, that contributes to poor outcomes in the CHR state [43].

Conclusions and further directions

The available studies support the effectiveness of CR when applied both in chronic patients with schizophrenia, in young first episode schizophrenia patients or in the early stages of the illness [5 6 34]. Therefore, exposure to CR may be an essential component to early-intervention programmes in psychoses [28]. Evidence emerging from the research literature indicates that targeting cognitive impairments early in the course of the disorder can result not only in cognitive improvement per se, but also in significant functional benefits in different critical domains such as social functioning, employment and major role functioning [44].

The few studies analyzing the efficacy of CR in the prodromal phase of schizophrenia or in subjects at-risk for psychosis provide first evidences of the feasibility and the potential advantages of delivering CR at the putative earliest stages of the disease process. Prodromal patients seem to exhibit a higher rehabilitative potential relative to cognitive functions in comparison to patients with fully manifested schizophrenia, and it is conceivable that cognitive training may facilitate neuroplastic phenomena and have a neuroprotective effect [44-46]. This is based on the premise that the potential recovery may be higher within the "critical period", in which the on-going neurodevelopment increases the possibility to alter the course of disease. The "protective" role of early effective intervention on the neurobiological and clinical deteriorating course of the disease, proposed for treatment with antipsychotics – especially with the 2nd generation compounds – may be extended to non-pharmacological approaches, such as CR [47 48]. Moreover, since cognitive deficits occur before the onset of psychosis and are significantly associated with poor premorbid adjustment and poor functional outcome in the prodromal phase of schizophrenia and in UHR individuals, there is a clear rationale for further research on CR in these populations [49]. Given the theoretical and clinical interest of the possible role of treatment for preventing the subsequent conversion in psychosis of subjects with "at-risk mental states", and the lively debate on the risk-benefit ratio and ethical concerns of exposing young people to antipsychotic treatment, it would be particularly relevant to examine whether non-pharmacological strategies of treatment could demonstrate a similar preventive efficacy [27 28]. Given the evidence for debilitating cognitive and functional difficulties occurring at or even before the onset of psychosis and the clear relationship between these two dimensions, the maximal benefits of CR are expected to occur early in the course of the illness, and even in its prodromal phase [49].

The studies reported in this narrative review have numerous methodological weaknesses, such as the small sample size, the inclusion in the same sample of "at-risk" subjects and patients with schizophrenia, the difficulties in understanding the contribution of each single intervention in integrated approaches, the lack of control groups and the absence of follow-up periods. Furthermore, many important questions remain open: i) the actual efficacy of CR in delaying or preventing the onset of psychosis; ii) the generalizability of the effects to broader areas of functioning; iii) the possible mediators and moderators of response; iiii) the role of social cognition and metacognition involvement in treatment effectiveness. Despite these limitations and the fact that further research on the effectiveness of CR applied in the prodromal phases of psychosis or in the so-called "at-risk mental states" is needed together with more rigorous experimental efforts, available findings indicate that CR should be considered as a key point for early intervention in schizophrenia.

Recently, it has been proposed a randomised, parallel group, observer-blinded clinical trial – the FOCUS trial – with an initial sample size of 126 patients meeting the standardised criteria of being at UHR for psychosis, with the aim to investigate whether CR can improve cognitive and psychosocial function in this population. FOCUS trial results will shed light on the effect of CR on cognition, functional outcome, and symptomatology, as well as long-term outcome in preventing transition to psychosis in subjects at-risk for psychosis [47].

Future research should use progress in cognitive neuroscience to identify neural circuits involved in the pathophysiology and in the treatment of CHR subjects, in order to develop new cognitive training strategies to prevent the onset of psychosis and to improve outcome. These CR programmes should be more engaging and appealing for young people yet without a diagnosed disease. Furthermore, there is the need to perform dose-response studies, estab-

lishing the time and the intensity of training necessary to generate clinically significant gains in cognitive and functional outcomes. Another key point for future research should be to identify more homogeneous groups of subjects at highest risk for psychosis as potential target group for treatment. Finally, it will be relevant to consider CR approaches within other evidence-based psychosocial integrated interventions to better provide the generalization of any obtained effect.

Take home messages for psychiatric care

- Cognitive impairment is a key feature of schizophrenia with considerable consequences on patients' functioning. Several quantitative reviews and meta-analyses have established that CR is effective in reducing cognitive deficits and improving functional outcome both in chronic schizophrenia and in the early stages of the illness
- Current literature underlines that subjects at risk for psychosis already show an impairment in cognitive domains, that is associated with functional dysfunction and with psychosis conversion. Thus, research in prevention of schizophrenia should focus on the improvement of these deficits before the onset of the illness, with the goal to prevent the conversion to psychosis
- Prodromal patients seem to exhibit a higher rehabilitative potential concerning cognitive functions in comparison to patients with fully manifested schizophrenia, and it is conceivable that cognitive training may facilitate neuroplastic phenomena and may have a neuroprotective effect, with the possibility to alter the course and trajectory of the disease. Thus, it has been proposed that exposure to CR may be an essential component of early-intervention programmes in psychosis
- Despite some methodological limitations, the few studies analyzing the efficacy of CR in the prodromal phase of schizophrenia or in subjects at risk for schizophrenia provide first evidences of the feasibility and the potential advantages of delivering CR at the putative earliest stages of the disease
- Although these findings indicate that CR should be considered as a key issue for early intervention in schizophrenia, many relevant questions still remain open and future rigorous research is needed for the implementation of more targeted interventions

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Claudia Delicato[1]
Camilla Vecchi[1]
Sarah Di Marco[1]
Eleonora Gattoni[1]
Gianluca Giovanna[1]
Alessandro Feggi[1]
Carla Gramaglia[1]
Patrizia Zeppegno[1,2]

[1] Institute of Psychiatry, Department of Translational Medicine, Università del Piemonte Orientale, Novara; [2] S.C. Psichiatria, AOU Maggiore della Carità di Novara

THE EFFECT OF ANTIPSYCHOTIC THERAPY ON SOCIAL INFERENCE AND EMOTION RECOGNITION IN SCHIZOPHRENIC PATIENTS

Abstract

Objectives: Social cognition is described as the mental operations underlying social interactions including the human ability and capacity to perceive intentions and dispositions of others and it is involved in functional outcomes. Pharmacological studies on this topic are few, therefore our goal is to compare the effect on social cognition and social inference of second, first-generation and long acting antipsychotics.

Materials and Methods: This work arises from the Italian Network Research on Psychosis (NIRP). From March 2012 to December 2015, 62 schizophrenic patients in stable psychopathological conditions were recruited. Each patient was tested with the Positive and Negative Syndrome Scale (PANSS), the Brief Negative Symptom Scale (BNSS), the Facial Emotion Identification Test (FEIT) and The Awareness of Social Inference Test (TASIT).

Results: Patients treated with atypical antipsychotics better recognize neutral expression at TASIT1 while patients treated with typical neuroleptics recognize a higher percentage of sadness at FEIT. Patients receiving long-acting therapy interpret better sincere remarks and paradoxical sarcasm at TASIT2 and have a higher percentage of correct answers at FEIT. Considering the entire sample, our study demonstrates a big impact of duration of the illness, independently from patients' age.

Conclusions: Our results highlight the need for further investigations about social cognition in schizophrenic patients in order to provide personalized and integrated programs and ameliorate clinical outcome of these patients.

Key words: social cognition, antipsychotic therapy, emotion recognition, social inference, schizophrenia

Introduction

Social cognition is described as the "mental operations underlying social interactions including the human ability and capacity to perceive intentions and dispositions of others" [1]. It is composed of five domains: theory of mind or mentalization, emotion recognition ability, attributional style, social knowledge and social perception or social inference [2].

Over the last decade, clinical investigators and behavioral scientists have increasingly employed social cognitive constructs to explore the symptoms and interpersonal deficits that characterize schizophrenia. Indeed, social cognition has emerged as a high priority topic within schizophrenia research as evidenced by a burgeoning empirical literature and increased attention in scientific meetings [2].

One of the most important aspects of social cognition is emotion perception. Deficits in this domain have been widely acknowledged in schizophrenic patients [3-6]. Social inference is another key domain of social cognition; it is related to community functioning, and should be

Correspondence

Patrizia Zeppegno
patrizia.zeppegno@med.uniupo.it

a target for interventions designed to enhance functional improvements in schizophrenic patients [2 7]. Until now, this issue has been relatively understudied in schizophrenia, despite evidence of the relationship between functional outcome and social cognition [7]. Although social cognition has not been commonly used as an endpoint for intervention studies, it is increasingly viewed as a treatment target for both pharmacological and non-pharmacological (psychosocial) interventions [2]. Currently, there are only few studies about the impact of medication on social cognition, and particularly on emotion perception. Moreover, a recent review of the literature, concluded that antipsychotics were unlikely to facilitate the recovery of social cognition deficits in schizophrenia [8].

The most investigated aspect of social cognition is emotion processing. Similarly to the results described by Kucharska Pietura & Mortimer [8], a review about facial emotion recognition found that antipsychotic medication did not seem to successfully treat this aspect of schizophrenia [9]. The literature about this issue reports mixed results; anyway, treatment effects are likely small, or affected by moderating factors such as age, gender or type of medication. Kee and coworkers reported a benefit in emotion perception for risperidone compared to haloperidol in a small (N = 20) double-blind pilot study with random assignment to medication. In an open-label study without random assignment (N = 52) [10], Littrell and coworkers found a benefit for olanzapine compared with a variety of first-generation medications on a social perception measure [11]. No benefit was reported for risperidone on emotion perception in a small (N = 13) crossover study in patients with first-episode psychosis [12]. Similarly, Harvey and coworkers found that patients randomly assigned to risperidone (N = 142) or quetiapine (N = 124) did not improve on a lone measure of emotion perception over the 8-week study period [13].

Briefly, the studies to date have involved either small samples, single measures of social cognition, or non-randomized designs, not allowing for definitive conclusions about the influence of antipsychotic medications on social cognition or the relative benefit of first- versus second-generation medications. Duration of illness has been shown to be a marker of poor prognosis and has been associated with poorer outcome [14], but regrettably most of the studies do not assess the possible impact of this variable.

The current research aimed to add to the current dearth of studies about the impact of antipsychotics on social cognition and social inference, focusing on the possible differences between second and first-generation antipsychotics.

Materials and Methods

Data collection for this research started in the context of the Italian Network for Research on Psychoses [15], a multicenter, observational, case-control study. This study was conducted from March 2012 to September 2013 in 26 Italian University psychiatric clinics and/or mental health departments. For this study, our center recruited 44 schizophrenic patients among those treated by the Psychiatry institute (SC Psichiatria) of the University Hospital "Maggiore della Carità", Novara. To increase our sample size, we continued the recruitment even after the end of the national project, until December 2015, enrolling 18 patients more.

Inclusion criteria were: a diagnosis of schizophrenia according to DSM-IV-TR criteria; 18 to 66 years of age; patients in good/stable psychopathological conditions (no treatment modifications and /or hospitalization due to symptoms exacerbation in the three months preceding assessment).

Exclusion criteria were: a diagnosis of dementia or moderate to severe mental retardation, history of head trauma with loss of consciousness, symptoms due to alcohol/substance abuse in the last six months, neurological disorders, current pregnancy or lactation, insufficient knowledge of Italian language.

Written informed consent was obtained from each patients or their legal guardians. The research was approved by our local Ethical Committee (Protocollo 283/EC, studio n EC 43/12).

We collected data on age, sex, type of medication, duration of illness and education, using all available sources of information (patient, family members and caregivers, medical records). The Positive and Negative Syndrome Scale (PANSS) [16] was used to assess symptom severity; negative symptoms were rated using the Brief Negative Symptom Scale (BNSS) [17 18]. Patients were tested with the Facial Emotion Identification Test (FEIT) [19 20] and The Awareness of Social Inference Test (TASIT) to investigate the recognition of facial expression and the social cognition [21].

The TASIT is an audiovisual tool based on 59 brief clips played by professional actors, designed for the clinical assessment of social perception. It assesses emotion recognition and the ability to interpret conversational remarks which are meant literally (i.e., sincere remarks and lies) or non-literally (i.e., sarcasm) as well as the ability to make judgments about

the thoughts, intentions and feelings of speakers [21].
The FEIT consists of 55 black and white pictures of male and female adults, presented trough a computerized presentation, showing 7 different facial emotion: happiness, sadness, fear, anger, surprise, disgust, neutrality. The patient has hence to match each images with the appropriate facial emotion [19 20].
Descriptive statistics were performed using frequencies and percentages tables for categorical variables. Continuous variables were analyzed with ANOVA and post-hoc analyses (Tukey method), and non parametric tests were performed as well (SPSS 21).

Results and Conclusions

Our total sample included 62 patients: 11 patients treated with first generation antipsychotics, 40 patients treated with second generation antipsychotics and 11 patients with an association of the two classes of drugs. Furthermore, we divided the sample into two subgroups based on the method of administration of the therapy: 46 patients were treated only with oral medication, while 16 patients received long acting injectable therapy.
Patients treated with second generation antipsychotics better recognized neutral expression at TASIT1 compared to those treated with a combination of typical/atypical drugs ($p < 0.05$), while we found no difference with patients treated with first generation antipsychotics. Patients treated with first generation antipsychotics recognized a higher percentage of sad faces at FEIT than patients treated with atypical neuroleptics ($p < 0.05$). Our study is one of the first about the impact of antipsychotics on the recognition of a single emotions at FEIT, usually in fact, literature studies use as an endpoint the total percentage of correct answer at FEIT without focusing on single emotions; it is therefore difficult to compare our results with the existing literature.
As far as long acting therapy is concerned, statistical analyses found that patients receiving long-acting therapy better interpreted sincere remarks and paradoxical sarcasm at TASIT2 than subjects in treatment with oral therapy ($p < 0.05$). Patients in therapy with long acting drugs had a higher percentage of correct answers at FEIT compared with patients treated only with oral therapy ($p < 0.05$). Our result confirm literature data about the impact on social functioning of long acting antipsychotics compared to the oral ones. Unfortunately, treatment outcome studies focused on this topic have used social functioning total scores as an endpoint and they do not consider subscales targeting specific domains (e.g. social, residential, and vocational), it is therefore difficult to make comparison of single domains with our results [22].
Considering the whole sample, our study showed a significant impact of illness duration on social inference and emotion recognition, independently from patients' age: patients with a longer history of the disease performed worse at both FEIT and TASIT. (See Table I) Consistent with our results, literature's evidence correlate duration of illness with poor prognosis; moreover duration of illness seems to be related with treatment efficacy [14]. It would be interesting to correlate the performance on FEIT and TASIT with the duration of untreated psychosis (DUP), in the light of evidence that suggests that DUP has a significant impact on clinical and social outcome [23].
In conclusion, our results failed to find a major efficacy of second generation antipsychotics on social

Table I.

		Pearson Correlation	Sig. (2-tailed)
Duration of illness	TASIT 1 surprise	-.298	.019
	TASIT 1 neutrality	-.359	.013
	TASIT 1 disgust	-359	.013
	FEIT% CORR ANS	-.266	.037
	FEIT% anger	-.287	.024
	FEIT% disgust	-.268	.044
	FEIT% M faces	-.257	.044
	BNSS asociality	.256	.045
	BNSS blunted affect 9	.254	.046
	BNSS blunted affect 10	.292	.021
	BNSS blunted affect 11	.302	.017
	BNSS alogia	.257	.044

inference and emotion recognition [10 11]. Anyway, as described above, the results about this issue are mixed, and some reviews found no benefit of second generation antipsychotics on emotion perception [12]. Briefly, literature results are heterogeneous, samples are frequently too small and the methods used are different, hindering the possibility to compare and generalize the results. Further investigations about social cognition in schizophrenic patients are warranted in order to allow the implementation of personalized and integrated treatment programs to improve the clinical outcome of schizophrenic patients.

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Franco De Crescenzo[1,2], Stefano Vicari[1], Luigi Mazzone[1], Maria Pontillo[1], Marco Armando[1]

[1] Child and Adolescence Psychiatric Unit, Department of Neuroscience, Children's Hospital Bambino Gesù, Rome, Italy; [2] Institute of Psychiatry and Psychology, Catholic University of Sacred Heart, Rome, Italy

A PHARMACOGENETIC-DRIVEN APPROACH IN TWO SEVERELY ILL NON-RESPONDER ADOLESCENT PSYCHIATRIC PATIENTS

Key words:
pharmacogenetics, adolescent, mental health

Introduction

Evidence is growing that pharmacogenetic outcomes are related to drug resistance. We undertook genetic tests in order to study pharmacogenetic variables in two severely ill adolescent patients who were resistant to therapy. These two patients had different psychiatric conditions (patient A with attention deficit and hyperactivity disorder, patient B with bipolar disorder). They presented at baseline with adverse events related to current psychopharmacological treatment. By using a pharmacogenetics test we were able to ascertain which medications would be most suitable for safely and effectively treating the patients. To that aim, we used the commercially-available Neuropharmagen test (AB-BIOTICS S.A, Barcelona, Spain), that evaluates genetic polymorphisms of pharmacogenetic relevance in 30 different genes, including all major cytochromes. The Neuropharmagen test was previously studied in epileptic patients [1] and has recently been shown to increase the odds of improvement and stabilization in psychiatric patients with different conditions, when compared to treatment as usual in a naturalistic setting [2].

Case Report

Patient A is a 16 year-old adopted boy, who presented to our inpatient unit with aggression, opposition, violent behavior and cannabis abuse. The history of substance abuse is not surprising since it have been associated with higher rate of misuse of stimulants in college students afflicted by ADHD [3]. He lived in South America until the age of 4 and then he moved to Italy. There was little anamnestic information, except for a report of a family history of unspecified neuropsychiatric disorders. One year before the current hospitalization he was diagnosed with conduct disorder and attention deficit and hyperactivity disorder (ADHD). Given the high severity of his clinical condition, at that time he was seen by the territorial service and was administered valproic acid (500 mg/die), gabapentin (300 mg/die) and risperidone (3 mg/die). He was still taking these medications when we saw him. However, he had suffered various adverse events related to the pharmacological therapy assumed, in particular somnolence, excessive weight gain and

Correspondence

Marco Armando
marco.armando@opbg.net

extrapyramidal symptoms. We therefore decided to undertake a pharmacogenetic evaluationin order to make further therapeutic choices. The results of the pharmacogenetic evaluation showed a higher risk of developing adverse events with some drugs (among which were risperidone and valproic acid), together with a higher probability to respond to other drugs (such as methylphenidate and aripiprazole). So, we decided to discontinue his therapy and to switch to methylphenidate (20 mg/die) and ariprazole (20 mg/die). The Recommendations on methylphenidate are based on genetic variants in LPHN3 [4] and CES1 gene [5]. After 3 months the patient's illness was much improved (score: 2) according to the Clinical Global Impression – Improvement scale (CGI-I). At the same time, the patient did not reported any adverse event.

Of course, the response to metylphenidate could have been surely related to the fact that this medication represents the treatment of choice for ADHD; however, we went for that treatment, otherwise not necessarily indicated in this case, following the indications of the pharmacogenetics test. Indeed, patient A presents an history of substance abuse which in college students with ADHD is associated with higher rate of misuse of prescription stimulants [5].

Patient B is a 15 year-old boy, who presented to our inpatient unit with insomnia, anxiety, grandiosity, accelerated thought processes, command hallucinations, delusions of reference, and hyperactivity. He was diagnosed as bipolar I, in a manic phase with psychotic symptoms. He was then administered risperidone, which was increased up to 4 mg, with only partial benefits and with the onset of adverse events, namely somnolence and weight gain. As in the previous case of drug resistance, we performed a pharmacogenetic evaluation by using the Neuropharmagentest in order to optimize the therapeutic choices. The results of the pharmacogenetic evaluation showed a higher risk of developing adverse events with some antipsychotics (including risperidone) and a higher probability to respond to other medications (including aripiprazole and lithium). Neuropharmagen analyses base the good response to lithium on the rs2284017 polymorphism of the CACNG2 gene, in agreement with findings obtained in 2 independent cohorts [6]. The selection of aripiprazole as a suitable medication is instead based on the assessment of 28 different haplotypes in gene CYP2D6. Indeed, the decreased activity of CYP2D6 significantly impairs the metabolism of aripiprazole, and the FDA currently recommends reducing the dose of aripiprazole to 50% of the standard dose in patients that are poor metabolizers of CYP2D6 (FDA-approved labelling from June 2014). Moving from these evidences, we decided to discontinue his therapy and to switch to carbolithium (900 mg/die) and aripiprazole (20 mg/die). As for patient A, the CGI-I scored 2, much improved, after 3 months of therapy and the patient had a partial remission of symptomatology, with a reduction of psychotic symptoms, and a consistent reduction of hyperactivity, anxiety and accelerated thought processes. Moreover, patient B did not have any adverse event following the pharmacogenetic-driven therapy.

Discussion

Adolescent psychiatric patients are among the most challenging to treat, and many of them undergo several different treatment regimens before showing improvement. Adverse drug reactions and lack of effect often lead to adherence problems, which further dampen the chances of achieving a good control of the condition, as well as to frequent changes in medication and higher drug costs.

Researchers are starting to develop clinical guidelines on how to make use of pharmacogenetic testing [7-9]. The implication is that just as family history or plasma levels can help predict the efficacy of any particular drug, the genetic background of a patient can also be used to help determine expected drug response. Indeed, the results presented herein are in line with a previous study analyzing the effect of pharmacogenetics in hospitalized pediatric psychatric patients [10]. However the pharmacogenetic approach remains in a very promising but pioneering stage, and the variance explained so far is modest.

In conclusion, we believe further research on this topic is warranted, so that clinical recommendations can be issued. We consider pharmacogenetic information could be especially useful in difficult to treat cases, such as polymedicated patients not responding to therapy, as per the two cases reported herein.

Take home messages for psychiatric care

- Evidence is growing that pharmacogenetic outcomes are related to genetically driven drug resistance
- Researchers are starting to develop clinical guidelines on how to make use of pharmacogenetic testing
- Pharmacogenetic information could be especially useful in difficult to treat cases, such as polymedicated patients not responding to therapy
- Pharmacogenetic approach remains in a very promising but pioneering stage

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PAST, PRESENT AND FUTURE OF TRANSCRANIAL MAGNETIC STIMULATION (TMS) IN THE TREATMENT OF PSYCHIATRIC DISORDERS

Beatrice Benatti[1*]
Laura Cremaschi[1*]
Lucio Oldani[1]
Francesca De Cagna[1]
Matteo Vismara[1]
Bernardo Dell'Osso[1,2]

[1] Department of Psychiatry, University of Milan; Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milano, Italy;
[2] Bipolar Disorders Clinic, Stanford University, CA, USA
[*] Equally contributing first authors

Abstract
Transcranial magnetic stimulation (TMS) is a brain stimulation technique used for the treatment of major depression and other psychiatric disorders. Initially used as a research tool in neurophysiology, TMS has been subsequently extended to the therapeutic area of depressive disorders and approved in many countries for this purpose. TMS uses magnetic fields to deliver electricity into specific areas of the cerebral cortex, mainly the dorso-lateral prefrontal cortex. Several randomized clinical trials (RCTs) conducted with TMS over the last decade have allowed its approval by the FDA for the treatment of major depressive episodes with poor response to standard antidepressants. In addition, meta-analyses and international treatment guidelines have more recently defined stimulation parameters and safety standards. Future directions in the field should further explore the clinical efficacy and safety of specific forms of TMS like deep TMS and theta burst stimulation, which allow to reach deeper anatomic targets and to shorten the overall duration of stimulation. The utility of maintenance session and the interaction with specific psychotropic compounds represent areas that need to be further investigated as well.
To date, TMS is likely the non-invasive brain stimulation intervention with the strongest evidence in terms of efficacy in psychiatric disorders, as documented by RCTs and meta-analyses. Nonetheless, the efficacy of TMS needs to be further investigated in other psychiatric disorders with preliminary, encouraging results in different fields. The tolerability and safety profile of TMS are advantageous, the technique being non-invasive, generally well-accepted and devoid of systemic side-effects.

Key-words: transcranial magnetic stimulation (TMS), major depression, guidelines, randomized controlled trials (RCTs), meta-analyses, future perspectives

Introduction

Transcranial magnetic stimulation (TMS) is a brain stimulation technique that has been used in the psychiatric field, over the last two decades, with therapeutic purposes, mostly in patients with mood disorders and partial response to standard antidepressants.
TMS uses magnetic fields to penetrate the skull and the brain and deliver electrical current to the cerebral cortex, typically at 2-3 cm of depth, through a stimulator generating brief pulses with variable frequency and intensity, and a stimulating coil connected to the stimulator. The TMS coil is usually round or figure-eight (butterfly) in shape, the latter producing a stronger and more focal field than the circular one. Different and novel coil have been developed over the last years indeed [1].
Differently from the direct application of electrical current, as for the electroconvulsant therapy, magnetic fields can easily cross the skull and penetrate the brain, then converting into electrical current that can inter-

Correspondence

Bernardo Dell'Osso
bernardo.dellosso@unimi.it

fere with and modulate cortical excitability, through mechanisms of long-term potentiation and long-term depression [1]. In particular, these changes occur when TMS is delivered in form of repeated trains of stimuli, as happens with its use in clinical practice as repetitive TMS (rTMS).

In terms of mechanism of action and rational for the use of TMS in depressive disorders, it should be kept into account that current pathophysiological models converge to indicate that two major groups of brain regions – a "dorsal" and a "ventral" network – seem to account for the formation of the different symptoms of affective disorders [2-4]. Within this theoretical framework, depression is hypothesized to involve concurrent hypoactivation of dorsal prefrontal regions and hyperactivation of ventral prefrontal regions, particularly in the left hemisphere [2-4]. Symptom remission, therefore, is supposed to require facilitation of hypoactive dorsal brain regions and inhibition of hyperactive ventral areas. Ultimately, transcranial neuromodulatory, brain stimulation techniques, like TMS, are supposed to restore the functional balance between the two hemispheres [2-4].

Different parameters characterize the clinical use of TMS as therapeutic intervention in neuropsychiatric disorders. One is represented by the frequency of stimulation, that identifies two main types of stimulation: low frequency (1Hz) and high frequency stimulation (10 Hz). The two types of stimulation are thought to exert opposite effects over the target area (inhibition for low frequency and enhancement for high frequency) [5]. Other important parameters are represented by the intensity of stimulation, which ranges from the 80% to 120% of patient's motor threshold – the minimal intensity required to produce contraction of the thumb (abductor pollicis brevis) –, the number of stimuli per single session of TMS, the total number of sessions (i.e., the duration of the trial), and the potential implementation of maintenance sessions.

TMS is currently considered a safe and well-tolerated intervention. Adverse reactions can include post-treatment mild and self-limited headache, scalp pain at the stimulation site, and potential transient hearing alterations due to the clicking sound of the machine. The most serious, although rare, potential adverse effect of TMS is the induction of seizure.

After having obtained the first FDA approval in 2008 for the therapeutic use (i.e., Neurostar device) in major depressive episode with poor response to at least one antidepressant trial, TMS obtained two further approvals for such indication (i.e., Magstim and Brainsway devices) and it has been extensively investigated as therapeutic tool also in a series of different psychiatric disorders, including bipolar disorder, schizophrenia, anxiety disorders, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), addictions, and other conditions [6 7]. The increasing number of studies, randomized controlled trials (RCTs) in particular, allowed the development of the first meta-analyses and subsequent treatment guidelines – updated in 2014 – by the major international associations of psychopharmacologists, neurophysiologists and psychiatrists, defining the standard parameters for the use of TMS in psychiatric clinical practice and opening the way for a field in continuous evolution. In the last two years, further reviews and meta-analyses providing the most recent updates have been published, confirming the growing interest of the scientific community on the topic [8-10].

The aim of the present review was to provide a critical perspective of most recent acquisitions, current directions and future perspectives in the field of therapeutic use of TMS for psychiatric disorders, taking into particular account guidelines indications and recent publications, after a Pub-Med/Scopus detailed search.

Treatment guidelines indications

In the last two decades, evidence-based guidelines elaborated by different international associations of experts in the field of clinical psychiatry, stemming from a consistent body of evidence in terms of RCTs, recognized the emerging role of TMS as therapeutic tool in a variety of neuropsychiatric conditions, in light of its non-invasiveness and favorable tolerability profile [11 12] (Figure 1). Although not being considered as the standard of care, guidelines recommendations may provide guidance for researchers and clinicians in order to offer TMS within a more individualized treatment plan.

For instance, the Canadian Network for Mood and Anxiety Treatments (CANMAT) [13] and the World Federation of Societies of Biological Psychiatry (WFSBP) [14] have been the first major associations providing updated evidence on the neurostimulation application in psychiatry, including a specific section on TMS. Even though the therapeutic utility of this stimulation technique has been claimed for depression, TMS also found application in acute mania, bipolar disorders, panic disorder, schizophrenia, OCD, PTSD, and drug craving.

In 2009, moreover, a group of international experts updated the previous safety guidelines for the appli-

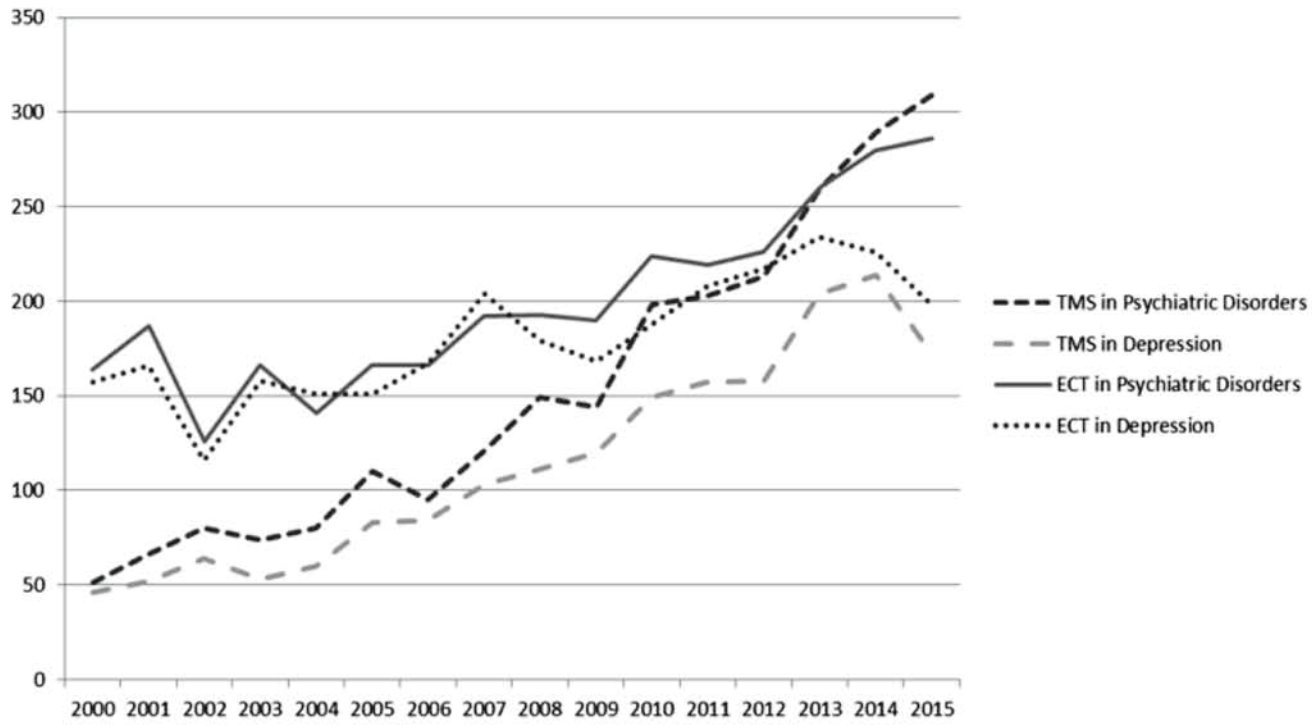

FIGURE 1.
TMS and ECT publications (PUBMED) from 2000 onward in psychiatric disorders and major depression.

cation of TMS in research and clinical settings [15].
Furthermore, in 2014, Lefaucheur and colleagues published the first evidence-based guidelines specifically focused on the clinical application of TMS in the treatment of different neuropsychiatric disorders: to date these guidelines represent the most complete and updated report on the topic [16].
According to CANMAT guidelines, rTMS has been recommended as a second-line therapeutic intervention in adult patients with major depression, who failed to respond to at least one antidepressant, with a good level of evidence in terms of acute efficacy and safety/tolerability (level 1), and a minimal evidence for maintenance and relapse prevention (level 3). It should be performed at high frequency on the left dorso-lateral prefrontal cortex (DLPFC), with a better outcome for 20 *vs* 10 sessions. Even though available data did not allow to clearly define predictors of positive outcome to TMS, or the optimal eligibility criteria for candidate patients, some clinical variables, such as a lower duration of current depressive episode and the absence of comorbid anxiety disorders, were indicated to positively affect treatment response. Moreover, the augmentative use of rTMS with antidepressant medication was found to accelerate response under sham-controlled conditions [13].
With respect to WFSBP guidelines, TMS has been recommended with a good level of evidence for the acute management of patients with moderate treatment-resistant depression (TRD) – preferably without psychotic symptoms during the index episode – either alone or in augmentation with medications. Typically, the eligible candidates should have shown an inadequate response to at least one trial with antidepressants, although some class I evidence supported the acute TMS efficacy also in drug-free unipolar depressed individuals. Insufficient evidence was available on its application as a maintenance/preventive strategy for depression, after acute response. In all these circumstances, a specifically trained equipe should provide TMS within a medical setting, under the supervision of a licensed medical doctor, able to properly manage potential adverse-events and related consequences during and after stimulation sessions [14].
Evidence-based guidelines elaborated by Lefaucheur and colleagues in 2014 considered the application of TMS in a large number of neuropsychiatric disorders including major depression, schizophrenia, and anxiety disorders [16]. Summary of level of evidence for the efficacy of TMS in these conditions is presented in Table I.
Indeed, major depression represents the main clinical indication for the use of rTMS. The efficacy of

Table I. Use of rTMS in psychiatric disorders other than major depression as formulated by Lefaucheur et al. (2014).

Psychiatric disorder	Evidence level
Schizophrenia	Potential efficacy (auditory hallucinations) Potential efficacy (negative symptoms)
Bipolar Disorder	Insufficient
Panic Disorder	Insufficient
Generalized Anxiety Disorder	Insufficient
Post-Traumatic Stress Disorder	Potential efficacy
Obsessive-Compulsive Disorder	Variable (different targets)
Craving and cigarette smoking	Potential efficacy

high frequency (HF) rTMS of the left DLPFC and low frequency (LF) rTMS of the right DLPFC in acute depression is definite, with a Level A of recommendation. Furthermore, rTMS is likely to have higher success rates when applied to individuals not older than 65 years, with partial treatment response or limited treatment resistance (one/two unsuccessful medical interventions, with or without the combination of focused psychotherapy).

As regards schizophrenia, preliminary but encouraging evidence supports the role of rTMS in reducing negative symptomatology (level B), probably related to the beneficial effect on the depressive component resulting from HF rTMS of the left DLPFC. In a previous comprehensive review, moreover, Fitzgerald and Daskalakis provided preliminary but limited data supporting the role of TMS in reducing negative symptoms and improving cognitive function in schizophrenia [17]. However, insufficient data recommended the use of TMS in the treatment of psychotic symptoms in schizophrenia. However, some studies suggest that TMS, in particular at the level of the temporoparietal area, may improve positive symptoms (i.e., auditory hallucinations) compared with sham TMS [18]. Moreover, according to a recent meta-analysis, low frequency TMS was found to be effective in treating resistant auditory hallucinations in schizophrenic subjects, although showing no effect on other positive symptoms or cognitive deficits [19].

In relation to anxiety disorders, rTMS should be considered a potential second-line treatment in PTSD, for individuals who failed to respond to conventional therapies. Up to date, results from the few studies investigating this issue in PTSD are heterogeneous, with the only recommendation (level C) for a potential effect of HF rTMS on right DLPFC [20].

LF rTMS specifically targeting the orbitofrontal cortex or the supplementary motor area seems to be the most promising use of TMS in OCD [21], given that rTMS of the DLPFC has shown poor evidence of superiority over sham therapy [22]. Nonetheless, a recent sham-controlled trial of rTMS of DLPFC reported a significant improvement in obsessions but not in compulsions, with Y-BOCS scores reduction, as well as relief in depressive and anxiety symptoms [23]. Ultimately, the guidelines level of evidence for the use of TMS in OCD is of possible efficacy, requiring further investigation.

Considering cigarette craving, a level C of recommendation has been reported for the possible efficacy of HF rTMS to the left DLPFC in reducing consumption.

Finally, Lefaucheur and colleagues stressed the need of further investigation, in order to better clarify specific issues including TMS efficacy in bipolar depression, non-response *vs* treatment-resistance level in candidate patients, potential concomitant pharmacotherapy, and the usefulness of maintenance protocols.

Potential limitations and new perspectives in the therapeutic use of rTMS in psychiatric practice

TMS is, at current time, one of the most promising novel and innovative treatments in clinical psychiatry, particularly for major depression. In the U.S., for instance, three different devices for TMS have received FDA approval for use in major depression, such indication being reimbursed by most insurance companies. Nonetheless, if, on one hand, previous and more recent treatment guidelines provide converging evidence on the efficacy and safety of rTMS in patients with major depression, some aspects beyond those already considered by the guidelines (e.g., interference of concomitant pharmacological therapy, usefulness of maintenance session, need for further studies in other psychiatric disorders) need to be taken into account in order to overcome current

limitations and barriers to the use of TMS in clinical practice.

To authors' opinion, two main issues may limit the use and diffusion of TMS in some psychiatric conditions and in specific populations: the limited depth of penetration and the duration of session and overall trial with traditional TMS. In fact, a first potential limitation for the use and extension of TMS in other psychiatric disorders is represented by its limited power of penetration (2-3 cm on average), allowing to mostly target the grey cortical matter up to the junction with white matter. Such characteristic is considered a potential limitation for the treatment of resistant patients and elderly patients, who may have different degrees of cortical atrophy, and patients with psychiatric disorders with pathophysiological mechanisms implying the prominent involvement of subcortical circuits. The availability of deep TMS seems to be of particular relevance for these and other cases.

With respect to the duration of a single session and entire course of TMS, these parameters are quantified around 30-45 minutes per session, 5 days per week, for not less than 3 to 4 weeks. Such features contribute to the overall costs of the intervention and limit its access to candidate patients for different reasons. In such perspective, the recent development of patterned TMS protocols, including Theta Burst Stimulation, might be of particular interest in order to reduce the overall duration of stimulation.

Deep TMS

A relatively new alternative to classic TMS is Deep Transcranial Magnetic Stimulation (DTMS), a form of rTMS operated with a particular coil, the so called H-Coil [24], that can lead to a non invasive stimulation of a deeper area of the brain, up to 6 cm of depth, compared with the classic figure-of-eight coils. This stimulation can affect extensive neuronal pathways, including deeper cortical regions and fibers targeting subcortical regions, reducing the stimulation of the superficial cortical areas [25-27]. In particular, main targets are the dorsolateral and ventrolateral frontal areas that projects to other centers of the brain reward system [28]. DTMS is considered a secure and safe treatment: scalp discomfort, transient headache and dizziness, insomnia, numbness in the right temporal and right cervical zone, and, very rarely, generalized seizures have been reported as possible side effects and adverse events [9]. In the recent years, DTMS has been thoroughly investigated [29-33] and in 2013, the Food and Drug Administration issued a specific approval for a DTMS device (Brainsway), indicated for the treatment of adult patients suffering from TRD.

The only large multisite RCT involving 212 patients with TRD suggested that DTMS monotherapy was significantly more effective than sham DTMS in reducing depression scores at the Hamilton Depression Rating Scale, with a 0.76 effect size, and in improving response (38.4% *vs* 21.4%) and remission rates (32.6% *vs* 14.6%) [34]. This study underlined also the safety of the procedure and a stable therapeutic effect for up to 12 weeks of maintenance phase.

Two recent reviews specifically assessed the efficacy of DTMS. The first one stated that a 20 session-HF-DTMS course was an efficacious and acceptable treatment in unipolar depressed, multi-resistant patients, with overall weighted response and remission rates of 60% and 29%, respectively [35]. The second literature review [36] showed also an anxiolytic effect for the procedure in unipolar depressed patients, even though such effect seems to be more heterogeneous among studies compared to the antidepressant action of DTMS.

HF-DTMS seems to be effective also on cognitive functioning in depressed unipolar patients, including visuospatial and working memory, executive functions, information processing speed, orientation, as recently highlighted [37] with a higher degree of improvement compared to ECT and rTMS [38].

If, currently, DTMS may be considered an effective intervention in the therapy of TRD, the technique has also shown some positive result in the treatment of other psychiatric disorders, such as bipolar depression [39 40], obsessive compulsive disorder [41], PTSD [42], cognitive and negative symptoms in schizophrenia [43] and neurologic disorders, like Parkinson's disease [44]. More in detail, different specific coils have been developed for some of the abovementioned conditions. In addition, it needs to be stressed that DTMS allows an overall shorter duration of session, approximately 20 minutes.

Theta Burst Stimulation

Theta-burst stimulation (TBS) is a form of rTMS in which short bursts of 50 Hz rTMS are repeated at a rate in the theta range (5 Hz, 500 ms), as a continuous (cTBS), or intermittent (iTBS) trains [45]. The effects of this technique on synaptic plasticity occur faster than with traditional rTMS protocols, and TBS can produce long-lasting results on corticospinal excitability, involving long-term potentiation or depression-like effects on cortical synapses, depending on the pattern applied [1]. In particular, studies on

the human motor cortex showed that iTBS, giving short TBS trains intermittently, produced a prevalent excitatory effect yielding long-term potentiation-like effects; cTBS, on the other hand, led to an inhibitory effect, inducing a long-term depression-like reduction of cortical excitability [46 47].

Over the recent years, TBS has been applied in patients with various types of neurologic diseases such as Parkinson's disease, dystonia, tics, stuttering, tinnitus, spasticity, or epilepsy; rehabilitation of aphasia or hand function after stroke; pain syndromes, such as neuropathic pain, visceral pain or migraine [47 48]. As regards psychiatric disorders, TBS has been utilised in TRD patients, with the underlying hypothesis that such individuals manifest a hypoactivity of the left DLPFC and a hyperactivity of the right DLPFC [49].

In 2010, Chistyakov and colleagues applied TBS to subjects with TRD in an open-label study, reporting clinical improvement after 2 weeks of treatment with left prefrontal iTBS (1200 pulses) and right prefrontal cTBS (1200, 1800 and 3600 pulses). Authors also showed a dose dependent effect, since 3600 pulses cTBS were significantly more effective than 1200 pulses cTBS in reducing depressive symptoms severity [50]. Moreover, a recent RCT of daily prefrontal TBS in patients with TRD by Li and colleagues showed that left prefrontal iTBS was more effective than right prefrontal cTBS and sham TBS; in addition, treatment refractoriness at baseline was an important and independent variable in predicting TBS antidepressant response [48].

Other stimulation parameters

From the first experiments of the technique in neurophysiology, TMS has obtained different approvals for the therapeutic use in neuropsychiatric disorders and is currently considered a safe and efficacious treatment for MDD and other psychiatric disorders [5]. Nonetheless, there are several ongoing directions to further refine the application of TMS in order to achieve superior therapeutic utility. First of all, the vast majority of TMS investigation has focused on the acute efficacy of the treatment with scattered and inconsistent data on the long term effect and the risk of relapse after treatment suspension [7 51]. Literature reports a high variable relapse risk, between 20% [52] to less than 80% [53] at six months. These findings suggest the need of a maintenance phase after the acute phase effect of TMS. In particular, maintenance phase is indicated for patients that showed a positive response after the acute phase without reaching remission or for individuals that relapsed after the acute phase treatment [5].

The efficacy of maintenance treatment has been supported by different reports from literature studies for both rTMS [54-57] and DTMS [34 58] in MDD and bipolar depression [59], even though, in mentioned studies, maintenance treatment was performed under different protocols in terms of duration and frequencies. Consequently, a univocal protocol is urgently needed. A recent study focusing on depressed patients who were medication free for one year maintenance period showed that maintenance TMS was not superior to "watch and wait" approach, although it was associated with a non-significantly longer time to relapse [60]. This study underlines how a better understanding of the interactions between pharmacologic treatments and TMS is needed for future investigation in order to implement optimal maintenance TMS plans.

In fact, patients undergoing TMS frequently receive other forms of therapy, such as psychotherapy, neurorehabilitation, and psychotropic medications, being the latter the primary safety concern for a possible interaction with TMS [15]. Actually, TMS produces limited side effects, and the most serious is the occurrence of seizures [61]. In particular, several antidepressants and neuroleptics may increase seizure risk, while anticonvulsants lower it [62]. Therefore, before starting a TMS protocol, clinicians should assess patients' seizure risk, taking also into account factors like medications dosages, speed of dose changes, and combination with other psychotropic drugs. In particular, the intake of one or a combination of the following psychotropic drugs poses a higher potential hazard for the application of TMS, due to their significant seizure threshold lowering potential: imipramine, amitriptyline, doxepine, nortriptyline, maprotiline, chlorpromazine, clozapine. In these cases, TMS should be performed, when required, with particular caution [15 63]. Certainly, the chapter of the interactions between TMS and specific classes of pharmacological treatments needs to be further investigated.

Conclusions

Among brain stimulation interventions used as therapeutic tools for psychiatric disorders with poor response to standard treatments, TMS certainly represents the technique with the largest body of evidence in terms of RCTs and meta-analyses, with multiple indications and specific approvals by major regulatory agencies, such as the American FDA, and recently updated international treatment guidelines.

Certainly the favorable profile of tolerability with no associated systemic side-effects and the very low potential to induce adverse events played a crucial role in the widespread diffusion of TMS.

While the efficacy of TMS, particularly in major depression with poor response to antidepressants, is supported by the available literature, its effects in other mental disorders are still under investigation with preliminary evidence in some contexts (i.e., auditory hallucinations and negative symptoms in schizophrenia, nicotine craving and consumption, PTSD) and encouraging findings in some anxiety disorders and OCD. Other clinical areas and aspects to be further investigated are represented by the efficacy of the technique in bipolar depression and by the usefulness of maintenance sessions in patients beyond the acute treatment.

Notwithstanding the significant growth of TMS as therapeutic tool in major depression and other psychiatric disorders, there are still some open and debated issues about its real placement within the treatment algorithm of major depression, given that the mean duration of a TMS course should not last less than 3-4 weeks, 5 days per week for an average duration of 30 to 45 minutes per session. Such characteristics make it necessary to perform specific analyses of cost-utility for the clinical use of TMS in order to place the technique in the most appropriate position within the therapeutic algorithms of public and private psychiatric services. This is why, over the future years, further investigation in the field of TBS and DTMS might provide new advantages in terms of time reduction of the overall trial and single sessions of stimulation as well as in terms of possibility to treat more resistant patients.

Undoubtedly, the last decade represented a major step forward in the investigation and clinical application of TMS in the treatment of psychiatric disorders, which, ultimately, allowed the technique to be considered among current international guidelines as a valid therapeutic option in the treatment of major depression. It is, therefore, more than likely that the future decade of research and clinical acquisitions in the field of TMS will allow to definitely complete the transition for the technique from an investigational to a practical level of use within the therapeutic interventions for major depression and other psychiatric disorders.

Take home messages for psychiatric care

- TMS is likely the non-invasive brain stimulation intervention with the strongest evidence in terms of efficacy in psychiatric disorders, in light of its non-invasiveness and favorable tolerability profile, as documented by RCTs and meta-analyses
- It has been approved by the FDA for the treatment of major depressive episodes with poor response to at least one antidepressant trial and then extensively investigated as therapeutic tool also in other psychiatric disorders
- We provided a critical perspective of most recent acquisitions on the use of TMS in psychiatric field, taking into account guidelines indications and more recent publications
- Future investigation should address the clinical efficacy and safety of specific forms of TMS (e.g., deep TMS, theta burst stimulation), which allow to reach deeper anatomic targets and to shorten the overall duration of stimulation.

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Bernardo Carpiniello[1]
Claudio Mencacci[2]

[1] Presidente Eletto, Società Italiana di Psichiatria (SIP);
[2] Presidente, Società Italiana di Psichiatria (SIP);

TERRORISM, MENTAL HEALTH AND MEDIA: BEYOND THE "CONTAGION EFFECT"

We have sadly become resigned to the recurrence of acts of ruthless and brutal terrorism by the most disparate groups of men trained to sow death and suffering, justifying their actions in the name of a misunderstood faith and of an avenging God. In recent times, mass murders perpetrated by single individuals defined as "lone wolves", often too arbitrarily labelled as terrorists have extended throughout Europe. Indeed, these fierce gestures in which single men kill dozens of innocent bystanders, at times blindly, at others according to a targeted design, are often carried out in the name of a faith or an exasperated and radical ideology; however, conversely, they may merely manifest the need for revenge against a specific person or thing. Particularly striking in recent events is the "sequential" repetition of these acts of violence, carried out at brief intervals one from the other, but in a wide extension of geographical locations and a variety of spatial and cultural contexts. This however is nothing new in the globalized world of today. The fact remains that the extremely rapid succession of such shocking episodes has forced the public to ask themselves whether the extensive media coverage of these acts could have led to a "contagion" effect - a possibility acknowledged by many, whilst being forcefully denied by others. Can the amplification of similar acts of violence by the media really result in emulation? The answer, based on reliable scientific evidence, is undoubtedly yes. Psychiatry has long acknowledged the so-called "Werther effect" [1,2], thus named after the protagonist of the famous novel by Goethe, whose "romantic" death by suicide was at the time emulated by many of his readers. For most people, the news of a suicide, which still today is often given excessive emphasis by the media despite the imposing of self-regulatory codes, may produce the dramatic and ultimate effect of inducing a minority of people to commit suicide. The presence of a "contagion" effect has also been demonstrated in the case of mass murder. Recently, a US study confirmed the existence of a significant increase in the probability (oscillating between 20 and 30%) of similar events during the 12-13 days following mass murder; moreover, 47% of the perpetrators of mass murder go on to committ suicide [3]. Awareness of the power of contagion linked to a frequently obsessive and excessive reporting of similarly dramatic acts of violence has led to a rethinking of the position occupied by the media, persuading several major newspapers, TV news and websites to limit or completely abstain from publishing headlines of this nature. As expected, this has stimulated a lively debate and a deep reflection both on the role of the media and freedom of the press; some people, even on an authoritative level, have been quick to defend this stance, arguing against any form of censorship or self-censorship. Unfortunately, the radicalization of positions generally fails to produce any appreciable result. It is not the freedom of press that is at stake, nor are the media expected to "conceal" specific realities, indeed an impossibility in current times given the multiplicity and substantial unaccountability of the media in the world at large. It is however legitimate to demand that these issues be governed by a series of defined forms of self-regulation, similar to the process implemented in numerous countries by the press following an invitation from the WHO, with regard to the reporting of suicide, although the self-regulations imposed continue to be not infrequently disregarded. The real issue therefore is not whether to

Correspondence

Claudio Mencacci
claudio.mencacci@gmail.com

inform but rather how to provide the information. In terms of a "contagion effect", it is not the diffusion of the news that counts, but the emphasis given to the news (use of images, obsessive reiteration of content, emphasis on gruesome details, tendency to propose simplistic or ideologized explanatory hypotheses etc.). One of the most widely debated issues focuses on the reason why the information given may induce certain people to undertake violent acts. In the same way as almost all complex phenomena, multiple and scarcely univocal levels of explanation may be involved. However, a series of common features have been repeatedly highlighted in literature. For many, the opportunity to be seen by the world as a martyr or an avenger allows them to avail themselves, at least once in their life, of an identity and/or to give meaning to an invariably marginal and purposeless existence. Literature reports describe a virtually identical identikit for a mass murderer [4]: male, young adult or teenager, deprived of meaningful relationships and of a supportive social network, unemployed or with lower and/or precarious working role; often victim of intra-family violence in childhood or bullying, with a compromised or entirely absent sense of personal identity; not infrequently attracted to strong or extremist ideologies, weapons and military life; mostly overloaded by resentment due to a sense of social exclusion experienced as an injustice; not infrequently with small criminal records in adolescence, and tendency to substance abuse. There is no doubt therefore that the contagion effect will find more fertile terrain in these socially and psychologically "fragile" people, with various studies indicating traits of narcissistic, obsessive or paranoid personality in these individuals [4]. This however does not justify the superficial attribution of "madness" to their gesture. All too often the media superficially label terrorists or mass murderers as "crazy", "depressed", or "psychopathic personalities". In attributing the label of "mentally ill" to these individuals, the media apply the well-known process of self-reassuring oversimplification, i.e.: being "mad", they are "different", which implicitly means "different from us" "normal people". Attribution of these gestures to mental illness indeed represents a pseudo-reassuring explanation, essentially a mystification.

Although hard to admit, violence is a basic component of the human race. How could we otherwise explain the impressive statistics for domestic violence, war brutalities and exterminations? Thousands and thousands of mentally ill murderers? Far too convenient, too easy. No one is denying that in some documented cases the murderer may have been affected by a mental disorder; however, in the majority of cases this is not so [4]. The risk of extremely severe violent acts among the mentally ill living in the community is considerably low [5]. Being affected by some form of mental disorder is indeed associated with an increased risk of violent behavior, but this risk is fundamentally conditioned by other, more important, concurrent psychosocial risk factors [6]. Indeed, to arbitrarily state that mental disorders, among others, may be a risk factor for violence certainly does not imply that *all* people affected by mental disorders are intrinsically violent. This is a prejudice, and is paramount to maintaining that Jews are all greedy exploiters, or that black people are less intelligent than white people. Regrettably, prejudice resides at the basis of stigma, and is capable of producing the discrimination, isolation and marginalization of the mentally ill from society. Indeed, stigma is one of the most potent barriers preventing access to the care system, both reducing and delaying the seeking of help [7]. As psychiatrists, we should be aware that the amplification of mass murders (whether due to acts of terrorism or for other reasons) by the media and their flippant attribution of these acts to a mental disorder may contribute towards further increasing both prejudice and stigma. The emphasis placed by the media on acts of violence committed by the mentally ill is well known [8], together with the consistent misrepresentation of mental illness in the media and conveying of two unequivocal messages: the association of the mentally ill with violence, and inference that the mentally ill are dangerous and should be avoided [9]. As psychiatrists however, we should likewise be aware of the relevant role to be played by the media in fighting stigma [10], recognizing that, as scientific societies, the time has come to set up solid and permanent forms of cooperation with the media, establishing together a "holy alliance" in the fight against stigma.

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