

Evidence based Psychiatric Care Journal of the Italian Society of Psychiatry

www.evidence-based-psychiatric-care.org



Vol. 07 | 4_2021

Evidence based Psychiatric Care

Journal of the Italian Society of Psychiatry

Vol. 07 4 2021

SOCIETÀ ITALIANA DI PSICHIATRIA

Contents

Original articles A PRogram for detection, Intervention and Monitoring first-Episode Psychosis (PRIME-P): a spokes-hub-spokes model of the Department of Mental Health of Lecce Local Health Trust P. Calò, S. Calò, F. De Luca, V. Perrone, L. Cavallo, G.M. Stasi, M.R. Grimaldi, S. De Giorgi Subjective experiences matter. What do we know about consciousness? B. Forti Role of the half-life in the development of substance addiction: focus on nicotine and benzodiazepine A. Morgillo, E. Marovino, S.C. Biader 17 Wernicke's encephalopathy in a young psychiatric patient with delirium: a diagnostic challenge G.M. Nicolino, S. Squarza, A. Grecchi	<i>Editorial</i> Vaccine hesitancy: is it a crazy stuff? B. Carpiniello	149
 A PRogram for detection, Intervention and Monitoring first-Episode Psychosis (PRIME-P): a spokes-hub-spokes model of the Department of Mental Health of Lecce Local Health Trust P. Calò, S. Calò, F. De Luca, V. Perrone, L. Cavallo, G.M. Stasi, M.R. Grimaldi, S. De Giorgi Subjective experiences matter. What do we know about consciousness? B. Forti Role of the half-life in the development of substance addiction: focus on nicotine and benzodiazepine A. Morgillo, E. Marovino, S.C. Biader Wernicke's encephalopathy in a young psychiatric patient with delirium: a diagnostic challenge G.M. Nicolino, S. Squarza, A. Grecchi Cabert study of psychiatric patient in Early District 	Original articles	
Subjective experiences matter.What do we know about consciousness?B. Forti15Role of the half-life in the development of substance addiction:focus on nicotine and benzodiazepineA. Morgillo, E. Marovino, S.C. Biader17Wernicke's encephalopathy in a young psychiatric patientwith delirium: a diagnostic challengeG.M. Nicolino, S. Squarza, A. Grecchi17	A PRogram for detection, Intervention and Monitoring first-Episode Psychosis (PRIME-P): a spokes-hub-spokes model of the Department of Mental Health of Lecce Local Health Trust P. Calò, S. Calò, F. De Luca, V. Perrone, L. Cavallo, G.M. Stasi, M.R. Grimaldi, S. De Giorgi	152
Role of the half-life in the development of substance addiction: focus on nicotine and benzodiazepine A. Morgillo, E. Marovino, S.C. Biader17Wernicke's encephalopathy in a young psychiatric patient with delirium: a diagnostic challenge G.M. Nicolino, S. Squarza, A. Grecchi17	Subjective experiences matter. What do we know about consciousness? B. Forti	158
Wernicke's encephalopathy in a young psychiatric patient with delirium: a diagnostic challenge G.M. Nicolino, S. Squarza, A. Grecchi 17	Role of the half-life in the development of substance addiction: focus on nicotine and benzodiazepine A. Morgillo, E. Marovino, S.C. Biader	170
Cohort study of povehistric nationts in Farl) District	Wernicke's encephalopathy in a young psychiatric patient with delirium: a diagnostic challenge G.M. Nicolino, S. Squarza, A. Grecchi	177
M. Pacetti, E. Monti, S. Sanchini	Cohort study of psychiatric patients in Forlì District M. Pacetti, E. Monti, S. Sanchini	179

Editors-in-Chief Enrico Zanalda Massimo di Giannantonio

Deputy Editors

Bernardo Carpiniello Giancarlo Cerveri Massimo Clerici Domenico De Berardis Guido Di Sciascio Paola Rocca Antonio Vita

International Scientific Board

Arango Celso, Madrid Fleischhacker Wolfgang, Innsbruck Fountoulakis Konstantinos N, Thessaloniki Grunze Heinz, Newcastle upon Tyne Leucht Stefan, Munchen Rihmer Zoltan, Budapest Jakovljevic Miro, Zagabria Gorwood Philip, Paris Demyttenaere Koen, Leuven Höschl Cyril, Praga Tiihonen Jari, Stockholm

Editorial coordinator and secretary

Lucia Castelli - Icastelli@pacinieditore.it Tel. +39 050 3130224 - Fax +39 050 3130300

© Copyright by Pacini Editore Srl - Pisa

Managing Editor

Patrizia Alma Pacini

Publisher

Pacini Editore Srl via Gherardesca1 - 56121 Pisa, Italy Tel. +39 050 313011 - Fax +39 050 313000 www.pacinimedicina.it

Journal registered at "Registro pubblico degli Operatori della Comunicazione" (Pacini Editore Srl registration n. 6269 - 29/8/2001)

ISSN 2421-4469 (online)

Digital Edition December 2021

Registration in progress at the Tribunal of Pisa

www.evidence-based-psychiatric-care.org

Evidence based Psychiatric Care

Journal of the Italian Society of Psychiatry

Editorial

Vaccine hesitancy: is it a crazy stuff?

Bernardo Carpiniello

Department of Medical Sciences and Public Health, University of Cagliari & Psychiatric Unit, University Hospital Agency, Cagliari, Italy; Past President SIP

Vaccine hesitancy is generally defined as a "behavioral pattern ranging from a delay in acceptance to a complete refusal of vaccine, in spite of vaccine availability" 1. According to the World Health Organization, it is one of the 10 greatest threats to public health ². Vaccine acceptance is variably represented in different Countries, with the lowest rates in Kuwait (23.6%), Jordan (28.4%), Italy (53.7), Russia (54.9%), Poland (56.3%), US (56.9%), and France (58.9%) 3. It is difficult to understand why such a relevant proportion of people is so reluctant to accept vaccination, taking into account the dramatic, individual and social consequences of the Pandemic and the fundamental role of vaccines for overcoming the infection. We acknowledge that the wide resistance toward vaccination cannot be seen per se as irrational or anti-scientific, reflecting sometimes legitimate concerns and/or doubts. However, we cannot ignore the important and very recent data from sociological research reporting that a wave of irrationality seems to be rising in our Country. This is what emerges from a series of beliefs shared by a relevant proportion of Italians such as the Earth is flat (5.8%), the man has never landed on the Moon (10%), the Covid does not exist (5.9%), the vaccines are useless and ineffective (10.9%), without also considering that 39.9% of Italians are embracing conspiracy beliefs ⁴. These data has led to wonder if (and to what extent) psychopathological determinants may explain such positions, with particular reference to vaccine hesitancy. The latter has been associated until now to a series of demographic and individual factors, including psychological ones ⁵, with a substantial gap of knowledge existing as regard to the association with psychopathology. Anyway, in spite of the relative paucity of papers published so far on this issue, findings from the available literature show a not negligible contribution of psychopathology to vaccine hesitancy.

The first source information regarding this issue is represented by studies on non-clinical samples, usually defined as community surveys, which are conducted on samples drawn from general population. Some of these studies show that unspecific anxiety and/or depressive symptoms seem to be unrelated to vaccine acceptation/hesitancy 6, while other studies report that anxiety/depression symptoms are related to both a higher propensity for vaccination 7 and to a higher vaccine hesitancy 8,9, in particular among women 8. These contradictory findings may be interpreted in light of other psychological factors mediating the behavioural response to emotional arousal, as we will see later. Other studies seem to indicate that vaccine hesitancy or acceptance may be related not so much to the anxiety dimension in general, but rather to specific types of anxiety. Indeed, fears of infection seem to be associated with vaccine acceptation while fears of social/economic consequences of the pandemics are more related to vaccine hesitancy ⁶. Phobic anxiety, in terms of blood-injection-injury fears ¹⁰, is of particular interest, not only for its frequency (approx 10% of the sample studied) but also for being a potentially surmountable barrier to vaccination. On the whole, data from studies on community samples indicate that the higher the scores at anxiety/depression are, the higher the propensity both for vaccine hesitancy and acceptance will be, depending on the nature of anxiety,





Bernardo Carpiniello

How to cite this article:

Carpiniello B. Vaccine hesitancy: is it a crazy stuff? Evidence-based Psychiatric Care 2021;7:149-151. https://doi. org/10.36180/2421-4469-2021-23

Correspondence:

Bernardo Carpiniello bcarpini@iol.it

This is an open access article distributed in accordance with the CC-BY-NC-ND (Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International) license. The article can be used by giving appropriate credit and mentioning the license, but only for non-commercial purposes and only in the original version. For further information: https:// creativecommons.org/licenses/by-nc-nd/4.0/deed.en

Open Access

© Copyright by Pacini Editore Srl

the concomitant presence of other related affects such as anger or depression and the mediating role of personality traits, generally considered as pathologic. However, in interpreting data emerging form non-clinical samples we should take into account the limitation constituted by the self-assessed evaluation of anxiety/depression according to the dimensional approach generally adopted in these studies, which may not be capable of discriminating between a clinically significant anxiety/depressive state and a unspecific condition of distress.

As mentioned above, studies on non-clinical samples have also highlighted a series of pathologic personality traits which emerge as significant factors associated to vaccine hesitancy/acceptance, such as the tendency to conspiratorial and paranoid beliefs, the impulsivity in thinking style, and the emotional instability ^{3,11,12}. Conspiratorial beliefs emerge as of particular importance, in light of their correlation with psychopatology. Indeed, the US National Comorbidity Survey-Replication (NCS-R), where conspiracy attitudes were analysed in a community sample of 5,645 people, 1,618 of these (26.7%) endorsed a conspirational belief. Individuals endorsing this belief had lower levels of physical and psychological well-being, higher levels of suicidal ideation, weaker social networks, less secure attachment style, difficult childhood family experiences, and, above all, were more likely to meet criteria for a psychiatric disorder, with the conspiracy belief highly associated (odds ratio = 7.81) with paranoid beliefs ¹³. Paranoia has been repeateldy related to cospiracy beliefs ^{14,15}. Several studies show as conspiratorial ideation may be also induced by a series of reasoning biases influencing individuals' likelihood of adopting epistemically-suspect alternatives to official versions of the facts, thus fostering paranoid thinking styles and distrust of the official sources of information, including scientists ¹⁶. Other authors have shown as bias toward reduced data gathering during reasoning may cause paranoia, increasing the perceived dangerousness of vaccines and thereby reducing willingness to vaccinate 17. The seemingly contradictory data regarding the role of anxiety in vaccine acceptance/ hesitancy has been explained by other authors calling into question the mediating role of personality traits: indeed, fears of death and emotional distress related to the current pandemic has been shown related in a very complex way to paranoia, conspiracy theories, mistrust in science, and consequently to the propensity to accept or not vaccines 12.

The second source of information is constituted by studies on clinical samples. The majority of these studies were conducted in western countries and fundamentally indicate that vaccine hesitancy among people affected by mental disorders is as frequent as in the respective general population or even lower ¹⁸⁻²¹, although a study found that a specific disorders, namely Substance Use Disorder, is associated with higher vaccine hesitancy ²² and another study found a higher hesitancy respect to influenza vaccination among psychiatric patients ²³. Vaccine

150

hesitancy seems to be related more to individual factors, which are substantially common to those of the population without mental disorders, than to the presence of psychopathology per se. In particular, the largest western study regarding psychiatric samples, conducted in USA, demonstrates that the higher prevalence of vaccine hesitancy which was found among patients with psychiatric disorders, was completely attenuated or disappeared when regression models of data analysis were applied, except than among subjects affected by substance use disorders and tobacco use, suggesting that the higher prevalence observed across conditions may be mostly related to the distribution of some socio-demographic characteristics associated to vaccine hesitancy ²². Another limit of the above mentioned studies is that all western studies don't include people affected by psychotic disorders. The only exception is constituted by a study from Israel, which considered an in-patient sample of subjects with severe mental illnesses ²¹. On the contrary, other studies, mainly conducted in eastern countries, report a higher rate of vaccine hesitancy, generally associated with low rates of vaccination, among psychiatric patients respect to general population ²⁴⁻²⁶. Two of these studies, both conducted in China, examined specifically patients with severe mental disorders, including schizophrenia ^{25,26}. Vaccine hesitancy seems to be substantially independent from diagnosis both in western and eastern studies ^{21,24,25}. However we should consider that one of these studies ²⁵ included specifically only severe mental illnesses (Major depression, Bipolar Disorders, Schizophrenia). Another large study found a vaccine uptake (i.e. the number of patients vaccinated) significantly lower among inpatients and patients with psychotic disorders; the latter were considered as less likely to take the vaccine due to their more frequent impairment of decisional capacity, whilst a lower vaccine acceptance (i.e. acceptance to be vaccinated) was found associated with having a lower insight, a factor considered as linked to a lower awareness of health-related needs ²⁶. In summary, data from studies on non-clinical samples indicate that affective psychopathology may have a role in contributing both to vaccine hesitancy and acceptance, partly in conjunction with pathological personality traits such as paranoia, which have seemingly a mediation role. Studies on clinical samples prevalently show that psychopathology linked to common mental disorders does not influence per se the attitudes toward vaccination, with the only exception of Substance Use Disorder and Phobias regarding injections, both associated to a higher vaccine hesitancy. On the contrary, a prevalent although not univocal association between severe mental disorders and vaccine hesitancy emerges from a limited number of studies published up to date. This means that further studies, possibly from different countries and regarding larger clinical samples with both in and outpatients, are needed to confirm this association. Unfortunately, no studies have been published so far regarding clinical samples of subjects affected by Personality Disorders. This represents

another significant gap in our knowledge of the relationship between psychopathology and vaccine hesitancy, considering the important role of pathological personality traits emerging from studies on non-clinical samples.

References

- ¹ Kumar D, Chandra R, Mathur M, et al. Vaccine hesitancy: understanding better to address better. Isr J Health Policy Res 2016;5:2. https://doi.org/10.1186/s13584-016-0062-y. eCollection 2016
- ² World Health Organization (WHO). Ten threats to public health in 2019. Available online: https://www.who.int/newsroom/spotlight/ten-threats-to-global-health-in-2019)
- ³ Sallam M. COVID-19 vaccine hesitancy worldwide: a concise systematic review of vaccine acceptance rates. Vaccines (Basel) 2021;9:160. https://doi.org/10.3390/vaccines9020160.
- ⁴ Censis. 55º Rapporto sulla situazione sociale del Paese. Milano: Franco Angeli 2021.
- ⁵ Joshi A, Kaur M, Kaur R, et al. Predictors of COVID-19 vaccine acceptance, intention, and hesitancy: a scoping review. Front Public Health 2021;9:698111. https://doi.org/10.3389/ fpubh.2021.698111
- ⁶ Bendau A, Moritz JP, Petzold B, et al. COVID-19 vaccine hesitancy and related fears and anxiety. Int Immunopharmacol 2021;97:107724. https://doi.org/10.1016/j.intimp.2021.107724
- ⁷ Murphy J, Vallières F, Bentall RP, et al. Psychological characteristics associated with COVID-19 vaccine hesitancy and resistance in Ireland and the United Kingdom. Nat Commun 2021;12:29. https://doi.org/10.1038/s41467-020-20226-9
- ⁸ Nguyen KH, Chen S, Morris K, et al. Mental health symptoms and association with COVID-19 vaccination receipt and intention to vaccinate among adults, United States. Prev Med 2022;154:106905. https://doi.org/10.1016/j. ypmed.2021.106905
- ⁹ Nazlı ŞB, Yığman F, Sevindik M, et al. Psychological factors affecting COVID-19 vaccine hesitancy. Ir J Med Sci 2021;14:1-10. https://doi.org/10.1007/s11845-021-02640-0
- ¹⁰ Freeman D, Lambe S, Yu LM, et al. Injection fears and CO-VID-19 vaccine hesitancy. Psychol Med 2021;11:1-11. https:// doi.org/10.1017/S0033291721002609
- ¹¹ Zhang X, Guo Y, Zhou Q, et al. The mediating roles of medical mistrust, knowledge, confidence and complacency of vaccines in the pathways from conspiracy beliefs to vaccine hesitancy. Vaccines (Basel) 2021;9:1342. https://doi.org/10.3390/ vaccines9111342
- ¹² Simione L, Vagni M, Gnagnarella C, et al. Mistrust and beliefs in conspiracy theories differently mediate the effects of psychological factors on propensity for COVID-19 vaccine. Front Psychol 2021;7:12:683684. https://doi.org/10.3389/ fpsyg.2021.683684
- ¹³ Freeman D, Bentall RP. The concomitants of conspiracy concerns. Soc Psychiatry Psychiatr Epidemiol 2017;52:595-604. https://doi.org/10.1007/s00127-017-1354-4
- ¹⁴ Darwin H, Neave N, Holmes J. Belief in conspiracy theories.

The role of paranormal belief, paranoid ideation and schizotypy. Personality Individ Differ 2011;50:1289-93. https://doi. org/10.1016/j.paid.2011.02.027

- ¹⁵ Freeman D, Waite F, Rosebrock L, et al. Coronavirus conspiracy beliefs, mistrust, and compliance with government guidelines in England. Psychol Med 2020;1-13. https://doi. org/10.1017/S0033291720001890
- ¹⁶ Pierre JM. Mistrust and misinformation: a two-component, socio-epistemic model of belief in conspiracy theories. J Social Polit Psychol 2020;8:617-641. https://doi.org/10.5964/ jspp.v8i2.1362
- ¹⁷ Bronstein MV, Kummerfeld E, MacDonald A, et al. Willingness to vaccinate against SARS-CoV-2: the role of reasoning biases and conspiracist ideation. Vaccine (Basel) 2021;S0264-410X(21)01553-X. https://doi.org/10.1016/j.vaccine.2021.11.079
- ¹⁸ Maguire PA, Reay RE, Looi JC. Nothing to sneeze at uptake of protective measures against an influenza pandemic by people with schizophrenia: willingness and perceived barriers. Australas Psychiatry 2019;27:171-178. https://doi. org/10.1177/1039856218815748
- ¹⁹ Miles LW, Williams N, Luthy KE, et al. Adult vaccination rates in the mentally ill population: an outpatient improvement project. J Am Psychiatr Nurses Assoc 2020;26:172-180. https:// doi.org/10.1177/1078390319831763
- ²⁰ Jefsen OH, Kølbæk P, Gil Y, et al. COVID-19 vaccine willingness amongst patients with mental illness compared with the general population. Acta Neuropsychiatr 2021;33:273-276. https://doi.org/10.1017/neu.2021.15
- ²¹ Danenberg R, Shemesh S, Tzur Bitan D, et al. Attitudes of patients with severe mental illness towards COVID-19 vaccinations: a preliminary report from a public psychiatric hospital. J Psychiatr Res 2021;143:16-20. https://doi.org/10.1016/j. jpsychires.2021.08.020
- ²² Eyllon M, Dang AP, Barnes JB, et al. Associations between psychiatric morbidity and COVID-19 vaccine hesitancy: an analysis of electronic health records and patient. Psychiatry Res 2022;307:114329. https://doi.org/10.1016/j.psychres.2021.114329
- ²³ Lorenz RA, Norris MM, Norton LC, et al. Factors associated with influenza vaccination decisions among patients with mental illness. Int J Psychiatry Med 2013;46:1-13. https://doi. org/10.2190/PM.46.1.a
- ²⁴ Uvais NA. COVID-19 vaccine hesitancy among patients with psychiatric disorders. Prim Care Companion CNS Disord 2021;23:21br03028. https://doi.org/10.4088/PCC.21br03028
- ²⁵ Bai W, Cai H, Jin Y, et al. COVID-19 vaccine hesitancy in community-dwelling and hospitalized patients with severe mental illness. Psychol Med 2021;17:1-6. https://doi.org/10.1017/ S0033291721004918
- ²⁶ Huang H, Zhu X-M, Liang P-W, et al. COVID-19 vaccine uptake, acceptance, and hesitancy among persons with mental disorders during the second stage of China's nationwide vaccine rollout. Front Med 2021;8:761601. https://doi. org/10.3389/fmed.2021.761601





Paola Calò

How to cite this article: Calò P, Calò S, De Luca F, et al. A PRogram for detection, Intervention and Monitoring first-Episode Psychosis (PRIME-P): a spokes-hub-spokes model of the Department of Mental Health of Lecce Local Health Trust. Evidence-based Psychiatric Care 2021;7:152-157. https:// doi.org/10.36180/2421-4469-2021-24

Correspondence:

Paola Calò paolacalo1911@gmail.com

Conflict of interest The Authors declare no conflict of interest.

This is an open access article distributed in accordance with the CC-BY-NC-ND (Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International) license. The article can be used by giving appropriate credit and mentioning the license, but only for non-commercial purposes and only in the original version. For further information: https:// creativecommons.org/licenses/by-nc-nd/4.0/deed.en



© Copyright by Pacini Editore Srl

Original article

A PRogram for detection, Intervention and Monitoring first-Episode Psychosis (PRIME-P): a spokes-hub-spokes model of the Department of Mental Health of Lecce Local Health Trust

Paola Calò¹, Salvatore Calò², Francesca De Luca³, Valentina Perrone³, Lucrezia Cavallo⁴, Giulia M. Stasi³, Maria Rosaria Grimaldi⁵, Serafino De Giorgi⁶

¹ NHS, Psychiatrist, Department of Mental Health, Community Mental Health Center, Campi Salentina, Lecce, Italy; ² NHS, Psychiatrist, Department of Mental Health ASL Lecce, Psychiatric Service for Diagnosis and Treatment, Hospital "V. Fazzi", Lecce, Italy; ³ NHS, Psychiatric Rehabilitation Technician, Department of Mental Health ASL Lecce, Community Mental Health Center, Campi Salentina, Lecce, Italy; ⁴ NHS, Psychologist, Department of Mental Health ASL Lecce, Prison Mental Health Service, Lecce, Italy; ⁵ NHS, Psychiatrist, Department of Mental Health ASL Lecce, Psychiatric Service for Diagnosis and Treatment, Hospital "Ferrari", Casarano, Lecce, Italy; ⁶ NHS, Psychiatrist, Director of Department of Mental Health, Lecce, Italy

Summary

Data show how it is essential, in prognostic terms, to set up adequate treatment for the psychosis onset. Several studies highlight that a longer duration of untreated psychosis (DUP) is associated with worse clinical and functional outcomes. In the last years, early intervention services have been implemented in various countries, also endorsed in Italy by the publication of national guidelines in 2007, and delivered through Community Mental Health Centers. In line with these recommendations, the Department of Mental Health (DMH) of Lecce, Italy, developed a program for detection, intervention and monitoring of first-episode psychosis (PRIME-P). The program is formed of two subprograms based on the service involved at the patient's first access, that is through the outpatient unit (otherwise referred to as Group SPRINT) or through the inpatient unit (otherwise referred to as Group STARTER). The guality of treatment for the first psychotic episode is guaranteed by continuous and structured training of the DMH staff and a shared pathway to care. The data collected in the first two years of the program (via both Groups SPRINT and STARTER - GSS, for a total of 137 subjects) were compared with a two-year retrospective sample, with similar characteristics, detected in the years 2011-2012 (Group AREP - GAREP, for a total of 95 subjects). Despite the homogeneity of the two groups in terms of main socio-demographic characteristics (sex, age, education, working condition), the results of our study show a significant reduction in the GSS group (22.63%; p = 0.011) in diagnoses of Psychotic Disorder not Otherwise Specified, when compared to the GAREP group (38.95%). In the GSS group we found a significantly lower DUP (GSS vs GAREP, 3.03 ± 2.98 vs 7, 83 ± 3.46). Although preliminary, those data show how continuous and structured training interventions can improve care practices, in terms of diagnostic adequacy as well as better ability to treat early psychosis.

Key words: early intervention services, first-episode psychosis, public mental health, spokes-hub-spokes model

Background

The diagnosis and treatment of psychotic disorders are complex processes, often conditioned not only by clinical or environmental aspects and their interrelation, but also by the activities that psychiatric services are able to provide ¹. A large number of recent studies highlights the decisive role of extra-clinical variables, connected to the timing and methods of the offer/use of services in relation to care needs, to the management and therefore to the outcome of the disorder ². The most relevant data show that in the great majority of cases, psychotic disorders come to treatment late in both instances of appearance of the first non-specific symptoms (Duration of Untreated Illness - DUI), and of full-blown psychotic onset (Duration of Untreated Psychosis - DUP), when symptoms are already evident and stabilized ^{3,4}.

Some authors, analyzing the clinical trend and the functional relapses of the disorder, have described as *critical period*, the period of time that goes from the appearance of the first symptoms to the following 2-5 years ⁵. After this period, the possibility that the interventions can lead to recovery, in terms of personal and social functioning, appears to be progressively reduced ⁶.

Therefore, the need for early interventions aimed at reducing the DUP appears crucial ^{7,8}.

In light of this evidence, several specific programs for patients with a first-episode psychosis (FEP) have been activated over the last 30 years, initially in Australia and subsequently in the United Kingdom, Europe and North America ^{6,9}.

Initially born as intervention models to facilitate the identification and care of young subjects with psychotic onset, over time they have generated a series of practices, with various degrees of structure, which can be grouped into three categories ^{10,11}.

The first category, mainly present in the United Kingdom, United States, Australia, New Zealand and Scandinavia, concerns specific early intervention services (EIS), with a specialized team distinct from the one present in services aimed at adults ¹².

This type offers indubitable advantages in psychiatric care, also in terms of reduction of disengagement from treatment, but it requires considerable resources; at the same time it may determine problems in the transition of patients towards generalist services ^{13,14}.

The second category provides for a central specialized service (hub) that supports generalist centers (hub-and-spoke model) ¹⁵.

The third category refers to the generalist services' adoption of the principles of recognition, taking charge and early treatment of subjects suffering from psychosis through team training ^{10,11}. Less costly in terms of investment of resources ¹⁶, this category may, however, be less suitable for FEP patients who need adequate supervision and more specific treatments ^{11,17}.

In 2007 the Italian National Institute of Health (Istituto

Superiore di Sanità, ISS) 13, that is the Scientific and Technical Body of the National Health Service that develops and promotes health interventions on the national territory, issued a paper on recommendations of early interventions in schizophrenia, to be provided through generalist services. like community-based mental health centers (CMHCs) ¹³, further updated in 2009. Although those guidelines recommend socio-health policies that guarantee a more consistent and homogeneous financial support in the Regional Health Services, to launch those programs, the lack of dedicated budgets and psychiatry specialists often puts the generalist services in the impossibility of running these initiatives. In 2013 the National Plan for Action in Mental Health (Ministry of Health, 2013) listed early interventions for psychosis as a priority target 18.

In an attempt to ensure an early treatment for young patients with psychotic disorders in an iso-resource condition, in 2012 the Department of Mental Health (DMH) of Lecce Local Health Trust (LHT) decided to implement a circular model defined Spokes-Hub-Spokes Model, aimed at improving the treatment delivered by outpatient (CMHCs; CePsIA: Centro di Psichiatria e psicoterapia per l'Infanzia e l'Adolescenza, an outpatient stand-alone centre for psychiatric and psychological disorder in childhood and adolescence; Child Neuropsychiatry Services, CNPs) and inpatient (General Hospital Psychiatric Wards - GHPWs) services (the spokes) through specific training, research and provision of dedicated interventions, supported by the Training and Research Center (Centro Formazione e Ricerca, CFR) of the DMH (the hub).

The aim of the CFR was not only to transfer information based on top-down approach, but also to elaborate interpretative models and design concrete solutions starting from the evaluation of problems emerging during the programmatic meetings with the teams of generalist centers' (spokes') teams based on a bottom-up approach. This model is the basis of the Program of Detection, Intervention and Monitoring for First-Episode Psychosis (PRIME-P).

In this report we will present the results of this first four years of the program.

Materials and methods

The Department of Mental Health of Lecce Local Health Trust (LHT)

The DMH of Lecce Local Health Trust (LHT) consist of a management direction, some staff services including the Training and Research Center (CFR), ten CMHCs, four CNPs, a centre for youth (CePsIA), four General Hospital Psychiatric Wards (GHPWs), an Eating Disorder Unit, a Prison Mental Health Unit. Lecce DMH covers a catchment area of 2,759 km² for a population of 800,000 inhabitants.

PRIME-P of Lecce DMH: resources and costs

The PRIME-P provides for the continuous commitment of the staff of the CFR team through regular meetings with the psychiatric services teams (CMHCs, GHPWs CNPs and CePsIA), doctors, psychologists, nurses, psychiatric rehabilitation technicians and social workers, which are set to take place on a quarterly basis. The frequency of meetings could vary according to the needs of the services.

The PRIME-P doesn't require additional resources, except for the budget already foreseen for the training of the teams and research. The package of care for FEP provided by CMHCs and other outpatients services includes pharmacological treatment, psychoeducation and cognitivebehavioral psychotherapy, family psychoeducation and support, social-skill training, cognitive remediation, vocational rehabilitation or supported education.

In 2012, the first step was to carry out a retrospective analysis of the interventions performed for patients with FEP who came into contact for the first time with the DMH services, in the previous two years (Analisi Retrospettiva Esordi Psicotici - AREP: First-Episode Psychosis Retrospective Analysis), with the view to assess the state of the art and related critical issues¹⁹.

After the 2013 analysis of those data, 2 subprograms for patients with FEP were launched, differentiated on the basis of the type of service (outpatient *vs* inpatient service) that accepted such patients for the first time. Those subprograms, although characterized by different steps that reflect the different specificities of the involved agencies, are inspired by the recommendations provided by the ISS about FEP ¹³.

The PRIME-P was approved by the Ethics Committee and by the General Management of the Lecce LHT, with Resolution No. 150 of 28 January 2019.

The SPRINT and STARTER programs

The 2 subprograms were identified with the acronyms of SPRINT (Schizofrenia Primo episodio e Riabilitazione Intensiva Nel Territorio: FEP and Intensive Outpatient Rehabilitation), and STARTER (SPDC nel Trattamento dell'Acuzie e invio alla Rete Territoriale degli EsoRdi: GHPWs in the Treatment of Urgency and patient's engagement by outpatient services). Started at the DMH of Lecce LHT in 2013 and still in course, their outcomes include:

- 1. optimize the detection and early psychiatric care of patients with FEP;
- 2. reduce the variability between clinicians in initial assessment and patient treatment;
- 3. provide more appropriate and evidence-based interventions even in a public generalist service;
- 4. monitor the effectiveness of the interventions delivered through a periodic follow-up, with psychiatric evaluations and periodic reviews of drug therapy for at least 5 years after the inclusion in the program (at 6, 12, 24,

36, 48, 60 months, or up to interruption/termination of treatment);

5. reduce the disengagement rate through the achievement of the first two points and the implementation of the continuous training of the teams involved.

The inclusion criteria for early intervention program are: a) patient with psychotic symptoms (delusions, hallucinations, disorganized thinking and disorganized behavior); b) age \leq 35 years; c) first contact with the psychiatric services of the Lecce DMH; d) onset of psychotic symptoms \leq 5 years; d) resident in Lecce Province. The exclusion criteria are represented by: a) organic mental disorder; b) medication-induced psychotic disorder or psychotic disorder due to general medical condition; c) moderate to severe intellectual disability.

In order to standardize and easily retrieve the information, every referral team collects data, since 2013, using the same computerized form (Scheda Unica per gli Esordi, SUE), which contains demographic, clinical and treatment data, and the results of administered rating scales, about clinical and psychosocial features.

Patients and family members give an informed consent for the use of the data for research purposes.

Comparison between ARES and the SPRINT and STARTER programs

In order to assess the ability of the PRIME-P to reach the outcome, data from 2-year retrospective analysis (AREP Group: GAREP) were compared with new cases included in the first two years of the program (SPRINT and STARTER Group - GSS, Fig. 1).

In the first group (GAREP), formed by 120 subjects surveyed by 2-year retrospective analysis, only 95 subjects met the inclusion and exclusion criteria.

From 2013 to 2015, 151 new cases were included in the SPRINT and STARTER sub-programs (GSS), and 137 subjects met the inclusion and exclusion criteria.

Statistical analysis

The two groups (GSS vs GAREP) were preliminarily compared on the basis of the socio-demographic characteristics detected at the baseline (age, sex, education level, type of occupation) using the χ^2 (non-parametric test) for the nominal variables (age, sex, marital status, occupation) and for the continuous variables (age) one-way ANOVA.

In order to evaluate the effectiveness of the PRIME-P model in terms of diagnostic accuracy, the two groups (GSS vs GAREP) were compared with respect to the diagnoses, according to the criteria of DSM-5: Schizophrenia spectrum disorders, Bipolar spectrum disorders. A third optional category was identified for subjects whose clinical characteristics can't be classified according a specific diagnostic category (Psychotic Disorder not Otherwise Specified). The comparison was made by χ^2 using the Yates correction.



Figure 1. PRIME-P Lecce DMH.

The two groups were compared with respect to the duration of untreated disease (DUP) by one-way ANOVA and the presence in comorbid use of substances (cannabis, cocaine, heroin, amphetamine) and/or alcohol (χ^2 by Yates correction).

The appropriacy of interventions was also assessed analyzing the prescribing characteristics in both groups. Specifically, the use of first (FGAs) and second generation (SGAs) antipsychotics both in mono and in polytherapy (combination with drugs of other classes) was evaluated; the use of long-acting antipsychotics (AP LAI); the use of other classes of drugs (antidepressants, mood stabilizers, benzodiazepines). Differences between the two study groups (GSS vs GAREP) were evaluated χ^2 using the Yates correction.

Statistical analysis was conducted with Stat software.

Results

The analysis of the socio-demographic characteristics showed a lower average age, although not statistically

significant, in the subjects of GSS group compared to GAREP group (23.50 \pm 3.96 vs 24.42 \pm 3.90). In both groups, most of the subjects were male; in GSS group this variable constituted 74.45% of the sample (M = 102), while in GAREP group 62.10% of sample (M = 59). The percentage of subjects who presented a stable relationship (marriage cohabitation) was around 10% both in the GSS group (8.76%) and in the GAREP group (12.63%), with no statistically significant differences (0.462). There were no differences in activity/study levels between the two groups (Tab. I). The assessment of familiarity for mental disorders (also considering first degree relatives) did not show statistically significant differences between the two groups (GSS = 49; GAREP = 39) (Tab. I).

The evaluation of the diagnoses highlighted a statistically significant equivalence between GSS and GAREP for both non-affective (61.32 vs 48.42%) and affective psychotic disorders (16.05 vs 12.63%). In GSS group (22.63%) we found a significant reduction (p = 0.011) in the diagnosis of Psychotic Disorder not Otherwise Specified, compared to the GAREP group (38.95%) (Tab. II).

Table I. Socio-demographic characteristics in the two study groups at baseline (GSS vs GAREP).

Socio-demographic vari	able	GSS (137)	GAREP (95)	P ª
Age (mean ± SD)		23.50 ± 3.96	24.42 ± 3.90	0.083
Gender, M/F, n (%)		102/35 (74.45/25.55)	59/36 (62.10/37.90)	0.062
Marital atatua	Single	125 (91.24)	83 (87.37)	0.462
Marilar Status	Married/cohabiting	12 (8.76)	12 (12.63)	0.403
	Student	31 (22.63)	29 (30.52)	0.230
Activity/study	Employed	22 (16.06)	12 (12.63)	0.591
	Unemployed	84 (61.31)	54 (56.85)	0.584
Family history of mental	disorders	49 (35.76)	39 (41.05)	0.497
a: χ^2 by Yates correction.				

Table II. Clinical characteristics of the two study groups (GSS vs GAREP).

Clinical variable	GSS (137)	GAREP (95)	P ^{a,b}
Diagnosis			
Schizophrenia spectrum disorder, n (%)	84 (61.32)	46 (48.42)	0.070 ª
Bipolar spectrum disorders, n (%)	22 (16.05)	12 (12.63)	0.591 ª
Diagnosis of Psychotic Disorder not Otherwise Specified, n (%)	31 (22.63)	37 (38.95)	0.011 ª
DUP, medium (SD)	3.03 (2.98)	7.83 (3.46)	0.001 ^b
Substance/Alcohol use, n (%)	71 (51.82)	61 (64.21)	0.082 ª
^a : χ ² by Yates correction; ^b : one-way ANOVA.			

Table III. Comparison of drug treatment in the two groups.

	GSS (137)	GAREP (95)	P ª
Psychopharmacological treatment, n (%)	134 (97.81)	92 (96.80)	0.971
Antipsychotic treatment, n (%)	128 (95.52)	85 (92.40)	0.482
Antipsychotics in monotherapy, n (%)	70 (52.23)	34 (36.95)	0.050
FGAs/SGAs in monotherapy, n (%)	11/59 (15.71/84.29%)	21/13 (61.76/38.24%)	0.001
Antidepressants, n (%)	20 (14.93)	35 (38.04)	0.001
Mood stabilizers, n (%)	47 (35.07)	30 (32.60)	0.809
^a : χ ² by Yates correction.			

Duration of Untreated Psychosis (DUP) was significantly lower in GSS group (3.03 \pm 2.98) than in GAREP group (7.83 \pm 3.46) (Tab. II).

In both groups, more than 50% of subjects had comorbid use of alcohol and/or substances, with higher percentage values in GAREP group (64.21%) than in GSS group (51.82%), although not statistically significant (p = 0.082) (Tab. II).

In both groups, almost all of the sample received a prescription of a psychopharmacological treatment (GSS vs GAREP; 97.81 vs 96.80%), mostly antipsychotic drugs (95.52 vs 92.40%), without statistically significant differences between the two groups (p < 0.05) (Tab. III). Significantly (p = 0.050) higher use of antipsychotics in monotherapy (52.23%) was found in GSS group than in GAREP group (36.95%), with a significant inversion, over time, in the ratio between first generation and second generation drugs (FGAs/SGAs) (15.71/84.29 vs 61.76/38.24%) (Tab. III).

The treatment with antidepressants was significantly lower in GSS group (14.93%) than in GAREP group (38.04%). There were no statistically significant differences in the use of mood stabilizers (35.07 *vs* 32.60%) (Tab. III).

Conclusions

This study establishes the feasibility and opportunity of early intervention programs in terms of greater ability to detect patients with FEP, compared to generalist interventions, with a lower average age and a significantly lower DUP in the sample recruited during the PRIME-P program (3.03 ± 2.98) compared to the 2-year retrospective sample (AREP: 7.83 ± 3.46). In our experience, this better detection capacity was associated to a more appropriate diagnosis; we found a significant reduction in diagnoses of Psychotic Disorder not Otherwise Specified in PRIME-P program (22,63% of the sample) compared to AREP (38.95% of the sample). This finding is related to a greater appropriacy of therapeutic interventions, such as an increase in monotherapy antipsychotic treatment, in particular with second generation drugs. The homogeneity of the sample of two groups, with respect to sociodemographic characteristics at the baseline, contributes to corroborate those initial findings, without excessive confounding factors.

Other emerging features of the sample, resulting from a comprehensive clinical, cognitive and functional assessment, or data related to treatment adherence, are not reported in this report, as they are not available for the retrospective group (GAREP); this call for a further analysis.

The shortage of collected assessment, as well as the lack of an adequate follow-up in the retrospective group (GAREP) did not allow to verify the impact of the PRIME-P in terms of reduction of the patients who dropped out from services, thus making its evaluation partial.

Despite those limitations, our report demonstrates how the investment in widespread training of operators through structured programs for early psychosis, like other interventions that involve the implementation of specialized teams, lead to a significant improvement in diagnostic-therapeutic pathways to care in public settings, with few or no additional resources.

The PRIME-P is successful and until today we have more than 400 new patients accepting the treatment,



Figure 2. A campaign against stigma in mental health, Lecce, Italy #IamStigmaFreeLecce.

also thanks to social media, campaigns against stigma (Fig. 2), education activity for student and citizens, started to advertise about the existence of a free program of early intervention in CMHCs and outpatient services of Lecce area ²⁰.

References

- ¹ Jablensky A, Sartorius N, Ernberg G, et al. Schizophrenia: manifestations, incidence and course in different cultures: a World Health Organization ten-country study. Psychol Med Monogr Suppl 1992;20:1-97.
- ² Fusar-Poli P, Bonoldi I, Yung AR, et al. Predicting psychosis meta-analysis of transition outcomes in individuals at high clinical risk. Arch Gen Psychiatry 2012;69:220-229.
- ³ Marshall M, Lockwood A. Early intervention for Psychosis. Cochrane Database Syst Rev 2004;(2):CD004718
- ⁴ Baldwin P, Browne D, Scully PJ, et al. Epidemiology of first-episode psychosis: illustrating the challenges across diagnostic boundaries through the cavan - Monaghan Study at 8 years. Schizoph Bull 2005;31:624-638.
- ⁵ Birchwood M, Todd P, Jackson C. Early intervention in psychosis. The critical period hypothesis. Br J Psychiatry Suppl 1998;172:53-59.
- ⁶ Cassidy CM, Norman R, Manchanda R, et al. Testing definitions of symptom remission in first-episode psychosis for prediction of functional outcome at 2 years. Schizophr Bull 2010;36:1001-1008.

- ⁷ McGorry PD, Killackey E, Yung AR. Early intervention in psychosis: concepts, evidence and future directions. World Psychiatry 2008;7:148-156.
- ⁸ Zhang C, Wang Q, Ni P, et al. Differential cortical gray matter deficits in adolescent- and adult-onset first-episode treatmentnaïve patients with schizophrenia. Sci Rep 2017;7:10267.
- ⁹ Drake RJ, Haley CJ, Akhtar S, et al. Causes and consequences of duration of untreated psychosis in schizophrenia. Br J Psychiatry 2000;177:511-515.
- ¹⁰ Dixon LB, Lieberman J. Early psychosis intervention services: a work in progress. Schizophr Bull 2015;41:23-24.
- ¹¹ Singh SP, Fisher HL. Early intervention in psychosis: obstacles and opportunities. Adv Psychiatr Treat 2005;11:71-78.
- ¹² Ruggeri M, Bonetto C, Lasalvia A, et al. GET UP Group. feasibility and effectiveness of a multi-element psychosocial intervention for first-episode psychosis: results from the cluster-randomized controlled GET UP PIANO trial in a catchment area of 10 million inhabitants. Schizophr Bull 2015;41:1192-1203.
- ¹³ De Masi S, Sampaolo L, Mele A, et al. The Italian Guidelines for Early Intervention in Schizophrenia: development and conclusions. Early Intervention in Psychiatry 2008;2(4).
- ¹⁴ Pelosi A. Is early intervention in the major psychiatric disorders justified? BMJ 2008;337:a710.
- ¹⁵ Castle DJ. Should early psychosis intervention be the focus for mental health services? Adv Psychiatr Treat 2011;17:398-400.
- ¹⁶ Whitwell D. Service innovations: early intervention in psychosis as a core task for general psychiatry. Psychiatr Bull 2001;25:146-148.
- ¹⁷ Craig T. A step too soon or a step too far? Early intervention in psychosis. J Mental Health 2003;12:335-339.
- ¹⁸ Ministero della Salute. Piano di Azioni Nazionale per la Salute Mentale. Rome: Atti della Conferenza Unificata del 24 Gennaio 2013.
- ¹⁹ Calò P, Grimaldi MR, De Giorgi S. Appropriatezza prescrittiva e riabilitazione precoce negli esordi psicotici: analisi di un campione di un Dipartimento di Salute Mentale. Abstract Book 11Th World Congress WAPR Milano, Interventi precoci: esperienze italiane 4184, p. 121. https://diazilla.com/ doc/490916/11th-world-congress
- ²⁰ Grimaldi MR, Calò P, Calò S, et al. Intervento precoce negli esordi psicotici: l'esperienza del Dipartimento di Salute Mentale di Lecce. Abstract Book V Congresso Nazionale AIPP, Associazione Italiana Interventi Precoci nelle Psicosi, 2014, p. 92. http://www.aipp-italia.com/wp-content/ uploads/2014/10/file-definitivo-abstract-book.pdf
- ²¹ https://studylibit.com/doc/5831855/atti-di-salerno-2014





Bruno Forti

How to cite this article: Forti B.

Subjective experiences matter. What do we know about consciousness? Evidence-based Psychiatric Care 2021;7:158-169. https://doi. org/10.36180/2421-4469-2021-25

Correspondence:

Bruno Forti bruno.forti@aulss1.veneto.it/ brunoforti4@gmail.com

Conflict of interest The Author declares no conflict of interest.

This is an open access article distributed in accordance with the CC-BY-NC-ND (Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International) license. The article can be used by giving appropriate credit and mentioning the license, but only for non-commercial purposes and only in the original version. For further information: https:// creativecommons.org/licenses/by-nc-nd/4.0/deed.en



© Copyright by Pacini Editore Srl

Original article

Subjective experiences matter. What do we know about consciousness?

Bruno Forti

Dipartimento di Salute Mentale, Azienda ULSS n. 1 Dolomiti, Regione del Veneto

Summary

Consciousness is one of the most difficult and enigmatic problems in the science of the mind. For more than three decades, it has been the focus of research by scholars of different backgrounds, with major contributions from philosophy, psychology, computer science, and neuroscience. Such debate is taking place almost completely outside the mainstream of psychiatric discourse, although a greater understanding of the problem could help better understand the role of consciousness in the development of mental disorders. There is still no consensus on how to define consciousness, but scholars agree that the core and most problematic aspects concern simple subjective experiences such as the redness of red or the painfulness of pain. Concepts such as gualia, subjectivity and what-it-is-likeness of experience have helped better define these aspects. One of the most promising approaches for understanding how phenomenal experience is related to brain activity is the study of Neural Correlates of Consciousness (NCC). It has been shown that the brain areas most specifically associated with conscious mental activity are the cortical areas and that extensive neural networks are involved. It is still unclear which cortical areas are most involved and what the nature of this correlation is, especially in order to explain how and why such neural mechanisms would produce subjective experience. Several theories have attempted to formalize how the brain implements consciousness. This article briefly describes and discusses two of the most influential physical models, the Integrated Information Theory (IIT) and the Global Neuronal Workspace (GNW) theory, which differ mainly in their level of conceptual abstraction and anatomical specificity.

Key words: consciousness, experience, mind-brain problem, Neural Correlates of Consciousness (NCC), Global Neuronal Workspace (GNW), Integrated Information Theory (IIT)

Taking consciousness seriously

Consciousness had engaged philosophers since at least the time of Aristotle, but only recently neuroscientists decided to set aside philosophical discussions on consciousness and instead search for its physical footprints ¹. For several decades, particularly since the late 1980s, consciousness has been the focus of multidisciplinary research by scholars of different backgrounds. These include neuroscientists (Pankstepp, Tononi, Koch, Llinàs, Libet, Damasio, Eccles, Dehaene, Changeux), philosophers and philosophers of mind (James, Nagel, Searle, Dennett, Chalmers, Block, Putnam, Churchland), experts in artificial intelligence and scholars involved in cognitive science (Fodor, Baars, Minskij, Marr, Noe, O'Regan), Nobel laureates (Edelman, Crick), as well as authors who take mystic and spiritual approaches. Apart from a few exceptions, this interest has been counterbalanced by the lack of attention paid by "insiders" such as psychiatrists and psychologists who, like the experts above, should deal with consciousness and its relations with the non-conscious sphere. For a psychiatrist, the subjective consciousness of the other is, together with behaviour, the primary area of interest. When considering the importance of phenomenological inquiry, it is also the main instrument of investigation. Therefore, it is something that psychiatrists deal with directly every day in their clinical approach. Yet, despite the fact that consciousness is today at the very forefront of scientific and philosophical debate, such debate, strangely enough, is taking place almost completely outside the mainstream of psychiatric discourse ².

Francis Crick wrote that, when he told people that he was working on the way we see objects, they were a bit embarrassed and wondered why there should be any difficulty about something as simple as seeing. "After all, we open our eyes and there the world is, large and clear, full of objects in vivid Technicolor, without our having to make any appreciable effort. It all seems so delightfully easy, so what can be the problem?" ³. Although it may seem paradoxical, something similar has happened to me more than once when I have discussed the topic with psychologists and psychiatrists. Consciousness seems to be something that does not concern them and they are surprised to hear that a psychiatrist would focus on this kind of issue.

After all, until recently, the topic of consciousness did not even appear in textbooks on general psychology or on the physiology of the central nervous system. Throughout much of the twentieth century, psychologists rejected introspection to focus instead on observable behaviours and the stimuli that caused them. Even in the 1970s and 1980s, as cognitive science became established, consciousness remained a controversial topic among scientists, who openly questioned whether it was a valid area of scientific investigation. Eventually, prominent scientists did decide to tackle consciousness, which ushered in a shift in thinking that surged in the 1990s, fuelled by the increasing availability of brain-scanning technologies such as functional magnetic resonance imaging (fMRI) and electroencephalography (EEG). At this point, scientists finally embarked on a major search for the mechanisms in the brain that are associated with the conscious processing of information 4.

In his famous article "Toward a philosophical structure for psychiatry", Kendler ⁵ seeks to sketch a coherent conceptual and philosophical framework for psychiatry that – at least with respect to consciousness – consists of four major propositions: 1) psychiatry is irrevocably grounded in mental, first-person experiences; 2) Cartesian substance dualism is false; 3) epiphenomenalism is false; 4) both brain-mind and mind-brain causality are real. Although the mind-brain problem (MBP) has marked implications for psychiatry, it has been poorly discussed in the psychiatric literature ⁶. Twenty-three papers, published in the three general psychiatry journals with the highest impact factor from 1995 to 2015, revealed several misrepresentations of theoretical positions and lacked relevant contemporary literature. Without further discussion or evidence, they presented the mind-brain problem as solved, dualism as an old-fashioned or superstitious idea, and physicalism as the only rational and empirically confirmed option.

According to Parnass et al. 2, symptoms and signs cannot be properly understood or identified apart from an appreciation of the nature of consciousness or subjectivity, which in turn cannot be treated as a collection of thing-like, mutually independent objects, accessible to context-free, "atheoretical" definitions or unproblematic forms of measurement (as is often assumed in structured interviewina). Abnormal mental phenomena. ie disorders of experience and expression, are "the object" of psychiatry as a science and as a pragmatic medical discipline ⁷. A psychopathological description involves converting the patient's experiences (lived in the firstperson perspective) into specific categories of symptoms and signs that are defined in third-person terms, thus providing "objective," sharable information for diagnosis, treatment, and research 8.

Anxiety and depression are pathological manifestations of emotions and feelings that are, at least in ordinary language, conscious. As abnormal forms of experience, the very symptoms of anxiety and depression occur on a conscious level. In almost all disciplines, disease is an important gateway to understanding normal functioning. But it cannot be so only for behaviour or its neural correlates. It should also be so with reference to manifestations whose functional or dysfunctional role occurs in the context of first-person, phenomenal experience. We never ask ourselves what their functional or dysfunctional role is as *conscious experiences* or as part of conscious experiences.

Studies on schizophrenia have mainly highlighted difficulties in patients' conscious experiencing and processing but rarely explored how unconscious and conscious mechanisms may interact in producing this experience. Giersh and Mishara ⁹ argue that focusing on unconscious, physiological and automatic processing of information in patients, while contrasting that processing with conscious processing, is a first required step before understanding how distortions or other impairments emerge at the conscious level. This justifies a focus on unconscious mechanisms and a distinction from those associated with consciousness.

Healthy individuals can be more or less aware of what they are thinking and perceiving in different situations. However, being too aware or dissociated from one's thoughts is linked to mental health disorders. People with depression, for example, often overthink and can feel like people are judging them. On the other hand, people who have experienced trauma can become out of touch with the self. Understanding more about how consciousness works could help us find treatments when things go wrong ¹⁰.

How have things changed over the last century?

At present, consciousness is the biggest mystery of the mind and one of the major unresolved questions in science ¹¹. But how have things changed over the last century?

At the beginning of the twentieth century, what was mysterious was not consciousness, which we mistakenly thought we understood. Freud and other scholars began to explore the unconscious part of our mind. After slightly more than a century, scholars realized that the real mystery lies not in unconscious processes, but in conscious ones. Over the last century it has become progressively clear that up to 95% of mental processes, even at a high level, are unconscious. Furthermore, our knowledge of mental processes relates *exclusively* to unconscious processes ^{12,13}.

Another major change in perspective concerns the level at which we seek consciousness. Many fall into the trap of equating consciousness with self-consciusness – to be conscious it is only necessary to be aware of the external world ¹⁴. For centuries, consciousness coincided with our spiritual and immortal soul, so we tend to identify it with something exclusively human, like verbal reasoning and self-awareness in its highest forms. Aristotle distinguished between the vegetative, sensitive and intellectual soul. For a long time, only the latter was investigated by philosophers and scientists.

However, scholars gradually realized that our conception of consciousness cannot ignore much simpler experiences, such as our feelings of red or pain. At the same time, the subjective nature of consciousness has become increasingly evident, so much so that Searle, in order to distinguish what is conscious from what is not, used the dichotomy between subjective, or first-person, ontology and objective, or third-person, ontology ¹⁵. The questions relating to these aspects of consciousness have turned out to be so challenging as to deserve the definition "hard problem of consciousness". The term was coined in 1994 by Chalmers ¹⁶ who distinguished it from the 'easy problems of consciousness', such as explaining how the brain integrates information, categorizes and discriminates environmental stimuli, or focuses attention. As stated by Chalmers ¹⁶, the hard problem of consciousness is the problem of explaining how and why it is that some internal states are felt states, such as heat or pain, rather than unfelt states, as in a thermostat or a toaster. In other words, the term sentience may be used as shorthand for phenomenal consciousness, the capacity to have any subjective experience at all 17.

A related issue is the question of animal consciousness. The traditional – and perhaps still intuitive to many people – way of thinking about consciousness is as primarily an innate endowment of humans, which other animals may or may not share in virtue of being sufficiently like us ¹⁸. In recent times, experts are increasingly accepting the idea that a number of animals also have some form of consciousness, albeit less evolved than ours. The idea that consciousness is something shared by a great number of species underlies a famous essay by the philosopher Thomas Nagel in which he asked "What is it like to be a bat?" ¹⁹.

The question of animal consciousness makes it even more pressing to address the problem of defining consciousness - also from a functional point of view - and of establishing to what extent it can be stratified into more or less complex and evolved forms. But the problem is above all a methodological one. In fact, it remains difficult to characterize convincing strategies of access to conscious experiences in other species, since we then have to rely on third-person access and mostly on behavioural data ²⁰. As we consider species that are progressively further removed from Homo sapiens in evolutionary and neuronal terms, the case for consciousness becomes more difficult to make. Two observations, one relating to complexity of behaviour and another one to complexity of the underlying nervous system, are critical. First, many animals are capable of sophisticated, learnt, non-stereotyped behaviours that we associate with consciousness if carried out by people. Second, the nervous systems of these species display a vast and still ill-understood complexity ²¹.

What is consciousness?

Medically speaking, consciousness is the state of the patient's awareness of self and environment and his responsiveness to external stimulation and inner need ²². According to Zeman and Coeberg ²³, consciousness has two key senses in colloquial English that are of relevance to clinical practice - wakefulness and awareness ²⁴. Consciousness, so defined, "begins when we wake in the morning from a dreamless sleep - and continues until we fall asleep again, die, go into a coma or otherwise become 'unconscious'. It includes all of the enormous variety of the awareness that we think of as characteristic of our waking life. It includes everything from feeling a pain, to perceiving objects visually, to states of anxiety and depression, to working out cross word puzzles, playing chess, trying to remember your aunt's phone number, arguing about politics, or to just wishing you were somewhere else. Dreams on this definition are a form of consciousness, though of course they are in many respects quite different from waking consciousness" ¹⁵.

One of the most frequently cited definitions of consciousness is the one by Stuart Sutherland ¹⁴: Consciousness – the having of perceptions, thoughts, and feelings; awareness. The term is impossible to define except in terms that are unintelligible without a grasp of what consciousness means. Many fall into the trap of equating consciousness with self-consciousness – to be conscious it is only necessary to be aware of the external world. Consciousness is a fascinating but elusive phenomenon: it is impossible to specify what it is, what it

does, or why it has evolved. Nothing worth reading has been written on it.

Thomas Nagel's ¹⁹ famous "*what it is like*" criterion aims to capture the subjective notion of being a conscious organism. According to Nagel, a being is conscious just if there is "something that it is like" to be that creature, i.e., some subjective way the world seems or appears from the creature's mental or experiential point of view. In Nagel's example, bats are conscious because there is something that it is like for a bat to experience its world through its echo-locatory senses, even though we humans from our human point of view cannot emphatically understand what such a mode of consciousness is like from the bat's own point of view ²⁵. Nagel argued that the purely objective study of an entity, such as the one science provides, does not allow any inference about the subjective character of being such an entity.

The qualitative aspect of the subjective sensations that characterise experience is often associated with so-called qualia. Philosophers use the term 'qualia' (singular 'quale') to refer to the introspectively accessible, phenomenal aspects of our mental lives ²⁶. The qualia of our experiences are what give each of them its characteristic "feel" and also what distinguish them from one another ²⁷.

This is how Chalmers summarises the issue of the definition of consciousness ¹⁶: "the really hard problem of consciousness is the problem of *experience*... If any problem qualifies as *the* problem of consciousness, it is this one. In this central sense of 'consciousness', an organism is conscious if there is something it is like to be that organism, and a mental state is conscious if there is something it is like to be in that state. Sometimes terms such as 'phenomenal consciousness' and 'qualia' are also used here, but I find it more natural to speak of 'conscious experience' or simply 'experience'".

What do all these definitions have in common? The fact that they are in the first person. Consciousness can only be defined by our subjective knowledge of it. According to Sutherland ¹⁴, it is "impossible to define except in terms that are unintelligible without a grasp of what consciousness means". As suggested by Chalmers ²⁸, consciousness coincides with what we know first-hand or have experienced. From this point of view, it is obvious and accessible. At the same time, it is unknowable and undefinable in the third person. From this point of view, it is mysterious and inaccessible. The problem of consciousness is radically unlike any other scientific problem. One reason is that consciousness is unobservable. You can't look inside someone's head and see their feelings and experiences ²⁹.

Within such a broad notion as consciousness it is of course possible to make distinctions. Edelman ³⁰ distinguishes between primary consciousness, which concerns sensations, images and perceptual experiences in general, and higher-order consciousness, which includes selfconsciousness and language. However, the main problem is the description of primary consciousness, because higher-order consciousness emerges from processes that are already conscious. Damasio ³¹ distinguishes between core consciousness, which corresponds to the transient process that is incessantly generated relative to any object with which an organism interacts, and during which a transient core self and transient sense of knowing are automatically generated, and extended consciousness, which requires the gradual build-up of an autobiographical self, a set of memories of the individual's unique past and expected experiences.

A fundamental distinction is the one between 'Phenomenal' Consciousness and 'Access' Consciousness 32,33. As proposed by Block in his seminal 1995 article, phenomenal consciousness is experience: the phenomenally conscious aspect of a state is what it is like to be in that state. The mark of access-consciousness, by contrast, is availability for use in reasoning, reporting and enabling rational control of action ³⁴. It also refers to phenomena that are closely related to consciousness in other aspects (e.g. attention or meta-cognition) ³⁵. Some theories of consciousness claim to be about exactly Phenomenal Consciousness and thus carry a distinct explanatory pretence ³⁶. It is worth noting that many conceptions of consciousness do not address this fundamental aspect. For example, Freudian consciousness is to all intents and purposes an access consciousness, since it can be defined as the part of mental life or psychic content that is immediately available to the eqo 37.

Neural Correlates of Consciousness (NCC)

During the last three decades, the advent and development of new scientific procedures, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), have allowed neuroscientists to study the activity of the living brain. These methods have been extensively used to identify with an acceptable degree of accuracy the neural correlates of any aspect of mental activity ³⁸.

Tracking the correlations between brain processes and states of phenomenal consciousness, such as feelings of pain, seeings of blue, hearings of trumpet sounds, is the basic method of scientific consciousness research ³⁹. Chalmers ⁴⁰ has provided the most informative and influential definition of NCC, according to which neural correlates are minimally *sufficient* for consciousness ⁴¹. The Neural Correlates of Consciousness (NCC) can be defined as the minimal set of neural events jointly sufficient for a specific conscious experience – given the appropriate enabling conditions ⁴². In other words, if we would stimulate or generate these neural events, a particular conscious experience would happen ⁴³.

Fink ⁴⁴ identified two constraints in the definition of NCC, the mere-sufficiency-constraint and the minimality-constraint. There are good reasons to reject a "necessity-constraint". For otherwise, neither artificial experiencers, i.e., non-biotic conscious machines, nor silicon brain

prostheses, nor redundancy (we rule out *a priori* that the activation of *different* populations of neurons in a brain could bring about the *same* experience) or plasticity are possible. On the other hand, under the assumption that the brain is sufficient to give rise to any given conscious experience, we cannot count the whole activation of a brain as a neural correlate of an experience.

Methodological issues

To unravel NCC, a common scientific strategy is to compare perceptual conditions in which consciousness of a content is present with those in which it is absent, and to determine differences in measures of brain activity ⁴³. The neural mechanisms that are jointly sufficient for being conscious in a broad sense, irrespective of the particular contents of experience, are usually identified through state-based approaches. These involve contrasting brain activity when consciousness is present, typically in awake healthy participants performing no task, with brain activity when consciousness is severely diminished – for example, during dreamless sleep, general anaesthesia or disorders of consciousness such as coma and vegetative states. Their correlates are also called full NCC, as opposed to content-specific NCC ⁴⁵.

The full NCC are the neural substrates supporting conscious experiences in their entirety, irrespective of their specific contents ^{41,45}. The content-specific NCC are the neuronal mechanisms, the activity of which determines a particular phenomenal distinction within an experience. For example, the NCC for experiencing the specific content of a face are the neurons that fire whenever a person observes, imagines or dreams a face, and are silent in other circumstances ³⁶. Paradigms looking for contents of consciousness survey conscious experiences through contrasting perceptual analysis (perceived vs. unperceived) and multiple psychophysical reporting paradigms. Examples include masked stimuli, high-contrast figures, binocular rivalry, flash suppression, motion-induced blindness and attentional paradigms, among others 46.

It is also important, both conceptually and empirically, to distinguish between the NCC and the background conditions for being conscious. These are the distal or proximal enabling factors that must be present for any conscious experience to occur, without contributing directly to its content – the heart must beat and supply the brain with oxygenated blood, various nuclei in the midbrain reticular formation and brainstem must be active, cholinergic release needs to occur within the cortico-thalamic complex and so on ⁴⁵.

Furthermore, it is necessary to distinguish between the prerequisites for and the consequences of conscious perception ⁴³. When brain events are found to covary with conscious experience, these brain events can be the neural substrates of the experience, as is often suggested, but they can also be neural prerequisites or

neural consequences of the experience ⁴⁷. At least part of the neural activity that co-varies with the perception of a particular conscious content reflects processes that precede or follow the experience – such as selective attention, expectation, self-monitoring, unconscious stimulus processing, task planning and reporting – rather than the experience itself ⁴⁵.

For example, for binocular rivalry it was proposed more than a century ago and shown recently ⁴⁸ that adaptation leading to weakening of reciprocal inhibition determines the alternations between competing stimuli. More precisely, neurons coding for the dominant stimulus adapt over time, which in turn weakens the inhibition of the suppressed stimulus, increasing its neuronal responses and thus bringing that stimulus into consciousness. Importantly, (reciprocal) inhibition could be seen as NCC-prerequisite, as it contributes to which target will be consciously perceived and is different between the two contrastive conditions. However, it is not part of the neural processes sufficient for generating or maintaining conscious experience of that target.

The existence of processes that are the consequences of conscious perception 47,49 is a logical consequence of assigning any function to conscious perception - if conscious perception enables certain processes that unconscious perception does not, these processes would inevitably appear in the contrast between trials with and without conscious perception, even if they are solely the consequences and not the direct correlates of consciousness. For example, it is known that neurons in the medial temporal lobe (MTL) respond in all-or-none fashion, closely following the subjective report of the patient ⁵⁰. However, damage to the MTL-system does not affect moment-to-moment conscious perception ⁵¹, but only the formation of a memory trace. That is, subjects will continue to have subjective experience but will have no memory of it.

Although experiences are private, we can usually infer that people are conscious if they are awake and act purposefully, in particular if they can report what they experience and if that report accords with what is experienced by others. In a clinical setting, simple behavioural criteria are often used to infer consciousness, such as the ability to respond to a command. In an experimental setting, the content of consciousness is typically evaluated by verbal report or by button-press by the participant in response to a yes or no question (such as "did you see a face?").

Empirical evidence

Early evidence on the neural correlates of consciousness was summarised by Chalmers ⁴⁰ (Tab. I), but only some of this evidence has been later confirmed. The literature on NCC, especially in terms of reviews, is not very extensive. In this area, the main contributions come from the work of Koch et al. ⁴⁵. With regard to subcortical structures, the cerebellum has four times more neurons than the

 Table I. Early evidence on the neural correlates of consciousness ⁴⁰.

- 40-Hz oscillations in the cerebral cortex ⁵²
- Intralaminar nuclei in the thalamus 53
- Re-entrant loops in the thalamocortical systems 54
- 40-Hz rhythmic activity in thalamocortical systems ⁵⁵
- Extended reticular-thalamic activation system 56
- Neural assemblies bound by NMDA ⁵⁷
- Certain neurons in inferior temporal cortex 58
- Visual processing in the ventral stream ⁵⁹
- Neurons in extrastriate visual cortex projecting to prefrontal areas ⁶⁰

cortex, is densely connected to the rest of the brain, receives mapped inputs from several modalities and is heavily involved in input and output control. Lesions of the cerebellum have little effect on consciousness and its contents, however ⁶¹.

By contrast, brainstem lesions typically cause immediate coma by damaging the reticular activating system and its associated neuromodulatory systems. However, neurological patients with a severely damaged cortex, but with relatively spared brainstem function, typically remain in a vegetative state. This suggests that brainstem activity is insufficient to sustain consciousness in a clinical sense. Rather, it is likely that the activity of heterogeneous neuronal populations within the brainstem, hypothalamus, and basal forebrain, which project diffusely to thalamic and cortical neurons and promote their depolarization, provides an important background condition for enabling consciousness by facilitating effective interactions among cortical areas ⁶². Unilateral or bilateral lesions of the basal ganglia can produce akinetic mutism, an abulic, emotionless state associated with preserved tracking of visual stimuli that is difficult to evaluate with respect to experiential content 63.

The role of the thalamus in consciousness remains controversial. Small bilateral lesions in the intralaminar nuclei of the thalamus can lead to coma, and chronic thalamic electrical stimulation may promote recovery in some patients with disorders of consciousness. Although the so-called core neurons in primary thalamic nuclei have focused connectivity, several higher-order thalamic nuclei are rich in widely projecting matrix cells, which may facilitate interactions among distant cortical areas. Thus, some thalamic cells may represent critical enabling factors for consciousness ^{45,64,65}.

Whether the primary visual cortex (V1) contributes to visual consciousness directly or whether it has only an indirect role is the subject of ongoing debate ^{60,66}. Several visual stimuli that are known to affect the activity of V1 neurons do not elicit a corresponding visual experience. Single-neuron recordings in monkeys, carried out during paradigms such as binocular rivalry, suggest that activity

in most V1 neurons is linked to the identity of the physical stimulus rather than the percept. This contrasts with the activity of neurons higher up in the visual hierarchy, which correlates with the percept rather than the stimulus ⁶⁷. In a series of elegant experiments, Logothetis ⁶⁸ recorded from a variety of visual cortical areas in the awake macaque monkey while the animal performed a binocular rivalry task. In primary visual cortex (V1), only a small fraction of cells weakly modulate their response as a function of the percept of the monkey. The majority of cells responded to one or the other retinal stimulus with little regard to what the animal perceived at the time. Conversely, in a highlevel cortical area such as the inferior temporal (IT) cortex, almost all neurons responded only to the perceptually dominant stimulus, implying that the NCC involves activity in neurons in the inferior temporal cortex.

Lesions of V1 lead to the striking phenomenon of unconscious vision or blindsight, whereby the affected participants report not seeing an item but still perform above chance on forced-choice tasks. Their subjective blindness could be a result of the insufficient feedforward activation of higher visual areas, or to lack of feedback to V1, in which case V1 would be necessary for conscious vision 69. Cortical neural responses to visual stimuli, such as natural scenes and faces, can occur quickly (within 120-140 ms) and presumably are mediated by a feedforward volley through the V1 into the extrastriate cortex and inferior temporal cortex. It has been suggested that a stimulus-evoked feedforward sweep only gives rise to a conscious percept when it is joined by a re-entrant sweep from the higher-level cortex coming back to the visual cortex 70.

Goodale and Milner ⁷¹ argue that humans possess two distinct visual systems. The ventral stream (also known as the "what pathway") leads to the temporal lobe, which is involved with conscious, stable visual object identification and scene formation. The dorsal stream (or "where pathway") leads to the parietal lobe, which is involved with the unconscious, moment-to-moment visual control of skilled actions ⁷². However, it is still unclear whether the former is predominantly related to conscious and the latter to nonconscious visual perception as argued in the literature ⁷³.

Conscious perception is believed to require more sustained, reverberatory neural activity, most likely via global feedback from frontal regions of neocortex back to sensory cortical areas ⁶⁶ that builds up over time until it exceeds a critical threshold. At this point, the sustained neural activity rapidly propagates to parietal, prefrontal and anterior cingulate cortical regions, thalamus, claustrum and related structures that support short-term memory, multi-modality integration, planning, speech, and other processes intimately related to consciousness. This is the core hypothesis of the global workspace model of consciousness ^{74,75}. In brief, while rapid but transient neural activity in the thalamo-cortical system can mediate complex behaviour without conscious sensation, it is

surmised that consciousness requires sustained but well-organized neural activity dependent on long-range cortico-cortical feedback ⁷⁶.

However, no-report paradigms suggest that frontal activation is more important for task preparation and execution than for conscious perception per se. More than a century of reports describing electrical brain stimulation carried out during neurosurgery suggest that it is difficult to directly elicit experiences from the stimulation of frontal sites, whereas it is easier to trigger specific experiences by stimulating the posterior cortex, such as the perception of faces or the feeling of wanting to move a limb. Most importantly, the commonly held view that the content of consciousness is linked to fronto-parietal activation ignores the ample evidence obtained from lesion studies that consciousness does not require an intact prefrontal cortex. For example, complete bilateral frontal lobectomy and large bilateral prefrontal resections do not impair consciousness⁴⁵.

Evidence across lesion, stimulation, and recording studies consistently point to regions in the "back" of the cortex, including temporal, parietal, and occipital areas, as a "posterior hot zone" that seems to play a direct role in specifying the contents of consciousness ⁷⁷.

Regarding the neurophysiological markers of consciousness, hopes that gamma activity or synchrony, or the ERP P3b, could be signatures of consciousness have proved illusory. An activated EEG, one of the oldest electrophysiological indices of consciousness, is a better marker of consciousness than these measures, as long as it is taken into account that it is the local rather than global EEG activation that is important ⁴⁵.

Consciousness theories

Several sophisticated models and theories have attempted to formalize how the brain implements consciousness using insights from philosophy, psychology, computer science, and neuroscience (Tab. II). These include two major and perhaps competing theories, the Integrated Information Theory (IIT) and the Global Neuronal Workspace (GNW) theory, which differ mainly in their level of conceptual abstraction and anatomical specificity ⁷⁹.

The Global Neuronal Workspace model

Capitalizing on the earlier concept of a *blackboard system* in artificial intelligence (a common data structure shared and updated by many specialized modules), Baars ⁷⁴ proposed a psychological model where the current conscious content is represented within a distinct mental space called *Global Workspace*, with the capacity to *broadcast* this information to a set of other processors. Baars ⁸⁰ emphasized the stark contrast between the few contents available in consciousness at any given moment and the large number of unconscious processes. Metaphorically, focal consciousness acts as a bright spot directed by attention at different actors on the stage. This bright spot is surrounded

by a fringe of events that are only vaguely conscious. The audience sitting in the dark receives the information transmitted by the bright spot. Behind the scenes, several systems contextualize the event.

The Global Neuronal Workspace (GNW) model ⁸¹ is a part of Bernard Baars's Global Workspace model ⁸⁰. It is a model according to which conscious access occurs when incoming information is made globally available to multiple brain systems through a network of neurons with long-range axons densely distributed in prefrontal, parieto-temporal, and cingulate cortices. Consciousness relates to the activity of a GNW that evolved to select and broadcast, in a brain-wide manner, a relevant piece of information, allowing it to be reported. The GNW hypothesis proposes that, in the conscious state, a non-linear network ignition associated with recurrent processing amplifies and sustains a neural representation, allowing the corresponding information to be globally accessed by local processors ⁸².

The GNW theory ⁸³ was empirically derived from EEG and imaging studies in humans and primates. These studies have shown that when a stimulus is presented but not consciously perceived, activation can be seen mainly in the associated primary sensory cortices. When the stimulus is consciously perceived, however, activation in primary cortical areas is followed by a delayed 'neural ignition' in which a sustained wave of activity propagates across prefrontal and parietal association cortices ⁸⁴. Conscious access corresponds to the "ignition" of workspace neurons, distributed in prefrontal and other associative cortices, and which send top-down signals back to all processors ⁷⁹.

According to the GNW theory, a subset of cortical pyramidal cells with long-range excitatory axons, particularly dense in prefrontal, cingulate, and parietal regions, together with the relevant thalamocortical loops, form a horizontal "neuronal workspace" inter-connecting the multiple specialized, automatic, and nonconscious processors. A conscious content is assumed to be encoded by the sustained activity of a fraction of GNW neurons, the rest being inhibited. Nonconscious stimuli can be quickly and efficiently processed along automatized or preinstructed processing routes before quickly decaying within a few seconds. By contrast, conscious stimuli would be distinguished by their lack of "encapsulation"in specialized processes and their flexible circulation to various processes of verbal report, evaluation, memory, planning, and intentional action, many seconds after their disappearance. This global availability of information is what we subjectively experience as a conscious state ⁸⁵.

Integrated Information Theory

An origin of the Integrated Information Theory (IIT), first proposed by Tononi⁸⁶, can be traced back to the association between consciousness and complexity. Why should the simple distinction between light and dark performed by the human be associated with conscious experience, while the distinction performed by the photodiode is not? To the

photodiode, the distinction between darkness and light is the only one available, and is therefore only minimally informative. To a human, by contrast, an experience of complete darkness and an experience of complete light are selected out of an enormous repertoire. What makes a conscious state informative is the fact that its presence discriminates among billions of different situations, each of which could generate different behaviours 87. High values of complexity correspond to an optimal combination of a high degree of functional specialization and functional integration. IIT does not address the hard problem from the brain and ask how it could give rise to experience; instead, it starts from the essential phenomenal properties of experience, or axioms, and infers postulates about the characteristics that are required of its physical substrate. The theory identifies five essential properties that are immediate, indubitable, and true of every conceivable experience, namely intrinsicality, composition, information, integration, and exclusion 88:

- intrinsicality (existing for the subject of experience, from its own intrinsic perspective, independent of external observers);
- composition (being structured by phenomenal distinctions and their relations, e.g. blue/book);
- information (being the specific way it is, differing from other possible experiences);
- integration (every experience is unitary, meaning that it is composed of a set of phenomenal distinctions, bound together in various ways, that is irreducible to non-interdependent subsets, e.g. left and right side);
- exclusion (being definite it contains what it contains, neither less nor more, e.g. less or more content)^{21,89}.

The physical substrate is intended as a system of connected units in a state, such as a set of active and inactive neurons in our brain. If every experience has the essential properties of being intrinsic, structured, specific, unified, and definite, its physical substrate must satisfy these properties in terms of cause-effect power. For something to exist in a physical sense, it must have cause-effect power – that is, it must be possible to make a difference to it (that is, change its state) and it must be able to make a difference to something.

- intrinsicality: a candidate substrate of consciousness must have cause-effect power upon itself, rather than just with respect to sensory inputs and motor outputs;
- composition: one must consider the structure of intrinsic cause-effect power – how various combinations of neurons can have causes and effects within the system (causal distinctions) and how these distinctions overlap causally (causal relations);
- information: the causes and effects specified by various combinations of neurons are specific states of specific subsets of neurons, yielding a specific causeeffect structure;
- integration: causal distinctions and relations, as well as the overall cause-effect structure they compose, only exist if they are irreducible – if they cannot be reduced to independent causes and effects;

exclusion: causal distinctions and relations, as well as the cause-effect structure they compose, must be definite, containing what they contain – neither less nor more. What defines the set of neurons that constitute the physical substrate of consciousness – as opposed to any of its subsets or supersets – is being maximally irreducible, as measured by integrated information (Φ) ^{21,89}.

Table II. Specific theories of consciousness ²⁵.

- **Higher-order theories**. A mental state is conscious as long as it is related to a simultaneous and non-inferential higher-order state whose content is the one actually in the mental state
- Reflexive theories. Like higher-order theories, they imply a strong link between consciousness and selfawareness. They differ in that they locate the aspect of self-awareness directly within the conscious state itself rather than in a distinct meta-state directed at it
- **Representationalist theories**. Conscious mental states have no mental properties other than their representational properties
- Narrative interpretative theories. Consciousness is the result not of determinate facts, but of a larger context of interpretative judgments, finally emerging as a narrative process devoid of intrinsic reality (Dennett's Multiple Drafts Model)
- **Cognitive theories**. Consciousness is associated with a distinct cognitive architecture or with a special pattern of cognitive activities. GNWT Theory describes consciousness as a competition among processors for a limited capacity resource that broadcasts information, which is conscious as long as it is available to the global workspace ^{80,81,83}
- Information Integration Theory (IIT). Consciousness is essentially defined by the integration of information; this integration is necessary and sufficient for consciousness, regardless of the substrate in which it is realized ^{86,89}
- Neural theories. Neural theories of consciousness come in many forms, though most in some way concern the so called "neural correlates of consciousness" or NCCs. Unless one is a dualist or other non-physicalist, more than mere correlation is required; at least some NCCs must be the essential substrates of consciousness ^{52,54,55}
- **Quantum theories**. The natural locus of consciousness is placed beyond the neural, at the micro-physical level of quantum phenomena ⁷⁸
- Non-physical theories. Consciousness is described as a non-physical aspect of reality, i.e. something that cannot be reduced to the natural/physical world (e.g. panpsychism) ¹⁶

On this basis, the Integrated Information Theory proposes an identity between a particular experience and the particular cause-effect structure specified by a physical substrate in its current state. The proposed correspondence is with the cause-effect structure unfolded from a neural substrate, not with the substrate as such. The goal is to account in physical terms for experience as such - the causal distinctions and relations that compose it - rather than merely for how the brain represents and performs functions. The fundamental identity of IIT states that the quality or content of consciousness is identical to the form of the cause-effect structure, and the quantity or level of consciousness corresponds to its irreducibility. A crucial advantage of the IIT is that it provides a mathematical metric of irreducibility (or integration), Φ , that can be related to the level of consciousness 88.

An index of the level of consciousness is the Perturbational Complexity Index (PCI). PCI measures the complexity of electroencephalographic (EEG) responses to transcranial magnetic stimulation. It is calculated by perturbing the cortex with transcranial magnetic stimulation (TMS) to engage distributed interactions in the brain (integration) and compressing the spatiotemporal pattern of these electrocortical responses to measure their algorithmic complexity (information) ⁹⁰. The perturbational complexity index showed a remarkable sensitivity in detecting minimal signs of consciousness in severely brain-injured patients ⁹¹.

Discussion and conclusions

When correlations are found between neural events and conscious experiences, we must consider all the following possibilities ⁹²:

- neural events cause conscious experiences;
- conscious experiences cause neural events;
- something else causes both of them;
- neural events are conscious experiences;
- we have so misconstrued one or the other that none of these is true.

With respect to these possibilities, positions may differ. The most straightforward approach is to try to explain the correlations in causal terms: NCC are the causes of the states of consciousness. To "go from correlation to causation" is a move typical of the sciences and it might seem intuitively appealing to treat brain states as the causal sources of states of consciousness. Still, this explanatory strategy is deeply problematic. A neurophysiological process causes a phenomenal state of consciousness; therefore, it is different from that state, because causes and effects are always distinct. However, materialist principles dictate that every conscious state must be implemented materially. Since the conscious state is different from the neurophysiological processes that are causing it, it must, on pain of dualism, be implemented by a material process distinct from its neural cause. Thus we end up with two material processes involved in the production

of the conscious mental state, not one ³⁹. Francis Crick, one of the initiators of the search for the neural correlates of consciousness, emphasized that he used the word "correlate" as an ontologically *neutral* term ⁵². Gallotto et al. ⁹³ affirm that the neural substrates of experience "are directly *causing*, or are *identical with*, the phenomenal conscious experience".

The GNW model is a dynamical global network approaches and therefore non-localist in principle ⁸⁵. The network is relevant; the nodes alone are not. GNW is often misunderstood as a fixed architecture encompassing the fronto-parietal cortices. In actuality, it comprises dynamic neural contributions that define this hypothetical global network. The only anatomical constraint is that relevant regions should be connected by long axons of pyramidal neurons ³⁶. However, perhaps the most significant problem is that these studies primarily aim to identify which particular neural circuits are involved in consciousness, but not how and why exactly such neural mechanisms would produce subjective experience ²⁴.

With regard to the two theories discussed in this review, it is unclear whether the GNW theory actually addresses the hard problem of consciousness. Even if the authors underscore that the global availability of information is what we subjectively experience as a conscious state ⁸⁵, the GNW theory is essentially an Access Consciousness theory. As such, it would not account for phenomenal consciousness. However, Naccache ³⁴ tries to show how a strict Access Consciousness theory can account for our conscious experience. In the global workspace, subjective reports are not conceived as the mere passive broadcasting of information, but as resulting from a dynamic and active chain of internal processes that include interpretative and belief attribution stages.

An attempt to explain the quality of experience is exemplified by IIT. IIT tries to identify the mechanisms behind the phenomenal character of experience, i.e. the quality of its content. In that vein, it poses that the quality of consciousness is in one-to-one correspondence with the geometry, concepts and relations encapsulated by the Maximally Irreducible Conceptual Structures ⁸⁸. IIT predicts that the contents of consciousness are entirely specified by the internal workings of elementary mechanisms of the main complex. Notably though, IIT's agenda to target quality is still in its nascent stages and has not gone beyond trying to explain the spatiality of experience yet ³⁶.

The problem lies not only in the identity between the form of a cause-effect structure and the quality of the experience ^{94,95}. Indeed, we must consider whether the properties identified by IIT can account for the quality of experience. Can we say that intrinsicality, composition, information, integration, and exclusion provide a comprehensive description of phenomenal experience as an explanandum? Although Haun and Tononi ⁸⁸ state that these five essential properties are immediate, indubitable, and true of every conceivable experience, whether the

current set of five axioms are truly valid, complete and independent remains open ²¹.

In conclusion, one may say that the major difficulty in understanding consciousness consists in what Levine 96 called the explanatory gap, i.e., the metaphysical gap between physical phenomena and phenomenal experience. The explanatory gap consists in the fact that, no matter how deeply we explore the structures of neurons and the chemical transactions that take place when they fire, there will always be something we cannot explain, in particular how and why these physical and objective changes - of whatever nature they may be - generate these subjective sensations, or any kind of subjective sensation. Whereas a basic robot can unconsciously detect conditions such as colour, temperature or sound, consciousness describes the qualitative feeling that is associated with those perceptions, together with the deeper processes of reflection, communication and thought 4. One thing is to provide neurological distinctions between qualia - to say that one group of neurons is activated by blue, another by salt, another by pain - but guite another to explain how blueness as you or I experience it comes out of what our brains are doing 97. Bridging this gap is known as the hard problem of consciousness 98.

To date, consciousness remains the biggest mystery of the mind and one of the major unresolved questions in science. "After decades of concerted effort on the part of neuroscientists, psychologists, and philosophers, only one proposition about how the brain makes us conscious – how it gives rise to sensation, feeling, subjectivity – has emerged unchallenged: we don't have a clue. Even enthusiasts for the new neuroscience of consciousness admit that at present no one has any plausible explanation as to how experience arises from the action of the brain. Despite all the technology and the animal experimentation, we are no closer now to grasping the neural basis of experience than we were a hundred years ago" ⁹⁹.

However, our knowledge is advancing. The interest in consciousness, which started at the end of the 1980s, has progressively increased, while the number of publications on the subject has been multiplying in recent years ¹⁰⁰. Consequently, we can be optimistic that the mystery around consciousness may at least partially dissipate in the coming decades.

References

- ¹ Koch C. What Is Consciousness? Scientific American 2018;318:60-64.
- ² Parnas J, Sass LA, Zahavi D. Rediscovering psychopathology: the epistemology and phenomenology of the psychiatric object. Schizophr Bull 2013;39:270-277.
- ³ Crick FHC. The astonishing hypothesis: the scientific search for the soul. New York: Charles Scribner's Sons 1994.
- ⁴ Sohn E. Decoding the neuroscience of consciousness. Nature 2019;571:S2-S5.
- ⁵ Kendler K. Toward a philosophical structure for psychiatry. Am J Psychiatry 2005;162:433-440.

- ⁶ Moreira-Almeida A, Araujo SF, Cloninger CR. The presentation of the mind-brain problem in leading psychiatry journals. Braz J Psychiatry 2018;40:335-342.
- ⁷ Marková IS, Berrios GE. Epistemology of psychiatry. Psychopathology 2012;45:220-227.
- ⁸ Parnas J, Zahavi D. The role of phenomenology in psychiatric classification and diagnosis. In: Maj M, Gaebel JJ, Lopezlbor N, et al. (eds.). Psychiatric Diagnosis and Classification. Chichester, UK: John Wiley & Sons Ltd 2002, pp. 137-162.
- ⁹ Giersch A, Mishara AL. Is schizophrenia a disorder of consciousness? Experimental and phenomenological support for anomalous unconscious processing. Front Psychol 2017;8:1659.
- ¹⁰ Ceurstemont S. Pinning down consciousness could improve mental health, brain disorder treatments. Horizon 2019.
- ¹¹ Jerath R, Beveridge C. Top mysteries of the mind: insights from the default space model of consciousness. Front Hum Neurosci 2018;12:162.
- ¹² Morsella E, Poehlman TA. The inevitable contrast: conscious vs. unconscious processes in action control. Front Psychol 2013;4:590.
- ¹³ Walla P. Editorial: sub- and unconscious information processing in the human brain. Appl Sci 2018;8:979.
- ¹⁴ Sutherland S. The International Dictionary of Psychology. New York: Crossroads Classic 1989.
- ¹⁵ Searle J. Mind: a brief introduction. Oxford, New York: Oxford University Press 2004.
- ¹⁶ Chalmers DJ. Facing up to the problem of consciousness. Journal of Consciousness Studies 1995;2:200-219.
- ¹⁷ Damasio AR. Emotion and the human brain. In: Damasio AR, Harrington A, Kagan JK, et al. (eds.). Unity of knowledge: the convergence of natural and human science. New York Academy of Sciences 2001, pp. 101-106.
- ¹⁸ Allen C, Trestman M. Animal consciousness. The Stanford Encyclopedia of Philosophy Winter 2016.
- ¹⁹ Nagel T. What is it like to be a bat? The Philosophical Review 1974;83:435-450.
- ²⁰ Newen A, Allen C, Montemayor C, et al. Animal consciousness in comparison to human consciousness. Proceedings of the Annual Meeting of the Cognitive Science Society 2021;43.
- ²¹ Tononi G, Koch C. Consciousness: here, there and everywhere? Philos Trans R Soc Lond B Biol Sci 2015;370:1-18.
- ²² Calabrò RS, Cacciola A, Bramanti P, et al. Neural correlates of consciousness: what we know and what we have to learn! Neurol Sci 2015;36:505-513.
- ²³ Zeman A, Coebergh JA. The nature of consciousness. Handb Clin Neurol 2013;118:373-407.
- ²⁴ van Hateren JH. A theory of consciousness: computation, algorithm, and neurobiological realization. Biol Cybern 2019;113:357-372.
- ²⁵ Van Gulick R. Consciousness. The Stanford Encyclopedia of Philosophy Spring 2018.
- ²⁶ Tye M. Qualia. The Stanford Encyclopedia of Philosophy Fall 2021.
- ²⁷ Kind A. How to believe in qualia. In: Edmond Wright, editor. The Case for Qualia. MIT Press 2008, pp. 285-298.
- ²⁸ Chalmers DJ. The puzzle of conscious experience. Scientific American 1995;273:80-86.
- ²⁹ Goff P. Why can't science explain consciousness? Livescience 2019.
- ³⁰ Edelman GM. Naturalizing consciousness: a theoretical framework. Proc Natl Acad Sci USA 2003;100:5520-5524.

- ³¹ Damasio AR. Investigating the biology of consciousness. Phil Trans R Soc Lond B Biol Sci 1998;353:1879-1882.
- ³² Block N. On a confusion about a function of consciousness. Brain and Behavioral Sciences 1995;18:227-247.
- ³³ Block N. Two neural correlates of consciousness. Trends Cogn Sci 2005;9:46-52.
- ³⁴ Naccache L. Why and how access consciousness can account for phenomenal consciousness. Philos Trans R Soc Lond B Biol Sci 2018;373:1755.
- ³⁵ Metzinger T. Minimal phenomenal experience. Phi Mi Sci 2020;1:7.
- ³⁶ Signorelli CM, Szczotka J, Prentner R. Explanatory profiles of models of consciousness - towards a systematic classification. Neuroscience of Consciousness 2021;7:1-13.
- ³⁷ Russell F. Unity and Synthesis in the Ego Ideal. American Imago 2012;69;353-383
- ³⁸ Nani A, Manuello J, Mancuso L, et al. The neural correlates of consciousness and attention: two sister processes of the brain. Front Neurosci 2019;13:1169.
- ³⁹ Polák M, Marvan T. Neural correlates of consciousness meet the theory of identity. Frontiers in Psychology 2018;9:1269.
- ⁴⁰ Chalmers DJ. What is a neural correlate of consciousness? In: Metzinger T (ed.). Neural correlates of consciousness. MIT Press 2000, pp. 17-39.
- ⁴¹ Owen M, Guta MP. Physically sufficient neural mechanisms of consciousness. Front Syst Neurosci 2019;13:24.
- ⁴² Koch C. The Quest for consciousness: a neurobiological approach. Roberts & Co. 2004.
- ⁴³ Aru J, Bachmann T, Singer W, et al. Distilling the neural correlates of consciousness. Neurosci Biobehav Rev 2012;36:737-746.
- ⁴⁴ Fink SB. A Deeper look at the neural correlate of consciousness. Front Psychol 2016;7:1044.
- ⁴⁵ Koch C, Massimini M, Boly M, et al. Neural correlates of consciousness: progress and problems. Nat Rev Neurosci 2016;17:307-321.
- ⁴⁶ Klink PC, Self MW, Lamme VA, et al. Theories and methods in the scientific study of consciousness. In: Miller SM (ed.). The constitution of phenomenal consciousness: Toward a science and theory. John Benjamins Publishing Company 2015, pp. 17-47.
- ⁴⁷ de Graaf TA, Hsieh PJ, Sack AT. The 'correlates' in neural correlates of consciousness. Neurosci Biobehav Rev 2012;36:191-197.
- ⁴⁸ Alais D, van Boxtel JJ, Parker A, et al. Attending to auditory signals slows visual alternations in binocular rivalry. Vision Res 2010;50:929-935.
- ⁴⁹ Melloni L, Schwiedrzik CM, Muller N, et al. Expectations change the signatures and timing of electrophysiological correlates of perceptual awareness. J Neurosci 2011;31:1386-1396.
- ⁵⁰ Quiroga RQ, Kreiman G, Koch C, et al. Sparse but not 'grandmother-cell' coding in the medial temporal lobe. Trends Cogn Sci 2008;12:87-91.
- ⁵¹ Postle BR. The cognitive neuroscience of visual short-term memory. Curr Opin Behav Sci 2015;1:40-46.
- ⁵² Crick F, Koch C. Towards a neurobiological theory of consciousness. Seminars in the Neurosciences 1990;2:263-275.
- ⁵³ Bogen JE. On the neurophysiology of consciousness, part I: an overview. Consciousness and Cognition 1995;4:52-62.
- ⁵⁴ Edelman GM. The remembered present: a biological theory of consciousness. New York: Basic Books 1989.

- ⁵⁵ Llinas RR, Ribary U, Joliot M, et al. Content and context in temporal thalamocortical binding. In: Buzsaki G, Llinas RR, Singer W (eds.). Temporal coding in the brain. Berlin: Springer Verlag 1994.
- ⁵⁶ Newman JB. Putting the puzzle together: toward a general theory of the neural correlates of consciousness. Journal of Consciousness Studies 1997;4:47-66.
- ⁵⁷ Flohr H. Sensations and brain processes. Behavioral Brain Research 1995;71:157-61.
- ⁵⁸ Sheinberg DL. Logothetis NK. The role of temporal cortical areas in perceptual organization. Proc Natl Acad Sci USA 1997;94:3408-3413.
- ⁵⁹ Milner AD, Goodale MA. The visual brain in action. Oxford, New York: Oxford University Press 1995.
- ⁶⁰ Crick F, Koch C. Are we aware of neural activity in primary visual cortex? Nature 1995;375:121-123.
- ⁶¹ Lemon RN, Edgley SA. Life without a cerebellum. Brain 2010;133:652-654.
- ⁶² Parvizi J, Damasio A. Consciousness and the brainstem. Cognition 2001;79:135-160.
- ⁶³ Bhatia KP, Marsden CD. The behavioural and motor consequences of focal lesions of the basal ganglia in man. Brain 1994;117:859-876.
- ⁶⁴ Van der Werf YD, Witter MP, Groenewegen HJ. The intralaminar and midline nuclei of the thalamus. Anatomical and functional evidence for participation in processes of arousal and awareness. Brain Res Brain Res Rev 2002;39:107-140.
- ⁶⁵ Panagiotaropoulos TI, Kapoor V, Logothetis NK. Subjective visual perception: from local processing to emergent phenomena of brain activity. Phil Trans R Soc London B Biol Sci 2014;369:20130534.
- ⁶⁶ Silvanto J. Is primary visual cortex necessary for visual awareness? Trends Neurosci 2014;37:618-619.
- ⁶⁷ Leopold DA, Logothetis NK. Multistable phenomena: changing views in perception. Trends Cogn Sci 1999;3:254-264.
- ⁶⁸ Logothetis NK. Single units and conscious vision. Phil Trans R Soc Lond B Biol Sci 1998;353:1801-1818.
- ⁶⁹ Weiskrantz L. Blindsight revisited. Curr Opin Neurobiol 1996;6:215-220.
- ⁷⁰ Lamme VA, Roelfsema PR. The distinct modes of vision offered by feedforward and recurrent processing. Trends Neurosci 2000;23:571-579.
- ⁷¹ Goodale MA, Milner AD. Separate visual pathways for perception and action. Trends Neurosci 1992;15:20-25.
- ⁷² Milner AD. Is visual processing in the dorsal stream accessible to consciousness? Proc Biol Sci 2012;279:2289-2298.
- ⁷³ Zhan M, Goebel R, de Gelder B. Ventral and dorsal pathways relate differently to visual awareness of body postures under continuous flash suppression. eNeuro 2018;5:0285.
- ⁷⁴ Baars BJ. A cognitive theory of consciousness. Cambridge: Cambridge University Press 1988.
- ⁷⁵ Dehaene S, Sergent C, Changeux JP. A neuronal network model linking subjective reports and objective physiological data during conscious perception. Proc Natl Acad Sci USA 2003;100:8520-8525.
- ⁷⁶ Mormann F, Koch C. The neural correlates of consciousness. Scholarpedia 2007;2:1740.
- ⁷⁷ Boly M, Massimini M, Tsuchiya N, et al. Are the neural correlates of consciousness in the front or in the back of the cerebral cortex? Clinical and neuroimaging evidence. J Neurosci 2017;37:9603-9613.

- ⁷⁸ Hameroff S, Penrose R. Consciousness in the universe: a review of the 'Orch OR' theory. Phys Life Rev 2014;11:39-78.
- ⁷⁹ Maillé S, Lynn M. Reconciling current theories of consciousness. J Neurosci 2020;40:1994-1996.
- ⁸⁰ Baars BJ. In the theatre of consciousness: Global workspace theory, a rigorous scientific theory of consciousness. Journal of Consciousness Studies 1997;4:292-309.
- ⁸¹ Dehaene S, Kerszberg M, Changeux JP. A neuronal model of a global workspace in effortful cognitive tasks. Proc Natl Acad Sci USA 1998;95:14529-14534.
- ⁸² Mashour GA, Roelfsema P, Changeux JP, et al. Conscious processing and the global neuronal workspace hypothesis. Neuron 2020;105:776-798.
- ⁸³ Dehaene S, Changeux JP. Experimental and theoretical approaches to conscious processing. Neuron 2011;70:200-227.
- ⁸⁴ Noel JP, Ishizawa Y, Patel SR, et al. Leveraging non-human primate multisensory neurons and circuits in assessing consciousness theory. J Neurosci 2019;39:0934.
- ⁸⁵ Dehaene S, Naccache L. Towards a cognitive neuroscience of consciousness: basic evidence and a workspace framework. Cognition 2001;79:1-37.
- ⁸⁶ Tononi G. An information integration theory of consciousness. BMC Neurosci 2004;5:42.
- ⁸⁷ Edelman GM, Tononi G. A universe of consciousness: How matter becomes imagination. Basic Books 2000.
- ⁸⁸ Haun A, Tononi G. Why does space feel the way it does? towards a principled account of spatial experience. Entropy 2019;21:1160.
- ⁸⁹ Tononi G, Boly M, Massimini M, et al. Integrated information

theory: from consciousness to its physical substrate. Nat Rev Neurosci 2016;17:450-461.

- ⁹⁰ Casali AG, Gosseries O, Rosanova M, et al. A theoretically based index of consciousness independent of sensory processing and behavior. Sci Transl Med 2013;5:198.
- ⁹¹ Sinitsyn DO, Poydasheva AG, Bakulin IS, et al. Detecting the potential for consciousness in unresponsive patients using the perturbational complexity index. Brain Sci 2020;10:917.
- ⁹² Blackmore SJ. Consciousness: an introduction. Oxford, New York: Oxford University Press 2003.
- ⁹³ Gallotto S, Sack AT, Schuhmann T, et al. Oscillatory correlates of visual consciousness. Front Psychol 2017;8:1147.
- ⁹⁴ Mindt G. The Problem with the 'Information' in Integrated Information Theory. Journal of Consciousness Studies 2017;24:130-154.
- ⁹⁵ Chalmers DJ. Consciousness and its place in nature. In: Stich SP, Warfield TA (eds.). Blackwell guide to the philosophy of mind. Blackwell 2003, pp. 102-142.
- ⁹⁶ Levine J. Materialism and qualia: the explanatory gap. Pacific Philosophical Quarterly 1983;64:354-361.
- ⁹⁷ Jackendoff R. Consciousness and the computational mind. MIT Press 1987.
- 98 Kanai R, Tsuchiya N. Qualia. Curr Biol 2012;22:R392-396.
- ⁹⁹ Noë A. Out of our heads: why you are not your brain, and other lessons from the biology of consciousness. Hill & Wang 2009.
- ¹⁰⁰ Michel M, Fleming SM, Lau H, et al. An informal internet survey on the current state of consciousness science. Front Psychol 2018;9:2134.





Amelia Morgillo

How to cite this article: Morgillo A, Marovino E, Biader SC. Role of the halflife in the development of substance addiction: focus on nicotine and benzodiazepine. Evidence-based Psychiatric Care 2021;7:170-176. https:// doi.org/10.36180/2421-4469-2021-26

Correspondence:

Amelia Morgillo dr.ameliamorgillo@gmail.com

Conflict of interest The Authors declare no conflict of interest.

This is an open access article distributed in accordance with the CC-BY-NC-ND (Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International) license. The article can be used by giving appropriate credit and mentioning the license, but only for non-commercial purposes and only in the original version. For further information: https:// creativecommons.org/licenses/by-nc-nd/4.0/deed.en



© Copyright by Pacini Editore Srl

Original article

Role of the half-life in the development of substance addiction: focus on nicotine and benzodiazepine

Amelia Morgillo¹, Edoardo Marovino², Sofia Caterina Biader³

¹ Department of Biological Science, University of Sannio, Benevento - Department of Medicine and Surgery, Saint Camillus International University of Health Sciences, Rome, Italy; ² Student at the Department of Drug Sciences, University of Pavia, Italy; ³ Department of Medicine and Surgery, Saint Camillus International University of Health Sciences, Rome, Italy

Summary

Introduction. The drugs of abuse circulating on the market today are an increasing number; the DSM in its latest (fifth) version eliminates the distinction between substance use, abuse and addiction and summarizes them under the generic term "substance use disorder", including tobacco, anxiolytics, opiates, stimulants, alcohol and cannabinoids. The purpose of this article is to evaluate how the half-life of the substance, related to its metabolism, modules the probability of developing addiction.

Materials and methods. A computerized search was carried out for the articles to be inserted through use of international databases such as pubmed, scopus, researchgate, google scholar, by typing in keywords such as "addiction, half-life, psychoactive substances, pharmacokinetics of nicotine, benzodiazepine", integrated with literature data. Also they are data from paper documents such as books and articles have been added. The articles related to the new therapies just approved or in the process of being approved and related studies conducted.

Discussion and conclusions. Among the pharmacokinetic properties of each xenobiotic, the half-life is a variable that depends both on intrinsic characteristics of the substance such as lipophilicity and absorption but also on the characteristics of the subject such as liver and kidney function and the presence of particular genomic polymorphisms in key genes which code for protein-enzymes of cytochrome P450 which are substrates of the xenobiotics themselves. It has been shown that substances with a short or ultra-short half-life cause addiction much more easily than those with a long half-life, giving rapid absorption peaks, resulting in rapid and intense feelings of well-being, but also short periods of permanence in the organsim with frequent and intense craving and interdose withdrawal symptoms. Much attention should be paid to the management of patients who take drugs of this type.

Key words: addiction, half-life, psychoactive, xenobiotics

Introduction

The use of psychoactive substances is a widespread practice in the general population, both as regards legal ones such as tobacco or alcohol, as well as those who are illicit. As for the former, for example, in Italy over 12 million people take nicotine daily through tobacco smoke while alcoholic drinkers are over 70 percent of the population ¹. In addition, due to the increasing prevalence of psychic pathologies linked to maladjustment such as anxiety, depression or insomnia, a significant percentage of people take psychotropic drugs, primarily benzodiazepines, with a tendency not only to an increase in "on label" prescriptions but also to you use "off label" and, unfortunately, to

illegal ones including drug dealing ². Any substance taken that is foreign to the body is referred to as a "xenobiotic," including drugs, supplements, or illicit substances. Not all substances, however, have the same abusive properties, while still causing psychoactive effects in all users. In the previous version of the Diagnostic and Statistical Manual of Mental Disorders (DSM 4) there was a distinction between use, abuse and addiction, which mainly consisted of 3 characteristics ²:

- the presence of a psycho-physical withdrawal syndrome upon suspension due to a state of dopaminergic and noradrenergic dysregulation, typical of the state of addiction and absent or minimal in that of abuse, and absent in simple use;
- the craving for the substance, or the strong psychic desire to take it in a compulsive and uncontrollable way by the will of the subject, despite for example the associated health complications or social, family or legal complications;
- 3. tolerance, or the need to take increasingly higher doses to obtain the same psychoactive effect that was previously induced by lower doses. It should be noted that tolerance is both pharmacodynamic (due to changes in the receptors of substances for downregulation and receptor internalization with reduced sensitivity to the substance, and pharmacokinetic type due to an increase in the rate of hepatic metabolization of xenobiotics with increased clearance).

The presence of these characteristics, that is the compulsive desire and difficult to control in consumption despite the related problems, an abstinence syndrome in case of not taking the xenobiotic (even after a few hours of not taking it as in the morning upon awakening) and the induction of tolerance over time determines the status of dependence on that substance. The current DSM fifth version eliminates the distinction between abuse and addiction and speaks the generic terms of "substance use disorder", encompassing both categories within it. In the induction of addiction phenomena, various characteristics relating to both the xenobiotic and the subject come into play and, among these, one of the main ones is the halflife which, together with the potency, the degree of lipo or hydrophilicity, at the receptor interaction and absorption, lead to a greater or lesser probability of developing phenomena of tolerance and improper use ³. From a pharmacokinetic point of view, by "half-life" of a xenobiotic we mean the rapidity with which plasma concentrations are reduced by half compared to the previous values, above all following the clearance or the volume of blood from which the xenobiotic is eliminated in the unit of weather. In general, the half-life of a compound is evaluated following the achievement of the "steady state", that is the maximum level of absorption in a given tissue or biological fluid (generally in the blood) (Fig. 1).

The half-life also determines the time needed to reach the "equilibrium state" of the xenobiotic in the plasma, that is the condition reached which, keeping the administered



Figure 1. Concentration-time curve of a xenobiotic in plasma.

dose constant, the plasma level remains constant since the additional dose is exactly equivalent to that eliminated. Once this state is reached, the substance concentration of the various compartments remains the same. Generally, the time to steady-state is equivalent to 5 half-lives ⁴. The elimination of a xenobiotic is the mirror image of its accumulation. In this article we want to clarify how the half-life of a psychoactive compound can influence the risk of addiction and how, on the other hand, it can also be useful for therapeutic purposes.

Materials and methods

A computerized search was carried out for the articles to be inserted through use of international databases such as pubmed, scopus, researchgate, google scholar, by typing in keywords such as "addiction, half-life, psychoactive substances", integrated with literature data. Also they are data from paper documents such as books and articles have been added. The articles related to the new therapies just approved or in the process of being approved and related studies conducted.

Discussion

As emerges from the literature data, most of the substances that most easily cause addiction and therefore dependence or abuse are those with a short or ultra-short half-life. This is for the following pharmacokinetic reasons:

- marked early "peak effect", i.e. the substance is capable of acutely and massively activating the mesolimbic dopaminergic circuits of the reward, causing feelings of gratification and inducing the subject to memorize the pleasant effect which, in turn, determines the thrust following the search for the same summarizing the substance;
- rapid elimination of the xenobiotic from the body, resulting in an equally rapid drop in the plasma levels of the substance, in equilibrium with the tissue ones, and therefore with interdose withdrawal symptoms.

Some specific substances will now be considered.

Nicotine

Nicotine is a natural alkaloid present in the leaves of nicotiana tabacum, belonging to the nightshade family, and is by far the most consumed psychoactive substance in the world. In Italy alone, over 23 percent of the population takes it daily through tobacco smoke, rapidly developing tolerance and addiction. It is also the substance that causes the most addiction problems given that only about 30% of smokers try to guit smoking and, of them. only about 5% every year definitively succeed ^{2,5}. Chemically it is composed of a pyridine molecule combined with a pyrrolidine dune, therefore with a very simple structure, but has the ability to massively activate the mesolimbic dopaminergic circuits like a few other substances. Nicotine has a short half-life of about 1.5-2 hours as it is metabolized in the liver by cytochrome P450 (CYP450) isoenzymes, which are also subject to considerable interindividual polymorphism, and is mainly converted into its metabolite cotinine, also present in blood level, which has a very long half-life of about 20 hours but is inactive (Fig. 2) 6.

The short half-life of nicotine, together with psychological aspects related to gestures and the context of intake, is the main cause of the high induction of tobacco addiction (Fig. 3).

This image shows the trend of the plasma levels of nicotinemia in the 24 hours of a standard smoker. The



Figure 2. Metabolism of nicotine.



Figure 3. 24-hour plasma nicotine concentration in a traditional smoker.

first cigarettes to smoke in the morning are generally in greater numbers as they are mainly used to bring back nicotinemia, which reached zero during the night, to levels deemed useful by the subject (the so-called "comfort zone", characteristic of every smoker) who experiences the gratification associated with consumption and all the other cigarettes smoked during the day have the goal of maintaining these levels constant as soon as the nicotinemia subsides due to the intense metabolism of the substance. This nicotine trend also explains any withdrawal symptoms during cessation, which appear almost immediately after the last cigarette and, despite being short-lived (a few days or weeks), are often not accepted by the smoker who returns to resume the substance. Heavy smokers often wake up at night to smoke again and bring drug levels back to or near their comfort zone, buffering any withdrawal symptoms. The reinforcing effect of nicotine, at the basis of the self-administration behavior, has also been studied in laboratory animals, in particular the self-titration characteristics of the plasma levels of the substance. Tolerance, very common and rapid, is linked both to the increase in the metabolization rate of the xenobiotic in the liver and to the phenomenon of receptor desensitization. In fact, in smokers, the cholinergic receptors, especially the alpha4beta2 subtype, undergo an up-regulation and reach 100 to 300 times greater in the brain of a smoker than that of a nonsmoker and this explains the dysregulation with excessive cholinergic stimulation in case of immediate cessation without pharmacological support but also the fact that the smoker "self-medicates" with the nicotine taken with smoking to deactivate the nicotinic receptors and reduce these negative effects 7. For this reason, during the early stages of cessation, it is useful to take replacement nicotine preparations by combining gradual release forms (transdermal patches) with instant preparations such as oral sprays or sublingual tablets, to reduce the desire to smoke overall and stop any transient craving episodes. In these cases, however, the difference does not concern so much the half-life of the substance, which is always the nicotine itself, but the pharmaceutical form and the release technology of the same.

Benzodiazepine

Benzodiazepines (BDZ) are a class of psychotropic drugs known mainly for their hypnotic and anxiolytic effects, but with a series of other therapeutic effects ranging from muscle relaxant to anticonvulsant to sedative and which make them not only the class of psychotropic drugs in absolute most prescribed but also, in general, one of the most commonly used types of medicines, especially among the elderly, where prescriptions have now reached levels comparable to that of antibiotics ⁸. It is believed that chronic consumers of BDZ in Italy are over 3 million people, or 5% of the population. Prolonged use of these drugs causes addiction in between 40 and 80% of cases, which can occur even after a short time, which is why in the technical data sheets of all these drugs a use that does not exceed 15 days is recommended. for insomnia and 1 to 2 months for anxiety 9. Unfortunately, dependence on BDZ is a neglected phenomenon, even though the withdrawal crisis is potentially serious or fatal, leading to the development of seizures and important autonomic symptoms ¹⁰. Z-drugs have no benzodiazepine structure but interact with GABAa (zopiclone-zolpidem-zaleplon). They have a particular indication for insomnia (Hypnoinducing): they preferentially interact with particular GABAa receptors with particular subunit ^{11,12}. The BDZ increases the probability of opening the GABA channel, therefore opening the chlorine currents, the barbiturates instead increase the opening time of the channel. The therapeutic index is, therefore, more favorable to BDZ (if used alone they do not induce death) because alone it cannot determine a hyperpolarization greater than that saturating the GABA ¹³. The clinical effect of BDZ also depends on the morphofunctional heterogeneity of the gabaergic neurons: these are all preclinical evidence in the animal model, for the clinic the most important evidence is alpha1 which mediates the sedative / hypnotic effect and anticonvulsant ¹⁴. All the other subunits help us little: we have not yet been able to find specific bdz for each subunit. The alpha12-3-5 subunit has a muscle relaxant effect.

Alpha5 present at the hippocampal level mediates amnesia and tolerance to the sedative effect.

Beta3 has been recognized as surgical tolerance as an immobilizing effect of some general anesthetics.

Alpha2 is involved in the anxiolytic effect and the architecture of sleep.

So the effects of BDZ are first of all anxiolytic (acts at the level of limbic areas and hypothalamus), muscle relaxant (on the spinal cord: sometimes it can be an effect sought in cases of spasticity or contractures, myasthenia which can depend on high sensitivity or overdose), anticonvulsant (cortical and subcortical areas ¹⁵. Like diazepam or clonazepam used in children, they also inhibit ethanol withdrawal convulsions), sedative and hypnotic (thalamus and cortex, also recalling the anesthetic effects), anamnestic with retrograde amnesia (hippocampus and cortex: the flunitrazepam is the rape drug or it can be useful in the surgical patient so he does not remember what happens) ¹⁶. Basically, the different effects are observed at different dosages: as the dosage increases, one passes from an anxiolytic to a muscle relaxant, anticonvulsant effect to end with the sedative/ hypnoic effect. All benzodiazepines are completely absorbed (with the exception of clorazepate), then they reach the nervous system and all other organs that receive high perfusion. The metabolic phase occurs in the liver and in many cases still active intermediates are formed which increase the duration of the drug's action. Their metabolism provide the substituent in position 1 of the ring is removed, hydroxylated in position 3 and conjugated

with glucuronic acid and excretion. Their half-life varies. We have diazepam (20-50 hours) and desmetildiazepam (50-120 hours) which have long half-lives, accumulate in the adipose tissue and can lead to prolonged and lasting problems, have short-ultra-short half-lives (recommended for hypnoic effect) triazolam, estazolam and brotizolam; lorazepam and oxazepam have a short half-life (useful during the day) ¹⁷. We also remind you that drugs such as oxazepam, lorazepam and thiolazolam do not give active metabolites that prolong the benzodiazepine effect. For those with a short half-life: boasting has little risk of accumulation and little residual effects; the disadvantage is greater risk of abstinence, risk of reduced efficacy in case of prolonged treatment. For those with a long halflife: the advantage is greater compliance and lower risk of abstinence; the disadvantage is the risk of accumulation and the risk of residual effects. This tolerance develops with the same initial dose following prolonged treatment and is due to the replacement of the alpha1 subunit with the alpha4 alpha6 subunit (there is the replacement of a histidine). Tolerance strictly influences the anticonvulsant effect (remember that diazepam is used for the treatment of epileptic seizures and not for long-term treatment of epilepsy) 18.

What are the effects of benzodiazepines on sleep?

BDZs alter both the macro and microstructure of sleep and do not induce physiological sleep: the latency, the number of awakenings, and the time of stage zero decrease (coincides with the waking stage), stage 1 (that of numbness), and stages 3 and 4 (the so-called wave sleep) decrease. slow, the latency of rem sleep increases, practically decreases the duration but increases the number of rem cycles: they produce restful sleep because they increase sleep time (stage 2) ¹⁹. When the drug is discontinued, a rebound effect can occur with an increase in REM sleep or if it is abused, it can then lead to insomnia. Benzodiazepines also have undesirable effects: dizziness, dysarthria, ataxia (be careful because in the elderly it is easy for the elderly to fall during the night and femur breaks are elevated in conjunction with the intake of BDZ), coordination and motor deficit, and reactivity to stimuli (then the severity must be assessed); menstrual and sexual irregularities (interferes with steroidogenesis); drowsiness, numbness, asthenia; respiratory depression (but compared to barbiturates it is not as frequent unless the patient has asthma or BPCO); paradoxical effects: anxiety, irritability, aggression; depressant effects of alcohol and opioids. If associated with alcohol, it can lead to death because the alcohol in the GABA behaves like barbiturates (hence the overdose effect) ²⁰.

Tolerance, addiction and abuse

Tolerance, especially of a pharmacodynamic type due to changes in receptor sensitivity, is more marked for the anxiolytic and hypnotic effects while it is less evident for the muscle relaxant and anticonvulsant effects, maintained over time and the speed of it is directly proportional to the amount of stimulation of the receptor ^{21,22}. BDZ withdrawal syndrome is linked to a chronic neuroadaptation of GABAergic and glutamate receptors as there is downregulation of the former and up-regulation of the latter ²³. This receptor imbalance explains on the one hand the need to continue to self-administer the substance to keep the excitatory circuits of glutamate "off" and on the other hand the fact that, following abrupt suspension or reduction of the dosage, excitatory symptoms such as tremors may occur. Ends in the hands, severe insomnia. anxiety, tachycardia, nausea, agitation which are similar to the original symptoms for which the patients took the drug. namely anxiety and insomnia. Patients therefore often confuse drug withdrawal symptoms with the exacerbation of those of origin for which it was prescribed: in general, withdrawal symptoms from BDZ have some specific characteristics 24:

- they begin in a variable way according to the half-life, therefore being early and often severe for compounds with a short half-life such as triazolam, alprazolam. lormetazepam or zolpidem and later (5-7 days after discontinuation) and less severe for long half-life compounds;
- they are aggravated by co-abstinence from other sedatives such as opioids or alcohol;
- in a percentage of cases of 2-5% they can progress to the development of seizures of the tonic-clonic type, typically in long-term users for years and at high doses.

In 70-80% of cases, the symptoms, however, are not serious and are self-limited in 7-10 days, however in particular populations such as the elderly, psychiatric patients or in polytherapy, a lot of attention must be paid to scaling, often monitoring the patient. Because chronic intake of BDZ is associated with a risk of addiction, the international guidelines recommended the decalage of it after 4-5 weeks of use with the reduction of the daily dose by 10% per week ²⁵. This allows the drug to be tapered slowly but safely, having no withdrawal symptoms and progressively reducing the dose down to zero. Clearly this approach, although easy for compounds with a long half-life and therapeutic doses (eg: 20 drops of diazepam per day or 2 tablets of clonazepam), becomes difficult for compounds with a short half-life, especially if at high doses, as the patient already shows interdose withdrawal symptoms and further scaling it worsens the clinical picture, or in case of high dose intake (cases of up to 30-40 tablets per day or up to 1-2 bottles per day of these drugs have been described). Taking advantage of the property of the half-life, it is possible to opt for a replacement by passing from the administration of a compound with a short half-life several times a day with a long half-life only one to three times a day, in order to maintain adequate coverage of blood levels of the substance and to cancel or minimize withdrawal symptoms. The guidelines therefore recommend the replacement of 30-40% of the declared

daily dose with an equivalent of diazepam or clonazepam, taking into account the equivalence table, gradually decreasing the dose of BDZ with a short half-life in the following days and increasing that with a long half-life up to to complete clinical stability assuming only the latter. later, after two or three weeks of maintenance, it is possible to gradually decrease the long half-life BDZ by 10% per week in a safer and less painful way for the patient ²⁶.

The knowledge of the half-life of the substance therefore allows to set up an adequate cessation program with low risk of drop-out and high efficacy and therapeutic adherence, sometimes with the need for hospitalization for high starting doses or for poly-drug users. It is important to be able to distinguish drug withdrawal symptoms from underlying disease exacerbations and to monitor the patient over time when prescribing these potentially additive drugs.

Half-life, pharmaceutical form and addiction: the example of benzodiazepines

As previously described, various factors related to both the substance and the patient come into play in the development of addiction. The half-life of is one of the main ones but it is also related to the systemic absorption modality of the same and, therefore, to the release system from the pharmaceutical form. In the case of BDZs, for example, we have discussed how compounds with short half-lives are more additive as they give rapid absorption peaks and are metabolized just as quickly and therefore easily indicate abstinence states even interdose 27. Let's see for example the case of alprazolam: this BDZ, marketed under various brands as well as as an equivalent, has a specific anxiolytic and in particular anti-panic activity, so much so that it is considered the reference drug to treat both acute and highly prescribed crises. also in association with antidepressants, in the first weeks as a prophylaxis of new episodes while waiting for the effect of the antidepressants themselves. Alprazolam has a short half-life and often lends itself to abuse, especially as an overdose of the prescribed daily dose and is available both as oral drops and as immediate or extended release tablets (Fig. 4).



Figure 4. Immediate and prolonged-release Alprazolam plasma concentration differences.

As you can see in the image, the prolonged-release formulation allows to obtain a greater coverage of plasma levels as the active ingredient is released into the circulation more slowly, with fewer rebound symptoms and greater coverage of anxiolysis with only one or two doses per dose. day. On the contrary, the immediate release is very useful in treating the acute anxiety attack in an instant way but over time it is the one that tends to give more dependence and abuse as it determines both typical mesocortic-limbic neurobiological alterations and also psychic conditioning (the patient must always have the tablet at hand in case of attack, a reassurance system of conduct which itself becomes the cause of addiction). Furthermore, the pharmaceutical form can also influence the additive capacity of the compound: in the case of BDZ, for example, the oral drops are more manageable especially in the induction or scaling phases but, in general, if used for a long time they are more additive as they are more concentrated. Furthermore, ethanol is often used as a vehicle, with or without other alcohols, to better solubilize the active principle which is not very soluble in water. However, the same ethanol can give tolerance and abstinence, especially for patients who abuse these drugs at high doses (cases of consumption of 2 or 3 bottles a day have also been described). moreover, even flavoring can induce craving in itself, with the patient's tendency not to dilute the drug but to take it directly from the bottle. The tablets, on the other hand, allow greater accuracy of the dose, are more chemically stable and do not contain ethanol or flavoring but are less manageable in the case of scaling as patients find it difficult to divide them (even if thanks to the pill cutters this is facilitated).

Conclusions

As described extensively, the possible developmental trajectories for a person taking substances depend on various factors relating to both the person and the substance. In the latter case, the half-life is a fundamental property, also in relation to the absorption and therefore to the release modality of the substance itself. For most substances of abuse, a short half-life facilitates the induction of gratification (and therefore of behaviors of dependence) and, in the case of BDZ, for example, of the therapeutic effect, giving rapid peaks in the brain and massively activating the dopaminergic circuits of gratification (especially meso-limbic) but, on the other hand, the fast plasma clearance determines more sudden and often more intense withdrawal symptoms. On the contrary, a long half-life facilitates the induction and decalage process and allows good coverage in 24 hours of the therapeutic effect with only one or two daily administrations but can be associated with systemic accumulation phenomena with an increase in some side effects, especially for substances of a lipophilic nature such as BDZ or opioids. These properties must be

carefully considered during a drug cessation therapeutic program, also in relation to the pharmaceutical form and the release mode of the active ingredient.

References

- ¹ Amato L, Pani P. Tossicodipendenze. Una guida alle basi razionali del trattamento. Il Pensiero Scientifico 2013.
- ² Lugoboni F, Zamboni M. In sostanza manuale sulle dipendenze patologiche. Edizioni CLAD 2018.
- ³ Roxas Amico M, Caputi PA, Del Tacca M. Compendio di farmacologia generale e speciale. Edra 2021.
- ⁴ Raja M, Raja S. Psicofarmacologia clinica. Edizioni Minerva Medica 2021.
- ⁵ Stahl S. Neuro psicofarmacologia essenziale. Basi neuroscientifiche e applicazioni pratiche. Edi-ermes 2016.
- ⁶ Schick SF, Blount BC, Jacob P, et al. Biomarkers of exposure to new and emerging tobacco delivery products. American Journal of Physiology 2017;313:L425-L452.
- ⁷ Chiamulera C. Meccanismi neurobiologici della dipendenza da nicotina. 20021. https://www.giornaledicardiologia.it/r. php?v=822&a=9169&l=12260&f=allegati/00822_2001_12/ fulltext/S1-2001_06%2030-33.pdf
- ⁸ Jin Y, Yu C-X. Progress in research on techniques for prolonging half-life of protein and polypeptide drugs Chinese Journal of Schistosomiasis Control 2012;24:594-597.
- ⁹ Sleep D, Cameron J, Evans LR. Albumin as a versatile platform for drug half-life extension. Biochimica et Biophysica Acta 2013;12:5526-5534.
- ¹⁰ Vinkers CH, Tijdink JK, Luykx JJ. Kiezen voor de juiste benzodiazepine: werkingsmechanisme en farmacokinetiek. Nederlands Tijdschrift Voor Geneeskunde 2012;155(35).
- ¹¹ Revet A, Yrondi A, Montastruc F. Règles de bon usage des benzodiazépines. Presse Medicale 2018;47:872-877.
- ¹² Hein M, Lanquart JP, Loas G, et al. Objective sleep alterations and long-term use of short or intermediate halflife benzodiazepine receptor agonists are risk factors for high blood pressure in individuals with insomnia: a study in 1272 individuals referred for sleep examinations. Sleep Medicine 2019;53:115-123.
- ¹³ Weintraub SJ. Diazepam in the treatment of moderate to severe alcohol withdrawal. CNS Drugs 2017;31:87-95.
- ¹⁴ Wang PS, Bohn RL, Glynn RJ, et al. Hazardous benzodiazepine regimens in the elderly: effects of half-life, dosage, and duration on risk of hip fracture. Am J Psychiatry 2001;158:892-898.
- ¹⁵ Helmes E, Østbye T. Associations between benzodiazepine use and neuropsychological test scores in older adults. Can J Aging 2015;34:207-214.
- ¹⁶ Hallfors DD, Saxe L. The dependence potential of short halflife benzodiazepines: a meta-analysis. Am J Public Health 1993;83:1300-1304.
- ¹⁷ Hemmelgarn B, Suissa S, Huang A, et al. Benzodiazepine use and the risk of motor vehicle crash in the elderly. JAMA 1997;278:27-31.
- ¹⁸ Passaro A, Volpato S, Romagnoni F, et al. Benzodiazepines with different half-life and falling in a hospitalized population: the GIFA study. Gruppo Italiano di Farmacovigilanza nell'Anziano. J Clin Epidemiol 2000;53:1222-1229.
- ¹⁹ Rickels K. Clinical trials of hypnotics. J Clin Psychopharmacol 1983;3:133-139.

- ²⁰ Greenblatt DJ. Pharmacology of benzodiazepine hypnotics. J Clin Psychiatry 1992;53:7-13.
- ²¹ Schweizer E, Case WG, Rickels K. Benzodiazepine dependence and withdrawal in elderly patients. Am J Psychiatry 1989;146:529-531.
- ²² Cano JP, Coassolo P. Notion de demi-vie et métabolisme des benzodiazépines. Etude critique. L'Encephale 1983;9(Suppl 2):75B-80B.
- ²³ Meier PJ, Ziegler WH. Benzodiazepine Praxis und Probleme ihrer Anwendung. Schweizerische medizinische Wochenschrift 1988;118:381-392.
- ²⁴ de Vries OJ, Peeters G, Elders P, et al. The elimination half-life of benzodiazepines and fall risk: two prospective observational studies. Age Ageing 2013;42:764-770.
- ²⁵ Ochs HR. Benzodiazepine: bedeutung der Kinetik f
 ür die Therapie. Klinische Wochenschrift 1983;61:213-224.
- ²⁶ Dundee JW, Collier PS, Carlisle RJ, et al. Prolonged midazolam elimination half-life. Br J Clin Pharmacol 1986;21:425-429.
- ²⁷ Smith DA, Beaumont K, Maurer TS, et al. relevance of halflife in drug design. J Med Chem 2018;61:4273-4282.

Original article

Wernicke's encephalopathy in a young psychiatric patient with delirium: a diagnostic challenge

Gabriele Maria Nicolino¹, Silvia Squarza², Alessandro Grecchi³

¹ Post-graduate School in Radiodiagnostics, Università degli Studi di Milano, Milan, Italy; ² ASST Grande Ospedale Metropolitano Niguarda, Unità Operativa di Neuroradiologia Diagnostica e Interventistica, Milan, Italy; ³ Department of Mental Health and Substance Abuse, ASST Santi Paolo e Carlo, Milan, Italy





Gabriele Maria Nicolino

Summary

Wernicke's encephalopathy (WE) is an acute neurological disorder caused by depletion of thiamine and characterized by the clinical triad of ataxia, confusion and ophthalmoplegia. Thiamine deficiency is characteristically associated with severe alcohol use disorder. We present a rare case of WE in a non-drinker patient affected by obsessive compulsive disorder who presented a dramatic worsening of the clinical situation after the administration of clomipramine, underlining how brain Magnetic Resonance Imaging (MRI) scan can play a key role for the correct diagnosis and clinical management.

Key words: Wernicke's encephalopathy, brain MRI, delirium, obsessive compulsive disorder, thiamine deficit

Introduction

Wernicke's encephalopathy is a neurological disorder induced by depletion of thiamine due to different causes including alcoholism, gastrointestinal surgery, prolonged vomiting and dietary imbalance.

Thiamine plays an essential role in carbohydrate metabolism in the brain; periventricular structures are particularly affected as the blood-brain barrier is physiologically less tight and there is a high rate of thiamine-related glucose and oxidative metabolism. This leads to the typical clinical presentation: confusion, cerebellar ataxia and ophthalmoplegia.

If unrecognized, Korsakoff Syndrome or death may ensue ¹.

Clinical history

A 27 year-old man with a diagnosis of Obsessive Compulsive Disorder (OCD) was admitted at our psychiatric first care service due to an acute anxiety episode in OCD.

Since two months he was having severe food restriction behaviors associated to an anxiety status based on intrusive thoughts. These restrictions brought to compromise his oral drug therapy for OCD (clomipramine) and the specific therapy for comorbidity (ulcerative colitis and hiccup).

At admission, blood tests showed abnormal values of RBC 4.10 x10^6/mL and low potassium 3.30 mmol/L. For the anxiety episode and considering the clinical picture, recovery of nutrition and intravenous therapy were started with clomipramine in glucose solution and chlorpromazine in physiologic solution. Potassium chloride (1,200 mg/day) was also administered.

How to cite this article: Nicolino GM, Squarza S, Grecchi A. Wernicke's encephalopathy in a young psychiatric patient with delirium: a diagnostic challenge. Evidence-based Psychiatric Care 2021;7:177-178. https://doi. org/10.36180/2421-4469-2021-27

Correspondence:

Gabriele Maria Nicolino gnicolino.md@gmail.com

Conflict of interest The Authors declare no conflict of interest.

This is an open access article distributed in accordance with the CC-BY-NC-ND (Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International) license. The article can be used by giving appropriate credit and mentioning the license, but only for non-commercial purposes and only in the original version. For further information: https:// creativecommons.org/licenses/by-nc-nd/4.0/deed.en



© Copyright by Pacini Editore Srl



Figure 1. A) FLAIR weighted axial MRI images showed bilateral and symmetric hyperintensity at fornices and mammillary bodies (red arrowhead) and periaqueductal gray (red arrow); the same signal features were present also in the postero-medial portion of both thalami (not showed in the Figure); **B)** Image B: after 45 days of treatment brain MRI scan showed normal signal in those areas.

Suddenly he developed an acute delirium with disorientation, confusion and visual hallucinations (meeting criteria of DSM 5).

Hypotheses of an infectious process or central anticholinergic syndrome due to antipsychotics, were considered.

Pharmacological treatment was suspended, and brain MRI, EEG and urgent neurological examination were requested. Neurological exam and EEG were not specific. MRI showed a mild hyperintensity in long TR sequences involving symmetrically the postero-medial portion of the thalami, fornices, mammillary bodies and periaqueductal gray; a corresponding mild restriction of the molecular diffusivity in Diffusion-weighted imaging sequences was found. MRI findings were consistent with diagnosis of Wernicke encephalopathy (Fig. 1). Subsequent neurological control revealed ophthalmoparesis and ataxic gait supporting the diagnosis.

Administration of thiamine hydrochloride 100 mg/ml was set two times/day and cyanocobalamin 1,000 mcg 1fl/ weekly intramuscularly.

During the following 48 hours since the start of the new therapy, an improvement in the acute situation was observed with a clinical residual of slowing down and disorientation.

Discussion

WE is an acute neuropsychiatric syndrome characterized by the classic triad of ataxia, eye movement disorders, and mental status change. The incidence of WE is 0.6% of the population. The majority of patients that develop WE have a history of chronic alcoholism and accompanying malnutrition. In non-alcoholics patients WE onset is generally acute, rarely with ocular and cerebellar signs. Vomiting and a restrictive diet are the most frequent causes ^{1,2}.

Intravenous administration of clomipramine (infusion in physiological solution, glucose and isotonic) is indicated in cases of severe obsessive-compulsive disorder when several therapeutic attempts do not lead to adequate results. The management of hiccups and vomiting through the correction of hypokalemia and intravenous administration of chlorpromazine is also indicated ³.

In our patient, immediately treated for the delirium in OCD with chlorpromazine and potassium, MRI made it possible to diagnose WE and set a correct therapy as is known the high sensibility of brain MRI for a correct and early diagnosis ⁴.

Reviewing the medical history of our patient and the first clinical setting it is possible to recognize several risk factors for WE development. He had a restrictive diet with predominant use of carbohydrate causing a relevant loss of weight in association with a possible malabsorption of nutrients, due to the chronic inflammatory disease of the patient; finally the administration of clomipramine with glucosal solution could have worsened the clinical setting as it is reported in literature in WE cases of pregnant women ⁵.

Immediate therapy with thiamine led to a functional recovery with a parallel improvement of the visible damage on MRI.

Conclusions

In conclusion, in our clinical practice, we have to know that WE could present without the typical clinical triad but just with delirium. Such an unusual clinical set must be considered in psychiatric patients as a diagnostic challenge.

References

- ¹ Zuccoli G, Santa Cruz D, Bertolini M, et al. MR imaging findings in 56 patients with Wernicke encephalopathy: nonalcoholoics may differ from alcoholics. Am J Neuroradiol 2009;30:171-176.
- ² Galvin R, Brathen G, Ivashynka A, et al. EFNS guidelines for diagnosis, therapy and prevention of Wernicke encephalopathy. Eur J Neurol 2010;17:1408-1418.
- ³ Karameh WK, Khani M. Intravenous clomipramine for treatment-resistant obsessive-compulsive disorder. Int J Neuropsychopharmacol 2015;19:1-5.
- ⁴ White ML, Zhang Y, Andrew LG, et al. MR imaging with diffusion-weighted imaging in acute and chronic Wernicke Encephalopathy. Am J Neuroradiol 2005;26:2306-2310.
- ⁵ Oudman E, Wijnia JW, Oey M, et al. Wernicke's encephalopathy in hyperemesis gravidarum: a systematic review. Eur J Obstet Gynecol Reprod Biol 2019;236:84-93.

Journal of the Italian Society of Psychiatry

Original article

Cohort study of psychiatric patients in Forlì District

Monica Pacetti¹, Eleonora Monti¹, Samantha Sanchini²

¹Mental Health Service (Forlì), Azienda USL Romagna; ²Unit of Addiction Treatment (Forlì), Azienda USL Romagna

Summary

Italy was the first Western country to set up mental health care in the network of local services. This allowed to open new horizons for research in the treatment of patients suffering from psychiatric disorders. The Emilia Romagna Region has actively participated in this process of change, constituting the Departments for Mental Health (DSM). The treatment plans of 5,976 adults, in the period from 1978 to 2014, residing in the Forlì area, were analyzed. The socio-demographic predictors relating to access to services are the fact of having an average age and being married according with literature. The analysis of the outcomes of the treatment plans shows that a third of the subjects stay in treatment, four out of ten abandon and two out of five complete it. Treatment retention appears to have had a decreasing trend, with very low values (18%) from 2005 to 2009, this data corresponds with the increasing practise to conclude treatments according with the "Stepped Care" model diffusion, promoted by the regional program "Giuseppe Leggieri". The integrated care model between mental health care professionals and general practitioners (GPs) is an effective strategy not only for prevention, but also for prognosis of mental disorders, according with literature especially for major mental disorders. The outcome of treatment evaluation highlights four different profiles of subjects, relate to different types of discharge from mental health centre. In our study most of concluding treatment are higher for females, married, widows, and for people over 50 years old.

Key words: psychiatric diagnosis, mental health treatment, mental health outcomes

Introduction

It emerges from scientific literature ^{1,2} that in richer countries there is greater attention to Mental Health and greater investment in human and economic resources.

Law 18 of 1978 brought about radical changes in the Mental Health care system in Italy, with the territorial services constitution, best known as the Mental Health services. Italy was the first Western country to set up mental health care in the network of local services. This allowed to open new horizons for research in the treatment of patients with psychiatric pathologies ³. The Emilia Romagna Region has actively participated in this process of change, establishing the Departments for Mental Health (DSM) as reported in the DGR n. 411/1998.

The Mental Health Centre (CSM) of Forlì, consistent with the national and regional programme, aims to promote mental health, prevent the distress of mental disorders and disabilities and differentiate the treatments paths of psychiatric pathologies.





Monica Pacetti

How to cite this article: Pacetti M, Monti E, Sanchini S. Cohort study of psychiatric patients in Forlì District. Evidence-based Psychiatric Care 2021;7:179-187. https://doi. org/10.36180/2421-4469-2021-28

Correspondence:

Monica Pacetti monica.pacetti@ausl romagna.it

Conflict of interest The Authors declare no conflict of interest.

This is an open access article distributed in accordance with the CC-BY-NC-ND (Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International) license. The article can be used by giving appropriate credit and mentioning the license, but only for non-commercial purposes and only in the original version. For further information: https:// creativecommons.org/licenses/by-nc-nd/4.0/deed.en



© Copyright by Pacini Editore Srl

This evolutionary process aimed towards a "services culture" highlighted some significantly critical issues, improved by Emilia Romagna Region through the 2009-2011 Mental Health Implementation Plan. The major criticalities highlighted were: an inefficient approach to rehabilitation and its consequent risks of chronicity the persistence of a social delegation and stigma.

According to the data collected in Italy in 2017 by the SISM (The Mental Health Information System) of the Ministry of Health ⁴, 851,189 individuals with psychiatric pathologies were assisted by specialised services; 335,794 were patients who, for the first time, get into with the Departments of Mental Health and 67.6% of the patients were over 45 years old. On a national level, the psychiatric pathologies most frequently found were depression (39.2 per 10,000 inhabitants), schizophrenia (35.8 per 10,000 inhabitants), and neurotic and somatoform syndromes (22.0 per 10,000 inhabitants) ³.

Analysing the causes of hospitalization derived from the diagnosis of hospital discharge, it appears that Affective Disorders are the first cause in women and the second in men, but by far lower rates; Schizophrenia and related disorders appear to be the leading cause of hospitalization in men 5. The rates of patients treated at a territorial level in specialised areas, by Diagnosisrelated groups, highlight important gender differences. Rates related to schizophrenic disorders, personality disorders, substance abuse and mental retardation disorders are greater in males than females, while the opposite occurs for affective, neurotic and depressive disorders. In particular, the rate of depression in female patients is almost double that of the male sex (29.2 per 10,000 inhabitants in males and 48.3 per 10,000 inhabitants in females) 6.

Objectives of the study

Evaluate the effectiveness of the different types of interventions carried out by the Forlì Mental Health Centre, of the Local Health Authority of Romagna, for the treatment of patients with mental disorders, regarding outcome and duration.

Materials and methods

Population

5,976 patients were studied under treatment at the Psychiatry Unit of Forlì in the period 1978-2014, all resident in the Forlì area, following an integrated treatment plan at the CSM, with the necessity of complex interventions.

The information database was extracted from the computerized medical records of the Romagna AUSL headquarters in Forlì⁷. Demographic variables were collected for each subject: sex, citizenship, age, housing situation, marital status, qualifications, employment status,

primary and secondary diagnosis, treatment received and period of treatment. The research ended on 31/12/2014. The results of the interventions analysed are: "in treatment" which means that the subject was still present at the CSM, "conclusion" indicates the subject was discharged with or without referral to the GP, "abandonment" means that the subject left the treatment without having completed it, not in agreement with the psychiatrist, "death" is when the subject died during treatment, "other" indicates discharge when the referral was not appropriate and therefore not a case of psychiatric relevance, and was therefore sent back to another AUSL service, or for other undefined reasons. The diagnoses carried out using ICD-9 were divided into the following diagnostic groups: schizophrenic psychosis (295), unipolar (296.2/296.3), bipolar (296 except 296.2/296.3), paranoid states (297), other non-organic psychosis (298/299), neurotic disorders (300), personality disorders (301), adjustment disorders(308/309/311/312/313), other psychiatric disorders (302/306/307/314/315/316), organic disorders (290/293/294/310/317/318/319), substance use disorders (291/292/303/304/305), non-psychic disorders (all other diagnoses).

In a subsequent analysis, the diagnoses were grouped into three categories:

- MAJOR PSYCHIATRIC DISORDERS which include schizophrenic (295), unipolar (296.2/296.3), bipolar (296 except 296.2/296.3) psychosis, paranoid states (297), other inorganic psychoses (298);
- MINOR PSYCHIATRIC DISORDERS including neurotic disorders (300), personality disorders (301), adjustment disorders (308/309/311/312/313);
- OTHER which include other inorganic psychoses (299), other psychiatric disorders (302/306/307/314/315/316), organic disorders (290/293/294/310/317/318/319), substance use disorders (291/292/303/304/305), nonpsychic disorders (all other diagnoses) and the missing diagnosis.

Statistic analysis

Statistical analysis is a multivariate tecnique using Poisson regression. The variables used in the model refer to the first consultation and are those available in the CSM archives (computerized medical records): sex, citizenship, age, housing situation, marital status, qualifications, employment status and the treatments received at the beginning of the treatment.

To analyze the data in relation to the time of the first consultation, the following time periods have been defined: \leq 1989, 1990-1994, 1995-1999, 2000-2004, 2005-2009, 2010-2014.

The calculation of person-years at risk, was calculated from the date of the first consultation until the termination of the treatment path (due to discharge, interruption, or death).

The calculation of the crude rate of discharge, interruption and death, was calculated in relation to the

characteristics of the patients. The 95% confidence interval (95% CI) of the rate was calculated by the approximate maximum likelihood method: exp [In (Rate) \pm 1.96 × Casi-1/2].

Univariate and multiple analysis to evaluate the relationship between the duration of the treatment and the outcome; the relationship between the characteristics of the patients and the type of treatment provided, using the Poisson regression to calculate the ratios between rates (RR) of discharge, interruption and death and their 95%. In the model were included variables relating to age, duration, gender, nationality, qualifications, and employment status. The analyzes were conducted with the Stata16 program.

Results of the analysis on the outcome of the treatment

Characteristics of the subjects of the cohort

5,976 subjects were enrolled in the study. The analysis of the data shows a statistical significance of the housing

situation and of the analysis relating to hospitalizations at the Intensive Therapeutic Residence (RTI - Tab. I).

The cohort is made up of 58.4% females, the average age at access was 47.7 years old, a significant fact was that only 19.5% were under the age of 30 and that 21.5% had the first contact with the mental health centre at the age of over 65, age of geriatric relevance. 9.2% did not have Italian citizenship. The housing situation was characterized by the fact that most of them lived with others (76.6%), 16.0% lived alone and 6.3% were placed in a structure; 43.4% were married, 35.2% single, 10.5% separated / divorced, and 9.4% widowed. 29.5% had a high educational qualification (high school diploma or university degree); the majority of patients were retired (36.3%), 31.9% were in employment and 14.3% were unemployed.

As far as the pathology is concerned, about one out of three people had a neurotic disorder as a primary diagnosis, 13.1% suffered from unipolar mood disorder, 12.2% bipolar, 9.5% suffered from adjustment disorders, 9.4% from schizophrenic psychosis, and 5.0% from organic disorders; the least represented diagnoses in the population were: paranoid states, other non-organic psychosis, personality

Table I. Characteristics of cohort's patients at baseline, distributed by gender.

		Mal	es	Fema	ales	Tot	al	01-12
		N	%	N	%	N	%	Cni
	Total	2,482	100.0	3,494	100.0	5,976	100.0	
Age	Mean age DS	45.4 (18.6)	100,0	49.4 (18.3)	100,0	47.7 (18.5)	100,0	
	≤ 17	70	2.8	55	1.6	125	2.1	
	18-29	531	21.4	510	14.6	1,041	17.4	-
	30-39	463	18.7	633	18.1	1,096	18.3	0 001
Age-classes	40-49	487	19.6	687	19.7	1,174	19.6	- p < 0.001
	50-64	483	19.5	799	22.9	1,282	21.5	-
	≤ 65	448	18.0	810	23.2	1,258	21.1	-
Nationality	Non-natives	194	7.8	354	10.1	548	9.2	0.002
	Alone	380	15.3	578	16.5	958	16.0	
Living	With others	1,903	76.7	2,677	76.6	4,580	76.6	0 104
conditiom	Facilities	166	6.7	209	6.0	375	6.3	- 0.134
	Other	33	1.3	30	0.9	63	1.1	-
	Single	1,182	47.6	924	26.4	2,106	35.2	
	Married	968	39.0	1,642	47.0	2,610	43.7	-
Civil status	Separate/divorced	226	9.1	402	11.5	628	10.5	p < 0.001
	Widower	78	3.1	483	13.8	561	9.4	-
	Other	28	1.1	43	1.2	71	1.2	-
Educational	Low	1,780	71.7	2,431	69.6	4,211	70.5	n - 0.001
Educational degree	High	702	28.3	1,063	30.4	1,765	29.5	- ρ < 0.001
	Employed	924	37.2	983	28.1	1,907	31.9	
Professional	Not employed	460	18.5	394	11.3	854	14.3	0.001
condition	Retired	880	35.5	1,291	36.9	2,171	36.3	p < 0.001
	Other	218	8.8	826	23.6	1,044	17.5	-

		Males		Fem	ales	Tot	01:12	
		Ν	%	N	%	Ν	%	Cni ²
	Schizophrenic psychosis	299	12.0	264	7.6	563	9.4	
	Paranoid state	57	2.3	73	2.1	130	2.2	-
	Other non organic psychosis	70	2.8	67	1.9	137	2.3	
	Major depression	272	11.0	513	14.7	785	13.1	_
	Bipolar disorder	279	11.2	452	12.9	731	12.2	_
	Neurotic disorder	664	26.8	1,151	32.9	1,815	30.4	
Primary	Personality disorders	107	4.3	103	2.9	210	3.5	n < 0.001
diagnosis	Adjustment reactions	222	8.9	344	9.8	566	9.5	p (0.001
	Other psychiatric disorders	17	0.7	44	1.3	61	1.0	
	Organic disorders	163	6.6	137	3.9	300	5.0	
	Substances use disorders	97	3.9	38	1.1	135	2.3	
	Non psychiatric disorders	45	1.8	42	1.2	87	1.5	
	Missing	190	7.7	266	7.6	456	7.6	
	Clinical psychiatric	2,376	95.7	3,395	97.2	5,771	96.6	0.003
	Psychoterapeutic	235	9.5	272	7.8	507	8.5	0.021
	Day care center	33	1.3	26	0.7	59	1.0	0.024
	Work transition programs	125	5.0	76	2.2	201	3.4	p < 0.001
Treatments	Socio-rehabilitative	430	17.3	372	10.6	802	13.4	p < 0.001
	RTI	228	9.2	350	10.0	578	9.7	0.284
	RTR	101	4.1	83	2.4	184	3.1	p < 0.001
	RSR	116	4.7	74	2.1	190	3.2	p < 0.001
	SPDC/SPOI	652	26.3	673	19.3	1,325	22.2	p < 0.001

disorders, other psychiatric disorders, substance disorders, and non-psychiatric disorders.

As for the treatment, almost all the subjects started a treatment plan with the psychiatrist (psychiatric clinical product - 96.6%), 22.2% underwent a hospitalization for acute psychiatric symptoms (SPDC/SPOI), 13.4% also undertook socio-rehabilitative treatment, 8.5% a psychotherapy cycle and 9.7% underwent at least one hospitalization in RTI (intensive treatment residence).

The analysis of characteristics by gender (Tab. I) shows that females accessed therapy on average at a later age than males (49.4 *vs* 45.4), a figure also confirmed by the breakdown by classes. One in ten of the female subjects were non-Italian as apposed to less than 8%. of the males. The percentages on the housing situation did not show gender differences; while, regarding marital status, the majority of males were single (47.6%) whereas the majority of females were married (47%), 13.8% of women were widows.

Males and females do not show percentual differences regarding qualifications. As far as employment is concerned, the percentage of retirees is similar, the percentage of the employed differs in so far as males are 37.2% vs females at 28.1%; the unemployed also differs: 18.5% males vs 11.3% females. The percentage of housewives is high.

With reference to the primary diagnosis, one out of three females and one out of four males suffered from a neurotic disorder; females were affected by unipolar mood disorder to a greater extent than males. Patients suffering from schizophrenic psychosis, organic disorders and substance disorders were mainly male.

Regarding the type of treatment received, there was a greater distribution in favour of males: psychotherapy treatment 9.5 vs 7.8%, grant jobs 5 vs 2.2%, socio-rehabilitation 17.3 vs 10.6%, acute hospitalization 26.3 vs 19.3%.

The analysis of the characteristics of the subjects by period of entry (Tab. II) is statistically significant for all

Table II. Cohort characteristics distributed by period of entry (1978-2014).

	≤ 1989 1990-1994 1995-199 9		-1999	2000	2000-2004 2005-2009		2010-2014		0b ;2				
	Ν	%	Ν	%	N	%	Ν	%	Ν	%	Ν	%	Cni
Total	613	100,0	322	100,0	407	100,0	971	100,0	2,203	100,0	1460	100,0	
Mean age, DS	35,0		40,1		43,8		50,0		51,0		49,3		
≤ 17	59	9,6	5	1,6	13	3,2	14	1,4	20	0,9	14	1,0	p < 0.001
18-29	187	30,5	99	30,7	97	23,8	153	15,8	296	13,4	209	14,3	
30-39	144	23,5	67	20,8	73	17,9	171	17,6	398	18,1	243	16,6	
40-49	127	20,7	56	17,4	78	19,2	167	17,2	416	18,9	330	22,6	
50-64	84	13,7	68	21,1	85	20,9	224	23,1	469	21,3	352	24,1	
>65	12	2,0	27	8,4	61	15,0	242	24,9	604	27,4	312	21,4	
Males	253	41,3	138	42,9	177	43,5	422	43,5	888	40,3	604	41,4	0,586
Females	360	58,7	184	57,1	230	56,5	549	56,5	1315	59,7	856	58,6	
Non-natives	8	1,3	4	1,2	11	2,7	69	7,1	240	10,9	216	14,8	p < 0.001
Lives alone	97	15,8	40	12,4	54	13,3	132	13,6	381	17,3	254	17,4	p < 0.001
With others	386	63,0	250	77,6	301	74,0	761	78,4	1,720	78,1	1,162	79,6	
Facilities	127	20,7	31	9,6	50	12,3	68	7,0	76	3,4	23	1,6	
Other	3	0,5	1	0,3	2	0,5	10	1,0	26	1,2	21	1,4	
Single	299	48,8	134	41,6	184	45,2	319	32,9	707	32,1	463	31,7	p < 0.001
Married	173	28,2	119	37,0	152	37,3	418	43,0	1,032	46,8	716	49,0	
Separate/divorced	88	14,4	38	11,8	40	9,8	100	10,3	221	10,0	141	9,7	
Widower	51	8,3	30	9,3	31	7,6	110	11,3	211	9,6	128	8,8	
Other	2	0,3	1	0,3	0	0,0	24	2,5	32	1,5	12	0,8	
Low educational degree	504	82,2	236	73,3	297	73,0	703	72,4	1,609	73,0	862	59,0	p < 0.001
High educational degree	109	17,8	86	26,7	110	27,0	268	27,6	594	27,0	598	41,0	
Employed	106	17,3	90	28,0	118	29,0	305	31,4	711	32,3	577	39,5	0.000
Not employed	90	14,7	40	12,4	61	15,0	138	14,2	262	11,9	263	18,0	
Retired	330	53,8	130	40,4	163	40,0	357	36,8	799	36,3	392	26,8	
Other working condition	87	14,2	62	19,3	65	16,0	171	17,6	431	19,6	228	15,6	
Schizophrenic Psychosis	202	33,0	74	23,0	79	19,4	83	8,5	100	4,5	25	1,7	p < 0.001
Paranoid state	16	2,6	13	4,0	13	3,2	26	2,7	38	1,7	24	1,6	
Other non organic psychosis	9	1,5	6	1,9	15	3,7	18	1,9	55	2,5	34	2,3	
Major depression	60	9,8	22	6,8	35	8,6	119	12,3	267	12,1	282	19,3	
Bipolar disorder	95	15,5	54	16,8	77	18,9	144	14,8	223	10,1	138	9,5	
Neurotic disorders	96	15,7	75	23,3	93	22,9	269	27,7	827	37,5	455	31,2	
Personality disorders	15	2,4	14	4,3	17	4,2	39	4,0	80	3,6	45	3,1	
Adjustment disorders	11	1,8	6	1,9	12	2,9	43	4,4	214	9,7	280	19,2	
Others psychiatric disorders	2	0,3	0	0,0	5	1,2	6	0,6	28	1,3	20	1,4	
Organic disorders	54	8,8	15	4,7	19	4,7	52	5,4	103	4,7	57	3,9	
Substances use disorders	5	0,8	4	1,2	10	2,5	22	2,3	48	2,2	46	3,2	

	≤ 1	989	1990	-1994	1995	-1999	2000	-2004	2005·	·2009	2010	-2014	06:2
	Ν	%	Ν	%	Ν	%	Ν	%	Ν	%	Ν	%	Chi
Non psychiatric disorders	5	0,8	0	0,0	4	1,0	5	0,5	19	0,9	54	3,7	
Missing diagnoses	43	7,0	39	12,1	28	6,9	145	14,9	201	9,1	0	0,0	
Psychoatherapeutic	76	12,4	39	12,1	50	12,3	80	8,2	158	7,2	104	7,1	p < 0.001
Day care center	9	1,5	9	2,8	10	2,5	10	1,0	17	0,8	4	0,3	p < 0.001
Work transition programs	22	3,6	24	7,5	33	8,1	38	3,9	64	2,9	20	1,4	p < 0.001
Socio-rehabilitative	212	34,6	101	31,4	114	28,0	133	13,7	177	8,0	65	4,5	p < 0.001
RTI	92	15,0	45	14,0	59	14,5	100	10,3	180	8,2	102	7,0	p < 0.001
RTR	39	6,4	20	6,2	20	4,9	35	3,6	45	2,0	25	1,7	p < 0.001
RSR	89	14,5	21	6,5	31	7,6	26	2,7	20	0,9	3	0,2	p < 0.001
SPDC/SPOI	138	22,5	83	25,8	109	26,8	195	20,1	451	20,5	349	23,9	0.006

variables except for the gender analysis. The results obtained highlight that the majority of subjects had a first access to MHC after 2000, with a greater distribution of new cases in the period between 2005 and 2009.

The average age at entry was about 50 years old, while in the past it was lower (35 years before 1989, 40.1 years from 1990 to 1994 and 43.8 years from 1995 to 2000). Also regarding the breakdown by access age, it can be noted that as the years go by, the percentages of the younger groups decrease and those of the older groups increase.

There are more females than males and this remains stable over time. Non-natives are constantly increasing, going from 1.3% in the " \leq 1989" range to 14.8% during 2010-2014.

As for the housing situation, those living with others increased from 63 to 79.6%, while those living in the structures decreased (20.7 to 1.6%).

The unmarried, who before 1989 were almost one in two, become one in three in the last five years of the study; married couples increased from 28.2 to 49%, the separated / divorced decreased slightly (from 14.4 to 9.7%), and the percentage of widows didn't change.

Over time, the level of qualifications increased, before 1989 17.8% of admissions had a high qualification, in the last five years of the study "2009-2014" the percentage doubled (41%). As regards to working conditions, the

employed increased (17.3 vs 39.5%) and retired people decreased (53.8 vs 26.8%).

Access diagnoses changed over time: Monopolar patients increased (9.8 vs 19.3%), as did those with neurotic disorders (15.7 vs 31.2%) and those who had adaptation reactions (1.8 vs 19.2%); bipolar patients decreased (15.5 vs 9.5%) especially after 2000, those with an organic disorder also decreased (8.8 vs 3.9%).

One in five people were admitted to a SPDC/SPOI which did not change over time, while the percentage of all other treatments dropped slightly (Psychotherapeutic, Day Center, Training-Transaction at Work Program, Socio-rehabilitation, RTI, RTR, RSR).

Characteristics of the outcomes of the treatment path

On 31 December 2014 (Tab. III) subjects under treatment were 29.0%, 43.5% had given up, 19.5% had finished the treatment, 4.6% had died and 3.4 had been discharged with other outcomes. No gender differences emerged. Up to 2000, Treatment retention had a percentage of about 40% and settled in the last five years of the study at 30%, it was very low from 2005 to 2009 at 18%. Subjects who completed the treatment plan increased over the last five years of the study.

The evaluation of the outcome of the treatment highlights

	Total		≤ 1989		1990-1994		1995·	·1999	2000	-2004	2005	-2009	2010	-2014
	Ν	%	N	%	Ν	%	Ν	%	Ν	%	Ν	%	Ν	%
Total	5,976	100,0	613	100,0	322	100,0	407	100,0	971	100,0	2,203	100,0	1,460	100,0
In care	1,736	29,0	250	40,8	139	43,2	165	40,5	279	28,7	410	18,6	493	33,8
Conclusion	1,167	19,5	75	12,2	47	14,6	68	16,7	171	17,6	413	18,7	393	26,9
Abandon	2,597	43,5	186	30,3	101	31,4	133	32,7	433	44,6	1,236	56,1	508	34,8
Died	272	4,6	75	12,2	29	9,0	31	7,6	61	6,3	63	2,9	13	0,9
Other	204	3,4	27	4,4	6	1,9	10	2,5	27	2,8	81	3,7	53	3,6

			Conc	lusion	Aba	ndon	l l	Death		Other	
		AP	RR	CI 95%							
	≤ 29	5,496	1		1		1		1		
Entry	30-39	8,773	0,90	0,81-1,00	1,04	0,96-1,13	1,44	1,12-1,83	0,71	0,58-0,88	
age	40-49	10,439	0,88	0,79-0,98	1,14	1,05-1,23	2,13	1,69-2,68	0,66	0,54-0,81	
classes	50-64	13,514	1,02	0,92-1,12	1,28	1,19-1,37	3,17	2,54-3,96	0,48	0,39-0,59	
	≥ 65	10,261	1,26	1,15-1,40	1,89	1,76-2,03	5,12	4,11-6,37	0,72	0,59-0,88	
Entry	≤ 2009	36,025	1		1		1		1		
period	2010- 2014	12,457	1,37	1,29-1,45	0,74	0,70-0,77	0,28	0,24-0,32	0,93	0,81-1,08	
	0-4 anni	19,022	1		1		1		1		
Duration	5-9 anni	11,196	0,80	0,74-0,86	0,67	0,64-0,71	1,21	1,07-1,36	0,86	0,73-1,01	
Duration	10-14 anni	6,995	0,75	0,68-0,82	0,59	0,55-0,63	1,34	1,18-1,53	0,83	0,68-1,01	
	≥ 15 anni	11,270	0,60	0,55-0,65	0,51	0,49-0,54	1,47	1,32-1,64	1,18	1,01-1,38	

Table IV. Rate ratio (RR) of treatment plan outcomes and 95% Confidence Interval (CI 95%) calculated by Poisson multiple regression containing covariates: entry period, age, duration.

four different profiles in relation to the four types (conclusion, abandonment, death in treatment, other).

In the first model (Tab. IV) the analysis concerned the time-dependent variables (age at first consultation, period, duration) and is statistically significant: the risk of concluding increased after the age of fifty, for those who had a recent access in 2010 and decreased with subjects having a longer treatment duration; the risk of dropping out increased with age, in the periods prior to 2009 and decreased with

subjects who have a longer treatment duration; death under treatment had a greater risk for those who entered with an advanced age, but for whom the treatment lasted longer, while it decreased for those who entered after 2010; the risk of having another outcome was lower for people over 65, for those who had an access period after 2010 and for those who had a process that lasted between 5 and 15 years. In the second model (Tab. V) the following sociodemographic variables were analyzed: sex, nationality,

Table V. Rate ratio (RR) of treatment plan outcomes and 95% Confidence Interval (CI 95%) calculated by Poisson multiple regression containing covariates: gender, nationality, civil status, living condition, educational degress, working condition, primary diagnosis and hospitalization in SPDC.

			Conclu	ision	Ab	andon	D	eath	C	ther
		AP	RR	CI 95%	RR	CI 95%	RR	CI 95%	RR	CI 95%
Cov	Male	20,522	1		1		1		1	
Sex	Female	27,961	1,09	1,03-1,16	0,99	0,95-1,03	0,61	0,55-0,66	1,08	0,98-1,20
Non nativos	No	46,337	1		1		1		1	
Non natives	Yes	2,145	1,02	0,89-1,16	1,49	1,39-1,61	0,41	0,29-0,59	1,53	1,27-1,85
	Single	21,160	1		1		1		1	
	Married	17,502	1,46	1,36-1,57	1,25	1,20-1,32	1,13	1,01-1,27	1,04	0,92-1,17
Civil status	Separate/ divorced	5,923	1,06	0,97-1,18	1,17	1,10-1,25	0,97	0,83-1,12	0,93	0,78-1,10
	Widower	3,736	1,44	1,29-1,62	1,44	1,35-1,54	1,23	1,06-1,43	0,88	0,72-1,09
	Other	161	3,17	2,44-4,49	1,11	0,88-1,42	4,82	3,42-6,80	1,80	0,98-3,30
	Alone	6,890	1		1		1		1	
Living	With other	35,445	0,82	0,75-0,89	0,92	0,87-0,98	0,81	0,70-0,94	1,18	1,01-1,39
situation	Facilities	5,843	0,45	0,39-0,52	0,59	0,55-0,65	3,22	2,80-3,71	1,02	0,82-1,26
	Other	304	0,84	0,58-1,23	0,71	0,55-0,93	0,42	0,21-0,82	2,21	1,42-3,45

		ΑΡ	Conclusion		Abandon		Death		Other	
			RR	CI 95%	RR	CI 95%	RR	CI 95%	RR	CI 95%
Educational degree	Low	36,311	1		1		1		1	
	High	12,171	1,04	0,98-1,12	1,01	0,97-1,06	0,68	0,60-0,76	0,79	0,69-0,90
Working condition	Employed	12,794	1		1		1		1	
	Unemployed	7,620	1,00	0,91-1,10	0,75	0,71-0,81	1,83	1,55-2,14	0,84	0,71-0,99
	Retired	20,144	0,94	0,88-1,02	1,01	0,97-1,06	1,66	1,44-1,91	0,85	0,75-0,96
	Other	7,925	0,96	0,88-1,05	0,97	0,92-1,03	1	0,83-1,21	0,92	0,79-1,07
Primary diagnosis	Severe Psychiatric Disorders	26,987	1		1		1		1	
	Minor Psychiatric Disorders	14,442	1,67	1,58-1,79	1,97	1,89-2,06	0,48	0,42-0,54	3,81	3,34-4,35
	Other	4,780	1,95	1,78-2,14	1,82	1,72-1,94	0,45	0,39-0,53	7,06	6,12-8,15
SPDC	No	13,084	1		1		1		1	
	Yes	21,160	0,86	0,81-0,93	0,45	0,43-0,48	0,8	0,71-0,89	0,44	0,38-0,52

marital status, housing situation, qualifications, working conditions, prevalent diagnosis and hospitalization in SPDC.

The risk of completing the treatment process was higher, in a statistically significant way, for females, the married, widows and for those with minor psychiatric disorders or other disorders, while it was lower for those who lived with others or in facilities, for those who were retired and for those who had had at least one hospitalization in the SPDC.

The risk of abandoning the process was higher for those not born in Italy, the married, the separated and the widowed, and for those suffering from minor psychiatric disorders or other disorders; on the contrary, the risk of drop-pot was lower for those who lived in structures or in an undefined housing situations, those who were unemployed and who had had at least one hospitalization in the SPDC.

The risk of death in treatment was higher for the married, widowed, those who lived in a structure, the unemployed, and pensioners; it was lower for females, non-natives, those who lived with others, those with a higher qualification, those suffering from minor psychiatric disorders and those who had had at least one hospitalization in SPDC.

The risk of having an "other" outcome was higher for those not born in Italy, those who lived with others or in structures, those who do not have major psychiatric disorders; while there was a lower risk for those with a higher qualification, those who were unemployed, retirees and those who had had a hospitalization in SPDC.

Conclusions

The evaluation of the effectiveness of the different types of therapeutic interventions offered to patients suffering from mental disorders related to the CSM of Forlì produced specific profiles, depending on the outcome of the clinical approach. The limit of the study is that the outcome is established by the psychiatrist, according to trend of the treatment plan, based not only on objective elements but also subjective elements.

The treatment plans of 5,976 adults, in the period from 1978 to 2014, residing in the Forlì area, were analyzed. The socio-demographic predictors relating to access to services are the fact of having an average age and being married as reported in the literature ^{1,5,6}.

From the analysis by period of entry, it is clear that the majority of subjects had a first access to the CSM after 2000, with a greater distribution of new cases in the period between 2005 and 2009; we could hypothesize that this incidence is determined by an increase in specialist referrals by GPs. This is the result of the Leggieri project, launched in 2004, which has fostered a greater awareness of GPs regarding psychiatric pathologies, through an organizational integration between primary care and psychiatrists of the mental health centers, in order to respond more effectively the person's needs. Another hypothesis that could explain this division is the growing computerization of medical records started in 2006, which has facilitated the compilation of patient records.

Despite the age of the target population of CSM being between 18 and 65 years old, observation of the patient's age at the first access shows a significant percentage of over sixty-fives (one in five); this data is visible from 2000 onwards, a date which coincides with the progressive development of the culture of territorial mental health promotion. This result could on the one hand constitute an attitude of individual and social stigmatization of psychiatric symptoms that are attributed primarily to personal characteristics rather than to psychiatric illnesses, thus delaying the request for help. In literature it is reported that people with a psychiatric pathology preferably turn to other local services before arriving at specialized mental health services ^{1,8}. On the other hand, it is possible to hypothesize a late recognition of the symptoms by the referrers, mostly General Practitioners, who tend to underestimate and misdiagnose the syndromic presentation.

It is also observed that over time the accesses of subjects receiving a diagnosis of "major depression", "neurotic disorders", according with literature ⁹, and adjustment disorders increased; this distribution can be attributed to a growing culture of territorial mental health carried out through public opinion awareness campaigns. This approach is now consolidated and present in some states of Europe and America ⁵. Another possible explanation may be linked to a more specific diagnostic attitude on the part of the psychiatrist.

Regarding the care available, it is important to note a statistically significant reduction over time in rehabilitation hospitalization, going from 14.5% in the period prior to 1989 to 0.2% in the 2000-2004 period. This trend could testify to the progressive cultural change, promoted by the Emilia Romagna Region, in continuity with the "National action plan for mental health" of 2010, according to which inclusion in a facility is no longer a definitive solution for the patient's life, but a temporary therapeutic-rehabilitative programme.

The analysis of the outcomes of the treatment plan shows that a third of the subjects remained in treatment, four out of ten abandoned, and two out of five completed the treatment. Treatment retention appears to have had a decreasing trend, with very low values (18%) from 2005 to 2009, this data corresponds with the increasing practise to conclude treatments according with the "Stepped Care" model diffusion, promoted by the regional program "Giuseppe Leggieri". The model is based on the gradualness of the treatment plan, favouring the integration between general practitioners and the public service and results in the treatment retention of the most serious cases, as reported in the multicentre study of countries belonging to the WHO World Mental Health Survey Consortium¹⁰.

The integrated collaboration with general practitioners is effective on the prevention, but also on the prognosis of mental disorders, as verified in literature especially for major disorders ^{7,8}.

The evaluation of the outcome of the treatment highlights four different profiles of subjects, depending on the type of discharge from the service. The risk of a patient terminating their treatment plan is statistically significantly higher for females, the married, widows and those with minor psychiatric or other disorders and increases after the age of fifty. The latter fact seems to be partly due to the referral to other specialised services for the onset of comorbidities in medical pathologies

Finally, it is noted that patients who had a first access in the period between 2010 and 2014 had a greater risk of completing the plan than those who entered before 2009, this could be attribuited to the presence of a mild psychopathological presentation, which is discharged and sent back to the general practitioner.

References

- ¹ Wang PS, Aguilar-Gaxiola S, Alonso J, et al. Use of mental health services for anxiety, mood, and substance disorders in 17 countries in the WHO world mental health surveys. Lancet 2007;370:841-850.
- ² Liese BH, Gribble R, Wickremsinhe MN. International funding for mental health: a review of the last decade. Int Health 2019;11:361-369. https://doi.org/10.1093/inthealth/ihz040
- ³ Alleva G. La salute mentale in Italia: cosa ci dicono i dati dell'Istat. In paper presentato al XXI Congresso Nazionale della Società Italiana di Psicopatologia. Roma: 2017.
- ⁴ Ministero della Salute. Rapporto salute mentale. Analisi dei dati del Sistema Informativo per la Salute Mentale (SISM). Roma 2017.
- ⁵ Bijl RV, de Graaf R, Hiripi E, et al. The prevalence of treated and untreated mental disorders in five countries. Health Aff (Project Hope) 2003;22:122-133.
- ⁶ Bijl RV, Ravelli A. Psychiatric morbidity, service use, and need for care in the eneral population: results of The Netherlands Mental Health Survey and Incidence Study. Am J Public Health 2000;90:602-607.
- ⁷ SISM Sistema Informativo dei Servizi di Salute Mentale adulti della Regione Emilia-Romagna. Circolare n. 1 del 31/1/2013, Bologna.
- ⁸ Preti A, Rucci P, Santone G, et al; PROGES-acute group. Patterns of admission to acute psychiatric in-patient facilities: a national survey in Italy. Psychol Med 2009;39:485-496.
- ⁹ Fernández A, Haro JM, Martinez-Alonso M, et al. Treatment adequacy for anxiety and depressive disorders in six European countries. Br J Psychiatry 2007;190:172-173.
- ¹⁰ Demyttenaere K, Bruffaerts R, Posada-Villa J, et al; WHO World Mental Health Survey Consortium. Prevalence, severity, and unmet need for treatment of mental disorders in the World Health Organization World Mental Health Surveys. JAMA 2004;291:2581-2590.
- ¹¹ Bower P, Gilbody S, Richards D, et al. Collaborative care for depression in primary care. Making sense of a complex intervention: systematic review and meta-regression. Br J Psychiatry 2006;189:484-493.
- ¹² Saraceno B. Mental health systems research is urgently needed. Int J Ment Health Syst 2007;1:2.