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Brief review

WHY IS IT IMPORTANT TO STAGE CASES OF SCHIZOPHRENIA?

Mark Agius[1,2], Michaela Agius[3] & Anton Grech[3]

[1]Psychiatric Studies Centre "CenStu.Psi", Provaglio d'Iseo (BS), Italy
[2]One time Clare Research Associate University of Cambridge, Cambridge, UK
[3]University of Malta, Msida, Malta

SUMMARY

In this article, we describe why we consider it important to stage cases of schizophrenia. Treatment in the three stages of Schizophrenia, that is: the At risk Mental State; the first episode and three year critical period; and the phase of Chronic Schizophrenia is different. We also describe how MRI studies provide the view of anatomical changes which underpin the stages.

Key words: *At risk Mental State - first episode of psychosis - critical period - Chronic Schizophrenia - MRI studies*

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INTRODUCTION

When dealing with an illness such as schizophrenia, which develops over time, and therefore may present differently at different points in its trajectory, it is important that patients are treated appropriately according to the symptoms that they present at the appropriate time in that Trajectory. This is the basis of the concept that we have advocated of staging the illness (Agius et al. 2010, 2023, 2024).

The purpose of this talk, which is a memoire rather than a formal presentation, is to explain how the idea of staging first developed in our group.

That the illness of schizophrenia develops over time did not begin with ourselves. Professor Max Birchwood at the North Birmingham NHS Trust had been pointing this out for a long time (IRIS Guidelines 1998). In the meantime, Pat McGorry in Melbourne, Australia had been researching the earliest manifestations of psychotic illness (McGorry 2002).

The treatment of patients with psychotic illness includes not only medication but also psychological treatment as well as the dealing with the housing, financial and other social needs of the patient (IRIS Guidelines 1999). It is very evident that, while all patients who have a psychotic illness will have all these needs, the requirements of a patient who only had the prodrome of a psychosis were totally different from those with a first full episode of psychosis, and again were totally different from patients who had well established schizophrenia.

THREE SCENARIOS

Thus the dose of medication in the three scenarios was completely different (in the case of the prodrome, the use of medication is still debated, first episodes require sufficient medication to safely and effectively treat the patient while patients with established schizophrenia could require depot medication or higher doses of oral medication) and the appropriateness and type of psychological treatment also varies between the three scenarios mentioned (IRIS Guidelines 1998).

This is also because the aim of treatment between the three scenarios mentioned is different. In Prodromal psychosis, the aim is to prevent the full development of Psychosis. In First episodes of psychosis the aim is to fully abort the symptoms of Psychosis and return the patient to normal functioning, while in fully developed schizophrenia, the aim of treatment is to restore functioning to the best degree possible and to improve deficits in functioning, including cognitive functioning (IRIS Guidelines 1998).

Thus, from the points of view of presentation of illness, of aims of treatment and of effectiveness and appropriateness of treatment, it was becoming obvious that there were three successive phases of psychotic illness, the prodrome, otherwise known as the "at risk mental state", the first episode, and subsequent episodes or the chronic phase, which differed in presentation, aims of treatment, and types of treatment (IRIS Guidelines 1998).

CRITICAL PERIOD

Furthermore, much evidence has accumulated that the First three years of psychosis are a critical period for the patient. Thus, from a social point of view, they affect young people at a key time for establishing social capital to draw on for their futures. The longer these developmental processes are compromised the worse the personal and social consequences (IRIS Guidelines 1998, 2012). From a psychological point of view, the experience of psychosis is traumatic and drives disabling psychological responses; accumulative cognitive disturbance. These are the psychological causes of disability; the longer they persist the more pervasive and enduring their effects will be (IRIS Guidelines 1998, 2012). From a biological point of view, structural brain changes have been found to appear very early in the illness. These changes, whether the cause-of or caused-by the illness process, need to be curtailed as soon as possible (IRIS Guidelines 1998, 2012).

Therefore, for several years, in the 1990s, It had become clear that there was a need to begin to describe Psychotic illness, or, indeed Schizophrenia, as at least three stages, the Prodrome or " At Risk Mental State", the first Episode, and the three years directly after this, which is a critical period in the illness, and a chronic phase, when schizophrenia had developed, and disabilities existed and persisted.

Describing these three stages made it possible to describe different forms of treatment for the different stages of the illness, and thus to use treatment in order to modify and improve the outcome of the illness (IRIS Guidelines 1998, 2012). This was the aim of describing the illness in different stages.

AT RISK MENTAL STATE

One should note that rather than describing the first stage as the prodrome , it was preferred to describe it as an "At risk mental state", because the patient was indeed at risk of developing a psychotic illness and treatment alleviated this risk, perhaps preventing the development of psychotic illness all together, or at least modifying the symptoms (IRIS Guidelines 1998, 2012).

DURATION OF UNTREATED PSYCHOSIS

Furthermore, the first episode and the three years after it, is a critical period, where the treatment will be different from the previous stage, but will also, if treatment is started effectively early within that period, the course of the illness could still be modified, but unfortunately, many patients present late in the critical period of the first three years, so that they suffer a long Duration of Untreated Psychosis (Novak Sarotar 2008a,b, Howes 2021), so that opportunity to modify the illness is progressively lost (IRIS Guidelines 1998, 2012).

THREE STAGES

The consequence of the above facts is that it became clear that, from a clinical point of view it became important to describe three stages in the development of Psychotic illness; Prodrome or " At Risk Mental State", the first Episode , and the three years directly after this, which is a critical period in the illness, and a chronic phase. Professor Pat McGorry in Melbourne Produced a number of papers advocating this view (McGorry 2010, 2006, 2007).

When writing the forward to the updated IRIS guidelines he pointed out the important clarification that the stage approach to schizophrenia had brought to light; " One of the best demonstrations of the stage specific principle is that in early psychosis much lower doses of antipsychotic medication are essential and that the second generation antipsychotic medications are generally superior because of a lower level of adverse effects and better adherence. The EUFEST study and other evidence supports this advantage which is not usually seen in later stages of illness. This distinction between early and late psychosis needs to be acknowledged more widely – one size does not fit all! However the metabolic problems which are usually increased by both first and second generation medications at similar rates must also be tackled from the very first episode, as the new IRIS guidelines emphasise strongly." (IRIS Guidelines 2012).

Optimized Medication needs to be accompanied by social, family and psychological interventions, continued Prof. Mc Gorry "A comprehensive array of individual, family and vocationally focused interventions must be on offer within an optimistic and intensive program of care." (IRIS Guidelines 2012).

Furthermore, as services evolve it has become more evident that the more assertive services which the new Early Intervention services, which work in the second stage of psychotic illness, that is, the first episode and the critical period of the first three years after the first episode may need to be extended further, to five years. Professor Mcgorry Continued " Recent evidence shows that the tenure of care within EIP services for most patients needs to be longer than two years and probably closer to five years, with a minority only then requiring sustained intensive care for even longer. Premature discharge to traditional adult community mental health teams has been shown to adversely affect outcomes and blending these types of services, an attractive option financially to health service managers, is clearly not in the interests of patients and families, as the evidence now confirms." (IRIS Guidelines 2012).

Unfortunately the serious incidents which occur when this guidance is not followed, two of which are detailed as a poster in this conference, illustrate the unfortunate consequence when this advice is not followed (Agius et al. 2025).

ANATOMICAL-PATHOLOGICAL STAGING - MRI

However, while the development of a staging system for schizophrenia or psychotic illness needs to be comparable to staging systems for other illnesses. It needs to be underpinned by demonstrable changes in the anatomy and pathology of the subject as the illness progresses. Thus Staging for Cancer is shown by the progress of the disease from simply being in the affected organ, to regional lymph-nodes, and finally to other organs (cancer.gov 2022).

It is not possible to carry out a similar system with the brain, because of the inaccessibility of the organ and the ethical inappropriateness of taking brain biopsies, but MRI imaging has enabled us to demonstrate the development of the illness pathologically in terms of

both deterioration of gray, and also of white Matter. Such demonstration of the deteriorating abnormality of in particular white matter underpins the observation of the clinical stages which we have described.

This began with the groundbreaking study of 2003 in which Pantelis et al demonstrated that patients with an "at risk mental state " who developed psychosis had less grey matter in the right medial temporal, lateral temporal, and inferior frontal cortex, and in the cingulate cortex bilaterally. When re-scanned to observe longitudinal change, individuals who had developed psychosis showed a reduction in grey matter in the left parahippocampal, fusiform, orbitofrontal and cerebellar cortices, and the cingulate gyrus, while, in those individuals who did notdevelop psychosis, longitudinal changes were restricted to the cerebellum (Pantelis 2003, 2006).

Equally, Meisenzahl et al. demonstrated showed gray matter volume reductions in individuals with an "at risk mental state " in the frontal, lateral temporal and medial temporal regions compared to a healthy control group (Meisenzahl et al. 2008).

Subsequent work from the Pantelis and Meisenzahl (2008) groups demonstrated the changes as patients developed from "at risk mental states " to full Psychosis, thus Pantelis reported; "These aberrant changes are observed most prominently in medial temporal and prefrontal lobe regions. In a further series of longitudinal studies in first-episode psychosis, we have identified changes in prefrontal regions that indicate an accelerated loss of grey matter in patients compared to healthy control subjects. We suggest that the available evidence is consistent with the presence of subtle regionally and temporally specific neurobiological changes through the course of psychosis including: (1) evidence for early (pre- and peri-natal) neurodevelopmental anomalies, (2) evidence for progressive grey matter loss involving medial temporal and orbital prefrontal regions around the time of transition to illness, and (3) evidence of late (post-pubertal) neurodevelopmental changes soon after the onset of psychosis, involving an acceleration of normal brain maturational processes, associated with significant loss of grey matter in dorsal prefrontal regions." (Pantelis 2006, 2007) and "Based on our review of recent findings, we suggest that the onset of psychosis is a time of active brain changes, wherein, for a proportion of individuals, (i) an early (pre- and perinatal) neurodevelopmental lesion renders the brain vulnerable to anomalous late (particularly postpubertal) neurodevelopmental processes, as indicated by evidence for accelerated loss of gray matter and aberrant connectivity particularly in prefrontal regions; and (ii) these anomalous neurodevelopmental processes interact with other causative factors associated with the onset of psychosis (e.g., substance use, stress, and dysregulation of the hypothalamic-pituitary-adrenal axis function), which together have neuroprogressive sequelae involving medial temporal and orbital prefrontal regions, as suggested by imaging studies around transition to active illness." (Pantelis 2005).

Similar Changes were tracked using brain retraction techniques by Sun et al. (2009a,b).

Further work by Takahashi et al indicated that there were grey matter reductions of the superior temporal gyrus are present before psychosis onset (Takahashi 2009), and that there was progressive gray matter reduction of thesuperior temporal gyrus during transition to psychosis (Takahashi 2009). Thus, Takahashi reported " A progressive process in the superior temporal gyrus precedes the first expression of florid psychosis; In cross-sectional comparisons, only the FEP group had significantly smaller planum temporale and caudal superior temporal gyrus than other groups at baseline, whereas male UHRP subjects also had a smaller planum temporale than controls at follow-up. In longitudinal comparison, UHRP and FEP patients showed significant gray matter reduction (approximately 2-6% per year) in the planum polare, planum temporale, and caudal region compared with controls and/or UHRNP subjects. The FEP patients also exhibited progressive gray matter loss in the left Heschl gyrus (3.0% per year) and rostral region (3.8% per year), which were correlated with the severity of delusions at follow-up" Hence, research had come to the state where underlying neurobiologic features of emerging psychotic disorders were beginning to be linked with specific symptoms such as delusions (Takahashi 2009).

The Meisenzahl group were also able to demonstrate progressive grey matter volume changes as patients developed across the "at risk mental state", "first episode" and chronic schizophrenia stages (Meisenzahl 2006, 2008a,b).

Regarding Chronic Sczophrenia, Velakoulis (2002) had found that in patients with chronic schizophrenia, a longer duration of illness is associated with a significant decrease in grey matter volume in the right medial temporal/anterior cingulate region of the brain (Velakoulis 2002).

Velakoulis et al. (2006) studied the changes in hippocampal and amygdala volumes in different stages of psychosis, that is,ultra-high risk for psychosis, first episode of psychosis and chronic schizophrenia. They found that chronic schizophrenia was associated with bilateral hippocampal volume reduction, while first-episode schizophrenia showed left hippocampal volume reduction (Velakoulis 2006). Amygdala volume enlargement was specifically identified in first-episode patients with non-schizophrenic psychoses. Thus again there were different anatomical findings in different stages of psychosis (Velakoulis 2006).

While grey matter changes during the development of psychosis are the most studied, white matter changes also occur. In one study, individuals who later developed psychosis were found to have larger volumes of

white matter in the frontal lobe, especially in the left hemisphere (Walterfang 2008). Individuals who developed psychosis demonstrated a reduction in white matter volume in the region of the left fronto-occipital fasciculus (Walterfang 2008). Participants who did not develop psychosis showed no reductions in white matter volume but white matter increases in a region subjacent to the right inferior parietal lobule (Walterfang 2008). The reduction in volume of white matter near the left fronto-occipital fasciculus may reflect a change in this tract which is associated with the onset of frank psychosis (Walterfang 2008).

Thus it became clear that, across different research groups, there was a consensus that anatomical changes, especially grey matter changes, could be linked with different stages of psychotic illness, and even sometimes with particular symptoms.

Hence it appeared possible to talk, on both clinical and anatomical grounds of different stages of the disease.

TRAJECTORY OF ILLNESS

However, as one stage merged into another, it was also reasonable to also describe a trajectory of the psychotic illness, a term often used today. Thus Pantelis said, "The pathological processes underlying such changes remain unclear and may reflect anomalies in genetic and/or other endogenous mechanisms responsible for brain maturation, the adverse effects of intense or prolonged stress, or other environmental factors. These findings suggest that early markers of impending illness may prove difficult to define, and that brain changes in psychosis may better be conceptualized as anomalous trajectories of brain development." (Pantelis 2007). We also use the idea of a trajectory of the psychotic illness (Agius et al. 2024), but within it we attempt to describe the point at which the particular illness is, by deciding the stage of the illness.

In Summary, longitudinal magnetic resonance imaging findings in individuals at ultrahigh risk for developing a psychotic illness show that there are excessive neuroanatomical changes in those who convert to psychosis. These aberrant changes are observed most prominently in medial temporal and prefrontal cortical regions (Wood 2008).

CONCLUSION

Ultimately, the primary value of staging in schizophrenia lies in its ability to characterise the progression of the disorder over time, thereby offering insight into the patient's longitudinal clinical course. This framework is essential for guiding the development of a comprehensive treatment strategy, encompassing pharmacological, psychological, and social interventions, tailored to the individual's current needs. Additionally, neurobiological research, particularly regarding grey and white matter changes observed through MRI, relies heavily on accurate staging to interpret findings across different phases of the illness. By mapping the trajectory of schizophrenia through staging, clinicians and researchers gain a clearer understanding of associated risks and the likely future course of the condition.

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References

1. *Agius M, Goh C, Ulhaq S, Mcgorry PD: The staging model in schizophrenia, and its clinical implications. Psychiatr Danub 2010; 22:211–220*
2. *Agius M, Agius M, Grech A: The Concept of Staging in Schizophrenia; 13 Years After the 'Agius Conceptof Staging'. Psychiatr Danub 2023; 35(Suppl. 2):4-24*
3. *Agius M, Agius M, Grech A: Assessing the Trajectory of Schizophrenia Effectively in Order to Treat Effectively. Psychiatr Danub 2024; 36(Suppl. 2):40-51*
4. *Agius M, Agius M, Grech A: The death of victims as a result of schizophrenia or other serious mental illness; what have we learnt over the years? Psychiatr Danub 2025; in press*
5. *Cancer Staging in https://www.cancer.gov/about-cancer/diagnosis-staging/staging last updated 2022*
6. *Howes OD, Whitehurst T, Shatalina E, Townsend L, Chika Onwordi E, Lun Allenis Mak T, Arumuham A, O'Brien O, Lobo M, Luke Vano L, Zahid U, Butler E, Osugo M: The clinical significance of duration of untreated psychosis: an umbrella review and random-effects meta-analysis. World Psychiatry 2021; 20;75–95*
7. *IRIS Guidelines: North Birmingham Mental Health Trust, 1998*
8. *IRIS Guidelines Update September 2012*
9. *McGorry PD, Killackey EJ: Early intervention in psychosis: a new evidence based paradigm. Epidemiologia e Psichiatria Sociale 2002; 11: 237–247*
10. *McGorry PD: Staging in Neuropsychiatry: A heuristic model for understanding, prevention and treatment. Neurotox Res 2010 Apr 3*
11. *McGorry PD, Hickie IB, Yung AR, Pantelis C & Jackson HJ: Clinical staging of psychiatric disorders: a heuristic framework for choosing earlie r, safer and more effective interventions. Australian and New Zealand Journal of Psychiatry 2006; 40:616-22*
12. *McGorry PD, Purcell R, Hickie IB, Yung AR, Pantelis C, Jackson HJ: Clinical staging: a heuristic model for psychiatry and youth mental health. Medical Journal of Australia. 2007 1;187(7 Suppl):S40-2*
13. *Meisenzahl EA et al.: Neuroplasticity in Brain Structure ofpatients with schizophrenia: a 6 year Follow-up MRIstudy. The second dual congress on Psychiatry and the Neurosciences. Book of abstracts. Athens 2006; 69*

14. *Meisenzahl EM, Koutsouleris N, Gaser C, Bottlender R, Schmitt GJ, McGuire P, Decker P, Burgermeister B, Born C, Reiser M & Möller HJ: Structural brain alterations in subjects at high-risk of psychosis: a voxel-based morphometric study. Schizophrenia Research 2008; 102:150-62*
15. *Meisenzahl EM, Koutsouleris N, Bottlender R, Scheuerecker J, Jäger M, Teipel SJ, Holzinger S, Frodl T, Preuss U, Schmitt G, Burgermeister B, Reiser M, Born C & Möller HJ: Structural brain alterations at differents tages of schizophrenia: a voxel-based morphometric study. Schizophrenia Research 2008; 104:44-60*
16. *Novak Sarotar B, Blinc Pesek M, Agius M, Pregelj P, Kocmur M: Duration of untreated psychosis and it's effect on the functional outcome in schizophrenia - preliminary results. Psychiatr Danub 2008; 20:179-83*
17. *Novak Sarotar B, Pesek MB, Agius M & Kocmur M: Duration of untreated psychosis and it's effect on the symptomatic recovery in schizophrenia – Preliminary results. Neuro Endocrinology Letters 2008; 29:990-4*
18. *Pantelis C, Velakoulis D, McGorry PD, Wood SJ, Suckling J, Phillips LJ, Yung AR, Bullmore ET, Brewer W, Soulsby B, Desmond P, McGuire PK: Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison.Lancet 2003; 25;361(9354):281-8*
19. *Pantelis et al.: The Neurodevelopmental Perspective of Schizophrenia; A reassessment. The second dual congresson Psychiatry and the Neurosciences. Book of abstracts. Athens 2006; 64*
20. *Pantelis C, Velakoulis D, Wood SJ, Yücel M, Yung AR, Phillips LJ, Sun DQ & McGorry PD: Neuroimaging andemerging psychotic disorders: the Melbourne ultra-highrisk studies. International Review of Psychiatry 2007; 19:371-81*
21. *Pantelis C, Yücel M, Wood, SJ, Velakoulis, D, Sun D, Berger G, Stuart GW, Yung A, Phillips L & McGorry P: Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. Schizophrenia Bulletin 2005; 31:672-696*
22. *Sun D, Phillips L, Velakoulis D, Yung A, McGorry PD, Wood SJ, van Erp TG, Thompson PM, Toga AW, Cannon TD & Pantelis C: Progressive brain structural changes mapped as psychosis develops in 'at risk' individuals. Schizophrenia Research 2009; 108:85-92*
23. *Sun D, Stuart GW, Jenkinson M, Wood SJ, McGorry PD, Velakoulis D, van Erp TG, Thompson PM, Toga AW, Smith DJ, Cannon TD & Pantelis C: Brain surface contraction mapped in first-episode schizophrenia: a longitudinal magnetic resonance imaging study. Molecular Psychiatry 2009; 14:976-86*
24. *Takahashi T, Wood SJ, Yung AR, Walterfang M, Phillips LJ, Soulsby B, Kawasaki Y, McGorry PD & Suzuki M: Superior temporal gyrus volume in antipsychotic-naive people at risk of psychosis. British Journal of Psychiatry. 2010; 196:206-11*
25. *Takahashi T, Wood SJ, Yung AR, Soulsby B, McGorry PD, Suzuki M, Kawasaki Y, Phillips LJ, Velakoulis D & Pantelis C: Progressive gray matter reduction of thesuperior temporal gyrus during transition to psychosis. Archives of General Psychiatry 2009; 66:366-76*
26. *Velakoulis D, Wood SJ, Wong MT, McGorry PD, Yung A, Phillips L, Smith D, Brewer W, Proffitt T, Desmond P & Pantelis C: Hippocampal and amygdala volumes according to psychosis stage and diagnosis: a magnetic resonance imaging study of chronic schizophrenia, first-episode psychosis, and ultra-high-risk individuals. Archives of General Psychiatry. 2006; 63:139-49*
27. *Velakoulis D, Wood SJ, Smith DJ, Soulsby B, Brewer W, Leeton L, Desmond P, Suckling J, Bullmore ET, McGuire PK, Pantelis C: Increased duration of illness is associated with reduced volume in right medial temporal/anterior cingulate grey matter in patients with chronic schizophrenia. Schizophr Res 2002; 57:43-9*
28. *Walterfang M, McGuire PK, Yung AR, Phillips LJ, Velakoulis D, Wood SJ, Suckling J, Bullmore ET, Brewer W, Soulsby B, Desmond P, McGorry PD, Pantelis C: White matter volume changes in people who develop psychosis. Br J Psychiatry 2008; 193:210-5*
29. *Wood SJ, Pantelis C, Velakoulis D, Yücel M, Fornito A & McGorry PD: Progressive changes in the development toward schizophrenia: studies in subjects at increased symptomatic risk. Schizophrenia Bulletin 2008; 34:322-9*

Correspondence:
Mark Agius, MD
"Psychiatric Studies Center" (Cen.Stu.Psi.)
Piazza Portici, 11, 25 050 Provaglio d'Iseo (BS), Italy
E-mail: mark.agius 52@ gmail.com