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Counter point

Schizophrenia: A developmental disorder with a risk of non-specific but avoidable decline

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ABSTRACT

The onset of schizophrenia is determined by biological and social risk factors operating predominantly during development. These result in subtle deviations in brain structure and cognitive function. Striatal dopamine dysregulation follows, causing abnormal salience and resultant psychotic symptoms. Most people diagnosed as having schizophrenia do not progressively deteriorate; many improve or recover. However, poor care can allow a cycle of deterioration to be established, stress increasing dopamine dysregulation, leading to more stress consequent on continuing psychotic experiences, and so further dopamine release. Additionally, long-term antipsychotics can induce dopamine supersensitivity with resultant relapse and eventually treatment resistance. Some patients suffer loss of social and cognitive function, but this is a consequence of the hazards that afflict the person with schizophrenia, not a direct consequence of genetic predisposition. Thus, brain health and cognition can be further impaired by chronic medication effects, cardiovascular and cerebrovascular events, obesity, poor diet, and lack of exercise; drug use, especially of tobacco and cannabis, are likely to contribute. Poverty, homelessness and poor nutrition which become the lot of some people with schizophrenia, can also affect cognition. Regrettably, the model of progressive deterioration provides psychiatry and its funders with an alibi for the effects of poor care.

1. The present status of the neurodevelopmental hypothesis

The idea that psychosis with early onset has a neurodevelopmental origin was suggested by the Scottish psychiatrist Thomas Clouston (1891; O'Connell et al., 1997), and as Stone et al. (2022) note, was also advocated by Southard (1915). Thereafter it was forgotten. The neurodevelopmental hypothesis that re-emerged (Murray and Lewis, 1987; Weinberger, 1987) proposed that schizophrenia originates from perturbed development of the nervous system in fetal or neonatal life. Subsequently, numerous epidemiological studies demonstrated a) an excess of pregnancy and perinatal complications in people with schizophrenia (Davies et al., 2020) and b) cognitive, emotional and behaviour deviations from the norm in preschizophrenic children (Jones et al., 1994; Khandaker et al., 2011).

However, only a minority of people diagnosed as having schizophrenia show evidence of aberrant neurodevelopment (Murray et al., 2017). Furthermore, certain environmental factors increase the risk of schizophrenia: childhood trauma, being a member of an ethnic minority, living in an inner city, and abuse of certain drugs (Stilo and Murray, 2019).

Thus, schizophrenia is not a simple neurodevelopmental disorder, at least not in the sense that autism spectrum disorder (ASD) or learning disability are; rather neural factors interact with social and drug risk factors. The original hypothesis has therefore morphed into the "developmental risk factor model" which encompasses both biological and social risk factors (Murray et al., 2017). Deficits in neuro- and social cognition, secondary to subtly compromised neural networks, set some children on a course of increasing asociality, isolation, and cognitive difficulties. Increasing deviance occurs, and finally drug abuse, or exposure to intrusive life events, result in dysregulated dopamine release, increased salience and frank psychosis (Howes and Murray, 2013).

Whether or not onset of psychosis results a single or multiple episodes depends on subsequent events. Most people diagnosed as having schizophrenia do not progressively deteriorate; many improve or recover (Bleuler, 1978). Indeed, a series of papers have suggested that the outlook is much better than had hitherto been supposed (Albert et al., 2011; Austin et al., 2013; Zipursky et al., 2013; Lally et al., 2017;

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O'Keafe et al., 2019). For example in the AESOP study, 19% of those initially diagnosed as having schizophrenia, had no psychotic symptoms and were no longer taking antipsychotics ten years after onset; a further 20% had no psychotic symptoms but were receiving antipsychotics (Morgan et al., 2014).

1.1. Dopamine dysfunction

Developmental alterations in glutamate and in GABAergic inhibitory interneuron function are regarded by many as the neurochemical mechanisms underlying neurodevelopmental deviance in schizophrenia (Beneyto and Lewis, 2011; Marin, 2016). These facilitate the increased synthesis of striatal dopamine found in schizophrenia which is widely regarded as causing a) the attribution of salience to irrelevant stimuli and resultant positive symptoms, and b) the reward processing dysfunction underlying negative symptoms. The dysfunction appears to be centred in the striatum during the early stages of psychosis. At this point, blockade of the dopamine D2 receptor can normalize learning-related brain signals such as prediction error, thus decreasing positive symptoms. Initially the cortex appears relatively spared but cortical abnormalities become more prominent in those patients in whom the illness becomes more chronic (Kesby et al., 2021), a process mimicked in the animal studies of Kellendonck et al. (2006). Eventually, this process can hardwire the psychotic interpretation into fixed delusions, which are relatively resistant to dopamine blockade.

Stone et al. (2022) remind us that first-episode patients require much lower doses of antipsychotics than patients with chronic schizophrenia. They conclude that this "suggests continued illness progression and the emergence of treatment resistance after the first episode." However, there is an alternative explanation. Animal studies show that when given chronically, antipsychotics effectively block dopamine D2 receptors for only a relatively short period; this is then followed by D2 receptor upregulation, and what Samaha et al. (2007) called "breakthrough" dopamine supersensitisation; increasing the dose reinstates the blockade temporarily. It seems likely that a similar process occurs in at least some patients treated with chronic psychosis. Servonnet and Samaha (2020) conclude that "In patients with schizophrenia, this dopamine supersensitivity could compromise treatment efficacy, promote relapse to psychosis and trigger movement disorder".

2. Cognition

2.1. Developmental deviance

Cognitive deficit is found at the onset of schizophrenia (Zanelli et al., 2010) and in those at clinical high-risk (CHR) of the disorder (Catalan et al., 2021); children destined to develop schizophrenia show, on average, IQ below that of the general population (Jones et al., 1994: Reichenberg et al., 2010). In a small number of cases, however, this latter can be directly attributed to the presence of a copy number variant (CNV) (Kirov, 2015; Thygesen et al., 2021). Hubbard et al. (2021) found that cognitive ability in CNV carriers was 0.5–1.0 standard deviations below that of non-carriers, with the greatest reductions seen in carriers of CNVs spanning loss-of-function intolerant genes.

Although CNVs are rare, low childhood IQ operates in the general population to increase risk of later psychosis (David et al., 1997; Khandaker et al., 2011). Furthermore, genetic studies have shown that premorbid IQ in schizophrenia is largely determined by the same multiple genetic influences that determine IQ in the rest of the population (Richards et al., 2020; Van Os, 2020: Legge et al., 2021), while IQ after onset is influenced by a modest additional effect of the polygenic risk for schizophrenia (PRS-SZ) Legge et al. (2021) state "The latter could affect cognitive ability via processes intrinsic to schizophrenia pathophysiologic factors and/or via consequences of having schizophrenia, such as medication effects or social isolation". Another developmental factor which can impair cognition in schizophrenia is obstetric complications (Wortinger, 2020: Teigset et al., 2020).

Developmental cognitive impairment is characterized by difficulty in acquiring cognitive skills (Bora, 2015). In individuals with severe neurodevelopmental abnormalities, cognitive dysfunction is apparent from early childhood; in those who have a lesser abnormality, cognitive dysfunction can manifest as a failure to acquire more advanced cognitive skills later, in the second decade of life following normal earlier development. This can be seen in relation to certain CNVs which in highly-penetrant form result in intellectual disability, in less penetrant form in ASD, and in lesser extent again in schizophrenia. This suggested to Owen et al. (2011) that schizophrenia sits at the milder end of a neurocognitive continuum of genetic risk. The widening gap over time in cognitive abilities between pre-psychotic individuals and healthy controls due to slower gain is highly suggestive of a neurodevelopmental process (Reichenberg et al., 2010); as is the lack of evidence for loss of acquired cognitive skills during the premorbid period.

2.2. After onset

Deficits in executive functions have frequently been reported to be more severe in chronic than first-episode schizophrenia (Stone et al., 2022) However, those cross-sectional comparisons ignore the fact that the chronic patients are frequently selected as samples of convenience from those attending clinics or in hospital. A proportion of those patients who presented at onset will have improved, and been discharged to the care of their family doctors; therefore they are not included in the sample. Since these patients are likely to show better cognitive function, this accounts for some of the disparity between first episode and chronic psychosis.

Bora and Murray (2014) carried out a meta-analysis of cognitive studies which followed up first-episode patients for up to 5 years. There was no evidence of overall cognitive decline. A few longer duration studies have subsequently been reported. Our AESOP follow-up (Zanelli et al., 2019) reported a small decline in cognition in schizophrenia (e.g. mean IQ loss = 2.8) over a decade. Because decline was also seen in other psychoses (predominantly affective) which are not generally thought to be neurodegenerative, this is most likely due to non-specific effects related to illness. Unfortunately we were not able to take into account effects of antipsychotics, anticholinergics, or anxiolytics nor continued drug abuse.

The Suffolk County follow-up study showed that in individuals with psychotic disorders, most cognitive functions showed declines which were "small to moderate in size" 2 decades after first hospitalization (Fett et al., 2020). As in the AESOP study declines were found in both non-affective and affective psychoses, again suggesting non-specific effects. Again, no account could be taken of the effects of drug consumption, licit or illicit.

Velthorst (2020) studied 2883 patients with psychotic disorders and 3301 controls, having attempted to obtain representative samples. As expected, patients with psychosis showed modest-to-large cognitive impairment compared with controls. But age and stage of illness had little effect, arguing against deterioration. Furthermore, the deficits were substantially reduced when the authors took into consideration symptoms and global functioning, while effects of antipsychotics appeared to account for half of the impairment in patients. Similarly, Husa et al. (2017) showed an association between cumulative lifetime antipsychotic dose and global cognition in schizophrenia patients.

As patients with treatment resistant schizophrenia show greatest cognitive impairment (Millgate et al., 2022) they might be considered likely to have shown progressive cognitive impairment. However, in the AESOP study, Kravariti et al. (2019) went back to assessments carried out at first onset and found that treatment resistant patients already showed much poorer cognition than those who were treatment responsive. The conclusion was that the impaired cognition most likely had a neurodevelopmental origin.

2.3. Dementia

There are reports suggesting that Individuals with schizophrenia have an increased risk of dementia (Brown and Wolf, 2018; Stroup et al., 2021). Jonas et al. (2021) have speculated that excess of dementia may be due to antipsychotics. Also a recent large study has also shown the impairing effects on memory of anticholinergics and suggested that their chronic use may induce dementia (Joshi et al., 2021).

Stone et al. interpreted the excess of dementia as indicating neurodegeneration. However, people with lower childhood IQ have lower cognitive reserve and are prone to develop cognitive deficits earlier than the general population, despite having the same amount of neurodegenerative changes (Chung et al., 2016; Nyberg et al., 2014). ASD is also associated with a higher prevalence of dementia compared to the general population (Vivanti et al., 2021).

Individuals with Down Syndrome (DS) develop dementia at an earlier age than the general population (Takenoshita et al., 2020). However, to date, there is no evidence for a schizophrenia-related genetic abnormality associated with both neurodevelopmental abnormality and pathology of a non-Alzheimer neurodegenerative dementing disorder, as in DS. Indeed, the most powerful evidence against people with schizophrenia being predisposed to progressive cognitive decline comes from studies of the polygenic risk score for schizophrenia (PRS-SZ) in the general population. For example, Kepinska et al. (2021) investigated the relationship of cognitive decline in 6817 adults aged >50 years to the schizophrenia polygenic score (PRS-SZ) over a 10-year follow-up. The PRS-SZ was associated with a stable deficit but not progressive cognitive decline; i.e., compatible with a neurodevelopmental but not neurodegenerative explanation. Again, Zhang et al. (2021) who studied associations of PRS-SZ in 400,000 people of average age 56 years found no association with dementia.

3. Neuroimaging

3.1. In development

Subtle brain abnormalities are present at, and even precede, illness onset (Rapoport et al., 2012). Two neurodevelopmental windows have been suggested as critical for schizophrenia: a fetal/early infancy period initially postulated to establish vulnerability (Murray and Lewis, 1987; Weinberger, 1987), and an adolescence/young adult period, during which conversion from vulnerability to psychosis occurs (Keshavan et al., 1994; Meyer and Lee, 2019).

The decreases in grey matter (GM) observed in the adolescent years of childhood onset schizophrenia (COS) patients become localised to prefrontal and temporal cortices by age 20, consistent with adult studies (Greenstein et al., 2006). Abnormal hippocampal development was linked to global functioning deficits and more severe negative symptoms by prospective investigation of COS patients, each with three or more MRI scans (Anvari et al., 2015). The mega-analysis from the ENIGMA early-onset psychosis group, including 263 COS patients and 359 healthy controls, identified a similar pattern of brain alterations in COS as observed in adult-onset psychosis, but with notably lower intracranial volume, suggesting disrupted neurodevelopment (Thompson et al., 2020; Gurholt et al., 2018). These observations strongly suggest that neuroanatomical abnormalities are present very early in life in some individuals who later develop schizophrenia.

Research on the second critical developmental period, the adolescent/young adult period, has focussed particularly on those at Clinical High Risk (CHR) for psychosis. The large meta-analysis by the ENIGMA-CHR consortium evidenced widespread lower cortical thickness in individuals at CHR, and similar abnormalities in CHR individuals who subsequently developed psychosis to those previously reported in psychosis samples (Jalbrzikowski et al., 2021).

3.2. Onset and after

In adult-onset schizophrenia, ENIGMA consortium studies have shown widespread reductions in cortical thickness and surface area (van Erp et al., 2018), subcortical volumes (van Erp et al., 2016), and white matter microstructure (Kelly et al., 2018). The changes found at first-onset (Falkenberg et al., 2017) are similar to those found in association with CNVs (Warland et al., 2020) and in those adults who were born premature or suffered prenatal hypoxia (Vanes et al., 2021). A systematic review (Costas-Carrera et al., 2020) examined people with schizophrenia who had suffered obstetric complications, and found that these increased risk of brain abnormalities, including decreased general grey matter volume and in volume of hippocampus.

Further neuroanatomical changes occur after illness onset (Fusar-Poli et al., 2012; van Erp et al., 2018). Stone et al. take this to represent a "neurodegenerative-like" process in a subset of schizophrenia patients. However, sequential studies show that antipsychotics exacerbate morphological abnormalities (Vita et al., 2015; Voineskos et al., 2020). In a prospective study in over 200 patients with schizophrenia who underwent serial MRI scanning from illness onset over a mean of 7 years (Ho et al., 2011), antipsychotics were linked to further decreases in grey and white matter.

Post-mortem studies in primates and longitudinal MRI studies with *post-mortem* confirmation in rodents, confirm that exposure for more than 4 weeks to clinically comparable levels of either haloperidol or olanzapine leads to reductions in whole brain and cortical volume; these reflect genuine tissue changes, are dependent on the dose and duration of drug treatment, and are mediated by blockade of dopamine D2/3 receptors (Dorph-Petersen et al., 2005; Guma et al., 2019; Vernon et al., 2014; Vernon et al., 2012; Vernon et al., 2011). Rodent MRI studies also provide evidence for grey matter volume *increases* in the striatum, which overlap with MRI findings in schizophrenia suggesting a relationship between antipsychotic dose and striatal hypertrophy (Andersen et al., 2020; Vernon et al., 2012; Chopra et al., 2021).

4. Cause of deterioration in cognition and brain structure

Apart from antipsychotics, do other illness-related factors influence regional grey and white matter volume in schizophrenia? To our knowledge, there are no studies asking whether genetic loading for schizophrenia is associated with brain changes after onset. However many studies have addressed the question of whether environmental factors other than antipsychotics might explain some of these changes.

4.1. Metabolic syndrome and cardiovascular risk

People with schizophrenia have a higher prevalence of metabolic syndrome (MS), cardiovascular and cerebrovascular disorder, and diabetes; the MS is associated with increased white matter burden and deficits in executive functions and processing speed (Bora et al., 2017). Hagi et al. (2021) have shown in a meta-analysis, that MS, diabetes, and hypertension are significantly associated with global cognitive impairment in people with schizophrenia. Furthermore, in a study examining nearly 10,000 subjects (mean age 62 years) in the UK biobank, higher vascular risk factors were related to MRI hallmarks of dementia risk: lower frontal and temporal cortical volumes, lower subcortical volumes, higher white matter hyperintensity volumes, and poorer white matter microstructure. Tobacco smoking, hypertension and diabetes showed the most consistent associations. All of these are found in excess among patients with schizophrenia.

4.2. Increased aging

Patients with schizophrenia are reported to show increased brain age (Koutsouleris et al., 2018; Kaufman et al., 2019). Schnack et al. (2016) found this present at or before onset of psychosis but stabilising after

about 5 years after onset: the brain age gap was associated with dose of antipsychotics. Elliot et al. (2021) who examined general population Dunedin cohort, found greater brain age at age 45 was associated with measures of poor brain health at age 3 and with worse childhood cognition. Thus, it seems that adult brain age in part reflects compromised brain health that has been present since childhood.

Epigenetic studies can estimate biological age of an individual. People with schizophrenia show the epigenetic signature of accelerated aging but Higgins-Chen et al. (2021) demonstrated that this is in part due to excessive smoking. Furthermore, increased aging is a phenomenon of psychiatric illness as a whole rather than just schizophrenia. Wertz et al. followed up 938 subjects in the Dunedin cohort to age 45. Participants who had experienced more psychopathology exhibited increased pace of aging in general and more cognitive difficulties. In a subsequent study in 1.7 million New Zealanders over 50, those who had received a diagnosis of any psychiatric disorder were 4 times more likely to develop dementia than the remainder of the population (Richmond-Rakerd et al., 2022). Thus, there is nothing specific about accelerated aging in relation to schizophrenia; sadly it is a general characteristic of people with psychiatric illness.

4.3. Drug abuse

People with schizophrenia abuse more drugs than the general population. Heavy abuse of (meth)amphetamine and cannabis are known to be associated with cognitive decline in the general population and in schizophrenia (Guerrin et al., 2019: Bourque and Potvin, 2021). Ferraro et al. (2022) applied cluster analysis to cognitive and premorbid function data from a large series of first-episode patients in the EU-GEI STUDY; one group which emerged whose academic and social function had deteriorated in adolescence; the most likely cause appeared to be cannabis use. Continued use of cannabis is also associated with a worse outcome (Schoeler et al., 2016).

5. Conclusions

The primary factors determining the onset and outcome of schizophrenia are developmental. However, some patients do suffer loss of social and occupational function, and indeed cognition, earlier than the general population. In neurodegenerative diseases, deterioration in social functioning is closely related to progressive cognitive decline. However, in schizophrenia, the greatest functional decline is typically observed in the first few years after onset of the disorder when cognitive function remains relatively stable (Allen et al., 2005). On the other hand, what evidence there is of cognitive decline occurs late in the illness. This dissociation of symptoms and cognition suggests that there are separate processes at work.

Any decline is not a direct consequence of genetic loading for schizophrenia but rather a consequence of the hazards that afflict the person with schizophrenia. These include chronic medication effects, increased cardiovascular and cerebrovascular events, obesity, poor diet, and lack of exercise. Drug use is likely to contribute, especially tobacco smoking but also abuse of cannabis, methamphetamine, and occasionally alcohol. Monotonous life-style, without the stimulation of work and social interaction may also affect cognition, and we should not ignore the effects of homelessness and poor nutrition which sadly become the lot of some people with schizophrenia. Mani et al. (2013) have also shown that poverty itself can impair cognition. We suggest that in future, research into such non-specific effects on cognition and outcome deserve at least as much attention as has been given in the past to the idea of intrinsic deterioration in schizophrenia.

Many psychiatrists, particularly Americans, are reluctant to let go of the idea of progressive deterioration. This may be a reflection of the dominance of the medical model in US psychiatry (Scull, 2021). It is noticeable that the word “social” appears only once in the paper by Stone et al. (2022). Many studies have shown that social and environmental variables have a major effect on outcome. For example, in the AESOP study, social disadvantage, unemployment, being from a minority ethnic group, and even area of living at onset, predicted poor outcome ten years later (Morgan et al., 2014).

The view that schizophrenia involves progressive deterioration has profoundly negative implications for patients. Bad enough to receive a diagnosis of schizophrenia with its risks of stigmatization, but then to learn that it is associated with brain deterioration, can be very demoralising. The Kraepelinian model predicting poor outcome is a self-fulfilling prophecy removing hope from patients and their relatives. Furthermore it permits psychiatrists to attribute decline in functioning to a notional intrinsic defect rather than their failure to provide the best care, or the failure of psychiatry in general to fight for adequate resources to ensure optimum care.

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To our patients who have disproved the idea that schizophrenia is progressive.

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