Neuroscience and Biobehavioral Reviews 79 (2017) 1–13

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

Progressive cortical reorganisation: A framework for investigating structural changes in schizophrenia

Lena Palaniyappan[*,a,b,c]

[a] Robarts Research Institute & The Brain and Mind Institute, University of Western Ontario, London, Ontario, Canada
[b] Department of Psychiatry, University of Western Ontario, London, Ontario, Canada
[c] Lawson Health Research Institute, London, Ontario, Canada

ARTICLE INFO

Keywords:
Neuroprogression
Degeneration
Developmental
Plasticity
Schizophrenia
Psychosis
Antipsychotics

ABSTRACT

One of the few well-replicated features of schizophrenia is the demonstration of neuroanatomical abnormalities affecting cortical and subcortical grey matter (GM). Evidence to date suggests that the greatest reduction in GM occurs in the immediate post-onset phase. The predominant view to date is that the accelerated grey matter (GM) loss represents an adverse process (degenerative or developmental deficit) contributing to the unfavourable course of schizophrenia. This prevailing emphasis on decompensation often overlooks the fact that human brain has an inherent capacity to remodel itself in response to insults that affect its function. In the wake of emerging insights into both micro- and macro-scale brain connectivity, a substantial amount of the longitudinal structural changes seen in patients with schizophrenia could result from a distributed, nevertheless inefficient, cortical reorganization response. Quantifying cortical reorganization in the early stages of illness can enable prospective grading of the underlying pathophysiological process in schizophrenia.

1. Introduction

The presence of neuroanatomical abnormalities affecting both grey and white matter of the brain is a well-established observation in schizophrenia (Glahn et al., 2008). While some of these abnormalities are notable even before the appearance of clinical symptoms, a distinct acceleration of tissue loss takes place in the early stages of schizophrenia, at a rate that is twice as high as the expected age-related reduction seen in heathy subjects (Hulshoff Pol and Kahn, 2008). Genetic risk factors (Hedman et al., 2016; Moran et al., 2013), as well as chemical agents including prescribed medications (Ho et al., 2011) and recreational substances (Malchow et al., 2013), and illness-related behavioural and lifestyle changes (Van Haren et al., 2013; Zipursky et al., 2013) have been posited as aetiological factors for the progressive grey matter changes in schizophrenia (PGMC).[1] To date, most authors have interpreted PGMC across various brain regions as a product of a pathological process that is common to the whole brain. On one hand, there has been a considerable debate whether this process relates to aberrant neurodevelopment or neurodegenerative in nature or a combination of both. But on the other, there seems to be a general acceptance that the accelerated grey matter (GM) loss is an adverse process contributing to the unfavourable course of schizophrenia (Andreasen, 2010; Pantelis et al., 2005; van Haren et al., 2008).

Accurate interpretation of progressive tissue loss has significant clinical relevance for patients and carers. While a developmental brain deficit is often interpreted to signify a degree of irreversibility, a degenerative change is often perceived as indicative of a relentlessly decompensating process. In recent times, observations relating to PGMC (Ho et al., 2011) have raised serious concerns about current long-term[1] antipsychotic treatment recommendations in schizophrenia (Alvarez-Jimenez et al., 2016; McGorry et al., 2013; Wunderink et al., 2013), already prompting some noticeable changes in clinical practice (Thompson et al., 2016). In this review, I put forward the view that PGMC may not represent a deficit or decompensation process per se. When viewed from the perspective of both micro- and macro-scale brain connectivity, a substantial amount of the longitudinal GM changes seen in patients with schizophrenia could be the result of a distributed, nevertheless inefficient, cortical reorganization response. I discuss the critical gaps in our current knowledge regarding the anatomical course of schizophrenia, and highlight some methodological issues that can be addressed in future longitudinal imaging studies.

[*] Correspondence address: Prevention & Early Intervention Program for Psychoses (PEPP), A2-636, LHSC-VH, 800 Commissioners Road, London, Ontario N6A 5W9, Canada.
E-mail address: lpalaniy@uwo.ca.

[1] The term 'progressive' is used only to convey the sense that there is an ongoing, time-varying process that alters grey matter, while not insinuating a degenerative interpretation.

http://dx.doi.org/10.1016/j.neubiorev.2017.04.028
Received 14 February 2017; Received in revised form 26 April 2017; Accepted 26 April 2017
Available online 10 May 2017
0149-7634/

1.1. Cortical reorganization in response to dysfunction

Adult brain has an inherent capacity to remodel itself in response to changes that affect its function. A plethora of factors that alter neural activity trigger cortical reorganization response. These include sensory deprivation (e.g. visual deprivation (Collignon et al., 2015)), limb removal (Jutzeler et al., 2015), hearing loss (Herraiz et al., 2009), direct tissue damage (e.g. stroke, traumatic brain injury (Cai et al., 2016; Castellanos et al., 2010), developmental defects (e.g. hippocampal sclerosis in temporal lobe epilepsy (Hamberger et al., 2007), congenital hemiplegia (Artzi et al., 2016)) or learning a new behaviour (Kleim et al., 2004; Siuda-Krzywicka et al., 2016). In many such cases, the reorganization involves functional dedifferentiation, i.e., non-specific recruitment of brain regions to perform the affected function (Cai et al., 2016). At synaptic level, such reorganization is thought to involve changes in spine density due to synaptic formation and elimination and both local and distant changes in excitatory/inhibitory synaptic balance (Benali et al., 2008). Especially in cases where the insult is developmental, reorganization is associated with gross functional and structural neuroanatomical changes that may affect normal brain asymmetry (e.g. unilateral hearing loss in children (Gordon et al., 2013), motor weakness (Artzi et al., 2016)).

While the spatial distribution of the reorganization may be specific to the nature of the provocation, the underlying process of reorganization itself appears to be a universal response to disruptions in neuronal activity that is strikingly similar to developmental plasticity (Nahmani and Turrigiano, 2014; Nudo, 2013). Reorganization processes are most intense in the period immediately after the insult, but may diminish during the course of recovery (Hübener and Bonhoeffer, 2014; Wahl et al., 2014). The behaviour of an organism after an insult is a potent modulator of the reorganization process (Kerr et al., 2011; Kleim et al., 2004; Nudo, 2013). Reorganization is not always beneficial (Moxon et al., 2014); in some situations, functional recovery fails to accompany cortical reorganization, while in the other, various pathological manifestations result directly from the process (e.g. phantom limb). Both injury and the treatment to alleviate the symptoms of an injury can result in cortical reorganization, with contrasting relationship to functional outcome (Abel et al., 2015; Kerr et al., 2011)). Further, some brain regions, when damaged, may require more elaborate reorganization response than the others to achieve functional compensation (Herbet et al., 2016).

Several clinical features of schizophrenia appear consistent with the occurrence of reorganization response; characteristic psychotic symptoms wax and wane or remit in a substantial number of patients, recurrent relapses or non-remission of initial episode relates to poor longer term outcome, whereas cognitive deficits of schizophrenia stabilize after an initial period of decline (Heilbronner et al., 2016; Szöke et al., 2008). In the following sections, I highlight several neuroimaging features seen in schizophrenia that are supportive of interpreting PGMC as a sign of cortical reorganization process.

1.2. PGMC is not specific to schizophrenia

Single time-point comparisons of structural changes between patients and healthy controls reveal relative grey matter reduction in various psychiatric disorders including bipolar disorder (Bora et al., 2010; Ellison-Wright and Bullmore, 2010), depression (Bora et al., 2012; Du et al., 2012), OCD (Radua et al., 2010) anxiety disorders (Radua et al., 2010), anorexia (Titova et al., 2013) and personality disorders (Soloff et al., 2008). The effect sizes of grey matter reduction in these cross-sectional studies appear comparable to the reduction reported in schizophrenia (for example, see (Bora et al., 2011a; Radua et al., 2010)), with many differences getting obliterated when head-to-head comparisons are made between schizophrenia and bipolar disorder (Bora et al., 2011a; Goodkind et al., 2015; Yu et al., 2010, p. −). In addition, diffuse grey matter deficits are also reported from morphometric studies of numerous neurological disorders (e.g. epilepsy, migraine (Alhusaini et al., 2012; Bernhardt et al., 2009; Hougaard et al., 2014)) and chronic pain syndromes (e.g. arthritis, fibromyalgia (Kuchinad et al., 2007; Rodriguez-Raecke et al., 2013), though the anatomical distribution appears to differ from schizophrenia at least partially (Crossley et al., 2015).

A number of studies have compared GM changes in schizophrenia and other psychoses using first-episode psychosis (FEP) cohorts. In FEP samples (typically recruited after illness onset), single time-point comparisons reveal mostly overlapping structural deficits (Ellison-Wright and Bullmore, 2010; Yu et al., 2010); nevertheless, in later stages of illness, the differences between schizophrenia and affective disorders become apparent with wider spatial distribution and higher magnitude of GM deficits observed in SZ (Liberg et al., 2016). In contrast, longitudinal imaging studies are somewhat inconsistent in identifying PGMC specific to schizophrenia. Some studies have failed to note any difference in PGMC between FES and FEAP in early-onset patients (Arango et al., 2012), while others note tissue increase or preservation in schizophrenia compared to controls and patients with affective disorders (de Castro-Manglano et al., 2011). Even those studies that show diagnostic differences in PGMC reported somewhat limited regional differences in PGMC involving anterior cingulate cortex (ACC), superior temporal gyrus (STG) and the insula. Within the ACC, Koo et al. noted subregional differences in PGMC with diffuse reduction noted in schizophrenia while only subgenual ACC deficits seen in affective psychosis (Koo et al., 2008). A similar schizophrenia-specific excess GM reduction may also affect the left STG, even before the onset of psychosis (Takahashi et al., 2009b). Frontotemporal GM reduction is more pronounced in first episode schizophrenia than in affective disorder (Arango et al., 2012; Farrow et al., 2005; Salisbury et al., 2007). Notably, though significant GM deficit of the insula is present in both disorders at the onset, progressive GM reduction in this region appears to be specific to schizophrenia compared to affective psychosis (Lee et al., 2016).

Schizophrenia-specific PGMC in frontotemporal regions and the insula appear to be associated with symptom burden. In a recent study, Rosa et al. noted that among FEP subjects, the status of clinical non-remission was a better predictor of PGMC than diagnostic status, with more pronounced GM reduction affecting left insula and STG in non-remitting schizophrenia when compared to both non-remitting FEAP and remitted SCZ (Rosa et al., 2015). Nakamura et al. reported more pronounced frontotemporal reduction in schizophrenia in association with worsening symptoms (Nakamura et al., 2007). One caveat in these comparisons is the differential effect of psychotropics which may confound the illness-specific PGMC; mood stabilisers and atypical antipsychotics are associated with GM increases (Nakamura et al., 2007), while typical neuroleptics are often linked to GM reduction.

In summary, the phenomenon of PGMC after illness onset appears unlikely to be specific to schizophrenia but occurs in a number of neurological and psychiatric disorders; but more pronounced GM reduction of certain brain regions (insula, STG and ACC) specifically occurs in those with persistent or worsening symptoms of schizophrenia.

1.3. Pre-onset GM changes are limited in space and magnitude

Patients with schizophrenia show a notable reduction in intracranial volume (magnitude of 2%) compared to controls, indicating a very early, subtle in utero deficit in cerebral development (Haijma et al., 2013). Nevertheless, the presence of increased extracerebral CSF in patients suggests that additional GM reductions take place at a later phase of life, after maximal skull growth (Stevens, 1991; Woods, 1998).

The GM deficits that are reported in high-risk subjects who do not yet satisfy the diagnostic criteria for a psychotic disorder appear limited in magnitude and spatial extent (Chan et al., 2011; Mechelli et al., 2011). Two distinct types of samples have been studied in this regard.