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A neurodegenerative perspective on schizophrenia

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Background

The issue of neurodegeneration in schizophrenia is a controversial one. The early descriptions by Kraepelin (1929) pointing to neurodegenerative features were supported by Alzheimer, who found evidence of cortical neuron loss and by Southard, who described cerebral atrophy. During the remainder of the past century though, the evidence produced by several investigators rendered the involvement of neurodegenerative processes highly unlikely, with absence of gliosis being the major distinguishing feature of it from classical neurodegenerative disorders, where gliosis is prominent. Thus all research work reframed schizophrenia as a neurodevelopmenta disorder and this is currently the prevailing hypothesis. The latter promotes insight into several features of the disorder, but nevertheless fails to account for a number of its cardinal features, such as the protracted period of symptomatic dormancy, the progressive clinical deteriration, affecting a significant subgroup of patients and recent evidence for changes in ventricular and cortical brain stuctures. New datasuggest that a neurodegenerative perspective could hold true filling the gaps of the neurodevelopmental model. In our poster we critically review work from the relevant domains and present the findings pertinent to a neurodegenerative involvement

Materials and methods

We reviewed studies from clinical, neurocognitive, neuroimaging, and neuropathology domains. In particular, from the clinical psychopathology and neurocognitive domain we reviewed six papers (Addington and Addington *JPN* 2002, **27**, Hambrecht *et al*. *BJP* 2002, **181**, Hoff *et al*. *AJP* 1999, **156** and 2000, **157**, McGlashan *Schiz Bull* 1988, **14**, Nopoulos *et al*. *Schiz Res* 1994, **14**). From the postmortem neuropathology domain we reviewed eight papers (Benes *et al*. *Arch Gen Psych* 1991, **48**, *Biol Psych* 2001, **50**, Cotter *et al*. *Brain Res Rev* 2001, **55**, Harrison *Brain* 1999, **122**, Pakkenberg *Arch Gen Psych* 1990, **47**, Young *et al*. *Biol Psych* 2000, **47**, Mattson *et al*. *Exp Neurol* 1998, **153**, Jarskog *et al*. *Sciz Res* 2001, **49**). In the neuroimaging domain we reviewed three cross-sectional structural studies (Gur *et al*. *Arch Gen Psych* 1998, **55**, Hulshoff Pol *et al*. *AJP* 2002, **159**, Schlaepfer *et al*. *AJP* 1994, **151**), five longitudinal studies (Cahn *et al*. *Arch Gen Psych* 2002, **59**, De Lisi *et al*. *Psych Res Neuroim* 1997, **74**, Gur *et al*. *Arch Gen Psych* 1998, **55**, Lieberman *et al*. *Biol Psych* 2001, **49**, Mathalon *et al*. *Arch Gen Psych* 2001, **58**), two functional studies (Andreasen *et al*. *Lancet* 1997, **349**, Weinberger *Arch Gen Psych* 1987, **44**), four spectroscopic studies (Hinsberger *et al*. *JPN* 1997, **22**, Pettergrew *et al*. *Arch Gen Psych* 1991, **48**, *Schiz Bull* 1993, **19**, Cecil *et al*. *Neuropsychopharmacology* 1999) and ten papers attempting to correlate neuroimaging data and clinical progression (Lieberman *et al*. *Biol Psych* 2001, **50**, Fannon *et al*. *AJP* 2000, **157**, Ho *et al*. *AJP* 2003, **160**, Hoff *et al*. *AJP* 2000, **157**, Cahn *et al*. *Arch Gen Psych* 2002, **59**, Gur *et al*. *Arch Gen Psych* 1998, **55**, Kasai *et al*. *AJP* 2003, **160**, Mathalon *et al*. *Arch Gen Psych* 2001, **58**, Davis *et al*. *Biol Psych* 1998, **43**, Jacobsen *et al*. *AJP* 1998, **155**, Loebel *et al*. *AJP* 1992, **149**). We focused mainly on the results and limitations on each one and whether comparisons could be made and conclusions could be drawn from the studies whithin each of the domains. No statistical evaluatin was attemptedand the issue of any type of validity was not evaluated.

Results

The weigth of the evidence from clinical psychopathology and neurocognition points to a progression of cognitive deficits duting the late premorbid, prodromal and early first-episode phases of the disorder.

While there is no evidence of classical neurodegeneration, there are definite neuropathological deficits. There are many confounding factors blurring the picture, but nevertheless a suggestion can be made of picture of mainly dendritic and synaptic deficits, possibly the result of a mild neurodegenerative process. Progress in the molecular techniques and genomic and proteomic analysis will improve our understanding of the picture.

In the neuroimaging domain, both cross-sectional and more importantly small longitudinal studies show progressive brain changes (although a neurodegenerative explanation of these findings has been challenged by Weinberger and McClure). Higher resolution longitudinal studies will clarify the matter. taken together, the functional and spectroscopic studies indicate only a limited neurodegenerative process in the disorder. Again longitudinal studies will be helpfull. Attempts at correlating neuroimaging and clinical progression present some evidence of it, but not in all studies or across the same brain structures or in the same clinical or cognitive clusters.

Discussion

The aetilogy of schizophrenia is complex and probably because of this will remain unknown for some time. It appears though that the current, prevailing neurodevelopmental hypothesis cannot explain the whole gamut of findings as it appears that its pathophysiology involves both neurodevelopmental and neurodegenerative processes.

The histopathology, showing neuronal atrophy and synaptodendritic reductions may be reflecting a limited neurodegenerative process. Neuroimaging studies seem to be supportive of this. Overall, progressive clinical, neurocognitive, neuropathological and neuroimaging findings show that neuroprogressive events take place in the prodromal and first-episode perods, suggesting that neurodegenerative processes could intersect with normal neuromaturational processes, such as myelination and synaptic prunning, taking place duting adolescence and early adulthood. This approach could mechanistically involve apoptotic pathways resulting in neurodegeneration by perturbing the normal synaptic prunning, so taking place at the prodromal and first-episode phases.

Thus, it appears that schizophrenia could be considered a limited neurodegenerative process following, temporally, various neurodevelopmental insults. Certainly though, more evidence in all domains is needed to establicsh this, but the trend is quite evident.

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