ABSTRACT – Patients with schizophrenia have a smaller volume of cortex than healthy controls. Nevertheless, the substrate of such deficit is not well understood. A progressive loss of cortical GM in schizophrenia seemed supported by early studies with magnetic resonance imaging (MRI) in which patients received typical drugs between the baseline and final scans. However, recent MRI results challenge this notion and suggest that structural changes may depend, at least in part, on the type of treatment received. These data may be relevant for a correct interpretation of the substrate of cortical volume deficit in schizophrenia. If that deficit can be even reversed by treatment, as suggested by recent studies, a neuronal substrate seems unlikely. Several lines of evidence instead support that glia cells may have a role in cortical structural and functional deficits in schizophrenia, which would be also in agreement with recent longitudinal results with MRI in patients treated with atypical antipsychotics. These evidences are reviewed in this paper.

Introduction

After several decades of intensive research, it is accepted that patients with schizophrenia (SZ) as a group have a smaller volume of cortex than healthy controls (Shenton et al. 2001). Nevertheless, the substrate of such deficit is not well understood although a deficit in the number of neurons seems not explain it (Selemon et al. 1999a).

Neuropathology is needed to clarify the basis of that cortical deficit, but this kind of studies in SZ are subject to powerful confounding factors (medication, social isolation, toxic consumption and post-mortem interval among others). These factors may obscure the interpretation of data, even more if we consider that the volume deficit attributable to SZ is quantitatively small (Woods et al. 2005).

Magnetic resonance imaging (MRI), in this context, can yield complementary results to neuropathology. There are at least two questions of great relevance for the meaning...
of cortical volume deficits in SZ that longitudinal MRI studies may answer: the temporal progression of volume deficits and the effect of different antipsychotics on it.

Effect of the type on antipsychotic on the outcome of cortical deficit

Early longitudinal studies using MRI in SZ described an accelerated decrease of gray matter (GM) volume in cerebral hemispheres and cerebellum (DeLisi et al. 1997), frontal (Gur et al. 1997, Mathalon et al. 2001) and temporal (Mathalon et al. 2001) lobes, and hippocampus (Lieberman et al. 2001) as compared to controls. Besides, a faster rate of ventricular (DeLisi et al. 1997, Lieberman et al. 2001, Mathalon et al. 2001, Nair et al. 1997) and frontal sulcal (Mathalon et al. 2001) spaces enlargement has also been described. Such volume changes have been viewed as a possible correlate of neuronal tissue loss although other factors may contribute to the GM changes evidenced by MRI. In these early studies, patients received typical antipsychotics (TA) during the follow-up period. In similar populations, also treated with TA, a significant association was noted between illness duration and the excess of volume in frontal and temporal sulcal cerebrospinal fluid spaces (Molina et al. 2002, Turetsky et al. 1995), suggesting a sustained progression of GM loss in that areas, filled up with cerebrospinal fluid. Finally, an inverse association between the frontal signal of N-acetyl-aspartate, considered a marker of the amount of viable neuronal tissue (Urenjak et al. 1993) and disease duration (Ende et al. 2000, Molina et al. 2005c) has also been found, but not in patients with longer chronicity (Block et al. 2000, Deicken et al. 1997, Lim et al. 1998). These data, as a whole, support a progression of the GM deficit in patients treated with TA.

However, more recent results challenge this notion and suggest that cortical changes may depend, at least in part, on the type of treatment received, as previously demonstrated in basal ganglia (Chakos et al. 1995). This new generation of studies coincides with the generalized use of atypical antipsychotics (AA) in SZ. Ho et al. did not find significant changes of cortical GM in 73 patients after a mean follow-up of 3 years (Ho et al. 2003). In this sample, 20 out of the 38 patients who received treatment during the whole follow-up period received only AA. Besides another group did not find significant changes in the outcome of hemispheric volumes between controls and SZ patients (13 receiving AA, 6 TA and 7 without treatment), after a 10 years of follow-up (DeLisi et al. 2004). Finally, another study in first-episode adults described frontal and temporal GM deficits in patients treated with TA for 8 weeks (n = 32) compared to untreated patients (n = 22), while another group of patients treated with AA (n = 30) presented a thalamic GM excess with no cortical deficit compared to the same untreated group (Dazzan et al. 2004). There is however not complete agreement on this. Another group a significant decrease in brain volume (1.2%) and cerebrum (2.9%), and an enlargement of ventricles (7.7%) described in the year following a first psychotic episode in patients treated with a variety of TA and AA, alone or in combination (Cahn et al. 2002a).

From these studies, it seems likely that greater rates of GM decrease can be found when treatment between scans consisted of TA. This is specially supported by the reversion of the previous GM volume deficits reported by two groups. Keshavan et al. (1998) have reported that the superior tem-
poral gyrus volume deficit may reverse with treatment in first SZ episodes, without describing the kind of treatment the patients received during follow-up. Moreover, Molina et al. (in press a) studied two groups of SZ patients (first episodes and treatment chronic resistant cases) at baseline and after two years of treatment, respectively with risperidone and clozapine. In this study, in both groups a significant increase of GM was found in parietal (mean chronic 7.3%, first episodes 1.2%) and occipital (mean chronic 14.9%, first episodes 6.2%) regions, after correcting for changes in intracranial volume between scans. Frontal GM also increased in the chronic group with clozapine (mean 6.8%). These authors calculated a quantitative measure (residuals) representing the volumetric differences in GM and WM as compared to controls. Both groups showed a significant GM deficit, more marked and extended in the chronic group. There was a significant inverse relationship between the baseline deficit and the longitudinal change (Figure 1). In another study of frontal GM changes in adolescents with SZ (n = 16, mean age at baseline = 18), an increase of 1.9% after 2 years of treatment with atypical drugs was reported (James et al. 2004). A sharp difference in the outcome of the brains in these patients seems therefore to depend on the type of treatment used, which is specially supported by the recent report of Lieberman et al. (2005). In a wide sample of first episodes, they studied the differences in outcome of the brain MRI measures between patients receiving haloperidol or olanzapine during follow-up. Haloperidol-treated patients exhibited significant decreases in gray matter volume, whereas olanzapine-treated patients did not.

These results have potentially important implications for the meaning of the volume deficits of GM found in SZ. The “dynamic” properties (its changes along time) of the structural deficits may give relevant clues for its correct interpretation. For example, if these deficits can be reversed by treatment, as suggested by recent results (James et al. 2004, Keshavan et al. 1998, Molina et al. in press a), are unlikely due to a neuronal number decrease. Other cellular (or non-cellular) elements in the brain with a plasticity reserve such than can be reflected in MRI studies can account for the treatment-related increase and also perhaps for the corresponding baseline volume deficits. Besides, if the outcome of the brain structure depends on the type of treatment received between MRI scans, we can wonder if typical drugs are neurotoxic and/or atypical drugs are “neuroprotective”.

Neurotoxic or neuroprotective effects of antipsychotics?

The debate around the possible neurotoxicity of antipsychotics is old, and yet unresolved. The outcome of patients in the neuroleptic era is better than in the previous one, which would be compatible with a protective role for antipsychotics against cerebral alterations.

Different arguments support the opposite views of a neurotoxic and a neuroprotective role of antipsychotic drugs. In support of the first position, results obtained in preclinical models support a neurotoxic profile for TA. It has been reported that these antipsychotics can induce neuronal apoptosis (Noh et al. 2000) or reduce synaptic density (Kelley et al. 1997). A decrease in brain-derived neurotrophic factor has also been reported in association with neuroleptic treatment (Angelucci et al. 2000). Moreover, a recent study performed in monkeys suggests that chronic exposure to haloperidol and olanza-
pine may decrease brain weight and volume (Dorph-Petersen et al. 2005). In this study, macaque monkeys were administered with haloperidol or olanzapine for 17 to 27 months to investigate the macroscopic effects of antipsychotics on the brain. They found that both treatments, given at higher doses than usual in humans, produced a slight, but significant, decrease in brain weight and volume, more pronounced in the frontal and parietal regions.

As these studies were preclinical, we cannot conclude that the human brain would show the same changes in the case of cerebral illness. It seems therefore important to assess the effects of neuroleptics in the brain structure of SZ patients, and neuroimaging offers the possibility to do so.

Figure 1. Relationship between the prior degree of atrophy and the longitudinal change in GM (hollow dots: CR group, solid dots: NN group). The X-axis shows the baseline atrophy / hypertrophy value and the Y-axis the corresponding longitudinal changes (see Molina et al. in press a for details). Values in X and Y axis are expressed in cubic centimeters.
This possibility has been explored by assessing the relation between cumulative dosage of antipsychotics and changes in MRI scans. Results are discrepant: on the one hand, an association between GM loss and cumulative dosage was reported (Cahn et al. 2002b, Madsen et al. 1999). On the other hand, it has been also reported that higher cumulative exposure to TA is associated with lower ventricular enlargement (DeLisi et al. 1997, Lieberman et al. 2001), coherent with a lower rate of gray matter decrease. These studies were performed in samples treated with TA, except for that of Cahn et al. (2002b), with patients receiving TA or any of 5 different AA. Besides, as previously mentioned, volumetric deficit in STG may even reverse with treatment (Keshavan et al. 1998). These discrepancies between MRI studies may relate to several factors. For instance, some patients may require higher dosages due to a more severe illness form, that may produce greater brain changes. Moreover, ventricular enlargement does not reflect exactly the same process than volumetric GM changes.

At this point, it is necessary to distinguish between TA and AA when it comes to determining the possible effect of neuroleptics on alterations in cortical volume. Its effects on brain structure and function are clearly different. It has been reported that clozapine has an effect of reversing increases in basal ganglia volume induced by TA (Chakos et al. 1995). It has also been found that AA do not produce an increase in basal ganglia volume in treatment-naïve patients (Heitmiller et al. 2004), which is a known effect of TA (Bartlett et al. 1994, Buchsbaum et al. 1987, DeLisi et al. 1985, Holcomb et al. 1996). Furthermore, AA have a greater capacity than TA for increasing NAA levels in the prefrontal (PF) cortex (Bertolino et al. 2001). Finally, as previously mentioned, recent longitudinal MRI studies using exclusively AA between scans have shown the absence on GM volume loss with olanzapine (Lieberman et al. 2005) and the gain of cortical GM volume with risperidone and clozapine, proportional to the pre-existing deficit (Molina et al. in press a). AA, or at least some AA, may thus exert a different effect on cortical volumes than TA. The observation by Cahn et al. (2002b) that patients treated, in part, with AA (clozapine, olanzapine, risperidone, sertindole or quetiapine) also showed an accelerated volume loss may contradict this idea. However, the results of these author could be due to a different structural effect among “AA”, as in our previous study differences between the anatomical effects of risperidone and clozapine were noted (Molina et al. in press a). Moreover, olanzapine did not produce GM gain, but a “detention” of loss (Lieberman et al. 2005).

What do we know about the basis of the structural effects of antipsychotics?

In theory, the first possibility would be that the lower rate of GM loss (or even GM gain) observed with AA were related to neurogenesis. This was supported by the report of a 2- to 3-fold increase in newly divided cells in the subventricular zone in the rat with AA. Some of these new cells in the subventricular zone and hippocampus also expressed a neuronal marker (Wakade et al. 2002). Another study showed that clozapine induced cell division in hippocampus, though the resulting neurons did not survive 3 weeks later (Halim et al. 2004). Then, although some neurogenesis may not be discarded with AA, it does not seem relevant in the cortex, and cells may not survive. Moreover, in primate cortex there was no...
increase of neuronal tissue after treatment with TA or AA neuroleptics (Selemon et al. 1999b). Thus, it seems unlikely that the increase of GM with AA is caused by the appearance of new neurons.

Another possibility is synaptogenesis. There is good evidence to support synaptogenesis by TA (Konradi et al. 2001), a factor that might contribute to the observed striatal enlargement induced by these drugs (Chakos et al. 1994). This enlargement coincides with a regional increase in metabolic activity (Bartlett et al. 1994, Buchsbaum et al. 1987, DeLisi et al. 1985, Holcomb et al. 1996), an expected correlate of synaptogenesis if we assume a direct association between synaptic activity and the signal detected by functional imaging (Jueptner et al. 1995).

The possibility that AA might induce synaptogenesis in the cortex to explain its particular anatomical effects is attractive in the light of the theories of reduced cortical connectivity in SZ (McGlashan et al. 2000). Formation of new neuronal elements such as synapses, seems in any case more likely than neurogenesis in the adult brain. Nevertheless, as previously stated, the absence of neuronal tissue increase in primate cortex after AA seems incompatible with such explanation (Selemon et al. 1999b). Moreover, a huge increase of connections would be required to explain a GM volume increase susceptible of being detected with MRI. Finally, treatment with AA do not produce a marked metabolic increase in the cortex (Cohen et al. 1997, Lahti et al. 2003a, Lahti et al. 2003b, Miller et al. 2001, Molina et al. 2003, Molina 2005a, Molina 2005b), at least to the degree produced by classicals in the basal ganglia. These reasons make unlikely that an increase of connections justifies the distinct structural effects of AA.

If we consider unlikely an action on neurons to explain the possible volumetric effect of AA, we can wonder if such morphological effect can take place through glial cells. Several findings support this possibility.

First, glial cell loss may be significant in SZ, at least in some regions (Coppen et al. 2001b, Stark et al. 2004). Numerical density of oligodendroglial cells may be reduced by a 25% in prefrontal areas in SZ (Uranova et al. 2001). According to these Stark et al. (2004), a 33% decrease (statistically significant) in glial cells was observed in the anterior cingulate region. The possibility of a role for glia in SZ is also supported by reports of decreased glial fibrillary acidic protein (GFAP), a protein specific of astrocytes in that illness (Johnston-Wilson et al. 2000, Rajkowska et al. 2002). GFAP immunoreactive astroglia in the prefrontal cortex in SZ was reported to be decreased by a significant 32% in the GFAP-area fraction, together with a 14% decrease in the width of the cortical layer V, as compared to the control subjects. None of these parameters were affected in layers III and IV in the patients. It may be investigated if such deficit relates to the structural deficit in SZ.

Second, proliferation of glial cells along with cortical hypertrophy has been observed in the prefrontal cortex of primates after treatment with AA (Selemon et al. 1999b). Besides, olanzapine can increase the number of dividing glial cells in the frontal cortex of the adult rat (Wang et al. 2004).

In our previous study (Molina et al. in press a), pre-existing volume deficits were found associated in first episodes and chronic patients with the increases in cortical volume respectively induced by risperidone and clozapine (Figure 1). Thus, if replicated, an association between the sus-
trate of cortical volume deficit and that of structural change induced by AA is suggested. In other words, an hypothetical interpretation of longitudinal MRI data would be that cortical volume deficit in SZ could be contributed by a glial deficit.

Changes in WM with AA

One of the most puzzling results of our mentioned study (Molina et al. in press a) was the co-occurrence in this sample of GM increase and decrease in WM (Figure 2). Both changes were however statistically unrelated, suggesting that, although coincident in time, had a different substrate. The WM volume decrease was not reported in longitudinal studies where patients had been treated with TA, but is consistent with the recent finding of a decrease in WM after four weeks of TA or AA treatment (Christensen et al. 2004). That WM decrease with AA can be of interest, given the data supporting that WM volume may indeed be increased in SZ (Lawrie et al. 1998).

If WM, in terms of volume is mostly formed by glial cells, how it comes that WM volume may decrease, with AA if we propose that GM volume gain was related to previously diminished glia? There is one plausible explanation for both findings (GM gain and WM loss) at expense of glial mechanisms. Astrocytes predomine in GM and have an important role in synaptic functions, while oligodendrocytes predomine in WM and mainly form myelin sheats (Pfrieger et al. 1996). These two types could be differently affected by AA. For instance, the decrease in WM due to AA could be explained by a blockade of factors stimulating myelin synthesis. Such a factor could have to do with a chronic glutamatergic hyperactivation state since hyperactivity...
relates to increased myelination in other disease states (Adamsbaum et al. 1996, Krishnan et al. 1994). Such an hyperactivity state might be present in SZ (Molina et al. 2005d, Volk et al. 2002). This possibility would be consistent with the observation that oligodendrocytes may be reduced in GM but not in adjacent WM in post-mortem data of patients treated with TA (Uranova et al. 2004). The metabolic down-regulation induced by clozapine in the frontal cortex in SZ patients (Cohen et al. 1997, Lahti et al. 2003b, Molina et al. 2005b) may be consistent decrease that hyperactive state, thus reducing myelin synthesis and WM volume. Although a similar effect has been reported for classical drugs (Holcomb et al. 1996), this effect may be more pronounced with clozapine (Molina et al. 2005b). At the same time, GM astrocytes may increase, by an unknown mechanism, as shown by the results in monkeys (Selemon et al. 1999b).

Discussion

Longitudinal MRI results in samples of SZ patients tend to support that, while on TA, an accelerated decrease of GM volume can be found. This may be an effect of treatment. However there is no evidence of neuron loss in patients treated for decades with these drugs (Selemon et al. 1999a), so we cannot conclude that TA are properly neurotoxics. The GM loss is not generally found in samples that received AA (alone or in combination with TA).

To explain this difference two possibilities arise: AA exert some compensation of illness-related problems or, AA simply do not cause the anatomical problems that TA would cause. The first possibility is more likely, as supported by the presence of anatomical deficits already in first episodes of SZ (Hirayasu et al. 2001, Molina et al. in press b, Nopoulos et al. 1995, Salokangas et al. 2002) and by the similar changes induced in this cases by AA than in chronic patients (Molina et al. in press a). In this context, we may presume that longitudinal studies on classical antipsychotics would show more GM loss perhaps because of a lesser effect on illness-related factors. It cannot be discarded, however, some direct effect of TA on brain-related factors. It provides only limited information about underlying changes.

Certain AA may have an effect on pre-existing deficit, as suggested by the association shown in Figures 1 and 2, together with other evidences mentioned in previous sections, let presume a role for glia in SZ. Such a role may not simply have anatomical consequences. Glial cells are now accepted to have roles in providing trophic support to neurons, neuronal metabolism, and the formation of synapses and neurotransmission (Pfrieger et al. 1996). Thus, a glial deficit may have important functional consequences, that can be reflected in functional imaging and the subtle neuropsychological problems in SZ. In this direction, an effect of AA on glial cells would agree with the increase of brain occipito-visual activity (Molina et al. 2005b, Molina et al. 2003), observed in patients partially overlapping with those of the longitudinal MRI study (Molina et al. in press a), given the role of glial cells in PET data (Magistretti et al. 2000).

The involvement of glia may be not specific of SZ, as may be also found in mood disorders (Cotter et al. 2001a, Ongür et al. 1998). This inespecificity may have to do with the findings that white matter endophenotypes associated with SZ and bipolar disorder are overlapping (McDonald et al. 2004).
In summary, the interpretation of recent longitudinal studies in SZ points to new lines of research. Following Berhard Bogerts (1983) ‘If the functional unit of the brain is not the neuron but rather the neuron-glial complex, then both neuronal and glial cells could be involved in mental diseases’. Adequate studies are needed to test the suggestions made by these interpretations.

References


Angelucci F, Mathe AA, Aloe L. Brain-derived neurotrophic factor and tyrosine kinase receptor TrkB in rat brain are significantly altered after haloperidol and risperidone administration. J Neurosci Res 2000; 60: 783-794.


Lawrie SM, Abukmeil SS. Brain abnormality in schizophrenia. A systematic and quantitative review of volumetric magnetic resonance imaging studies Br J Psychiatry 1998; 172: 110-120.


Mathalon DH, Sullivan EV, Lim KO, Pfefferbaum A. Progressive brain volume changes and the clinical course

McDonald C, Bullmore ET, Sham PC, Chitnis X, Wickham H, Bramon E et al. Association of genetic risks for schizophrenia and bipolar disorder with specific and generic brain structural endophenotypes. Arch Gen Psychiatry 2004; 61: 974-984.


Nair TR, Christensen JD, Kingsbury SJ, Kumar NG, Terry WM, Garver DL. Progression of cerebroventricular enlargement and the subtyping of schizophrenia. Psychiatry Res 1997; 74: 141-150.


Uranova NA, Vostrikov VM, Orlovskaya DD, Rachmanova VI. Oligodendroglial density in the prefrontal cortex in schizophrenia and mood disorders: a study from the


Volk DW, Lewis DA. Impaired prefrontal inhibition in schizophrenia: relevance for cognitive dysfunction. *Physiol Behav* 2002; 77: 501-505.


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