

Neurotoxicity, Neuroplasticity, and Magnetic Resonance Imaging Morphometry

Recently, Weinberger and McClure¹ offered a provocative and cautionary perspective in connection with mounting longitudinal neuroimaging evidence of progressive brain volume decline in schizophrenia. Unfortunately, they confuse this increasingly well-documented phenomenon with a neurodegenerative hypothesis of schizophrenia. We agree with the authors that neurodegenerative processes involving inflammation and neuronal loss are unlikely based on the neuropathology literature, and that volumetric magnetic resonance imaging (MRI) data cannot elucidate the cellular or molecular mechanisms underlying progressive volume loss. This does not diminish the importance of longitudinal neuroimaging studies, whose rationale is to examine whether brain dysmorphology is static or progressive. This rationale is as valid today as it was in 1988² and 1994,³ when Dr Weinberger's group reported nonprogressive ventricular enlargement in schizophrenia and cited these findings as evidence that schizophrenia is a static neurodevelopmental encephalopathy.⁴ In contrast with these early studies, most of which used computed tomography, recent positive studies are generally based on quantitative volumetric MRI methods, including gray-white segmentation, and larger sample sizes, including carefully chosen control groups, and may therefore warrant greater weight. Moreover, progressive brain changes do not preclude a neurodevelopmental insult in schizophrenia, since an inherited neurodevelopmental abnormality can also exhibit progressive features. Examples include Huntington disease, Down syndrome, and probably autism, to name a few.

Weinberger and McClure¹ question the longitudinal neuroimaging data because some of the progression rates reported in schizophrenia appear to be unrealistically high. First, they note that if the rates are extrapolated beyond the interscan interval, little brain tissue would be left. While they acknowledge that progression may not be linear over the course of the illness, they counter that similar rates of progression have been reported in schizophrenic patients at all stages of the illness. However, they fail to cite 2 articles relevant to this point: In one,⁵ rates of cortical gray matter loss are consistent with rates from several other studies. In another,⁶ effect sizes for ventricular enlargement and cortical gray matter decline from several longitudinal MRI studies were shown to vary systematically with the ages of the samples studied: effect sizes are greatest in adolescent patients and smallest in middle-aged patients with

chronic disease. Second, they note that the progression rates reported in schizophrenia are sometimes on a par with known neurodegenerative diseases, such as Alzheimer disease, which progress much faster. This argument is based on selective and somewhat arbitrary comparisons of change rates from different neuroimaging laboratories using different methods. For example, they state that Mathalon et al⁷ reported a 2% per year reduction in frontal gray matter (they were 0.97% and 1.72% per year for left and right hemispheres, respectively) and note that this is close to the rate of hippocampal volume loss reported in Alzheimer disease by Laakso et al.⁸ It can be countered that the rates of expansion of frontal sulcal (0.07 mL/y) and ventricular (0.8 mL/y) cerebrospinal fluid volume reported by Shear et al⁹ in patients with schizophrenia were much lower than the rates estimated in patients with Alzheimer disease (cerebrospinal fluid volume: frontal, 0.8 mL/y; ventricular, 5.0 mL/y) in the same laboratory, applying similar region of interest definitions to computed tomography data. Various sources of measurement error can reduce the accuracy of absolute change estimates in longitudinal MRI studies, making them appear unrealistic at times. However, provided that these errors are randomly distributed across groups, they do not undermine the validity of between-group comparisons.

As a further criticism of the longitudinal MRI data, Weinberger and McClure¹ cite variability across studies in the rates of change and regions affected, although such variability is hardly surprising given the differences in patient samples and scanning methods across laboratories that have also contributed to inconsistencies in cross-sectional studies.¹⁰ The general convergence of recent findings despite these myriad sources of variance supports the likelihood that progressive morphometric changes in schizophrenia do occur, albeit in regions and at rates that have yet to be definitively established. Moreover, the heterogeneity of schizophrenia likely contributes to inconsistencies in the literature. It is possible that progressive brain changes may be more pronounced in different subgroups of patients, such as childhood onset,¹¹ poor-outcome,¹² or more severely psychotic¹³ patients.

Weinberger and McClure¹ further criticize the neuroimaging literature because symptom change and brain volume change do not show a consistent pattern of correlations across studies. In most neuroimaging studies, symptoms generally improve over the interscan interval as a result of regression to the mean: patients tend to be recruited during clinical exacerbations and followed-up during relatively stable outpatient visits. This tendency complicates the interpretation of correlations between brain volume decline and clinical change, including the

counterintuitive report of a relationship between greater decline and clinical improvement.¹⁴ While surprising, it would be premature to dismiss this correlation as spurious since it does suggest a plausible hypothesis: The brain parenchyma lost during progressive volume decline may include some of the pathological neural circuitry underlying symptoms. Moreover, since symptoms wax and wane in schizophrenia, more trait-like aspects of the clinical course are important to consider in addition to symptom change. For example, several reports find clinical severity to be associated with faster brain volume decline,^{12,13} possibly reflecting a more malignant pathophysiological process.¹⁵ More studies are needed to clarify how progressive brain changes are related to clinical features, illness stage, patient subgroups, and medication effects. In addition to the substantive issues discussed above, it should be noted that the summary table provided by Weinberger and McClure¹ contains several factual errors in connection with the Mathalon et al⁵ study. The follow-up period was erroneously listed as 3.3 years instead of 3.6 years. The change rates for several regions were incorrectly labeled with plus or minus signs, indicating the wrong direction of change: right frontal sulci and posterior temporal sulci should be labeled with a plus sign, indicating expansion, and posterior temporal gray should be labeled with a minus sign, indicating decline. In addition, significant decline in frontal gray was mistakenly identified as left instead of right hemisphere.

The mechanisms underlying progressive brain volume decline in schizophrenia may include “reversible physiological changes and neuroplastic adaptations to the environment or to the experience of being psychotic” as suggested by Weinberger and McClure,^{1(p 556)} consistent with emerging concepts of experience-dependent neuroplasticity. For example, several models have hypothesized that factors possibly related to loss of neuropil in schizophrenia,¹⁶ including *N*-methyl-D-aspartate receptor dysfunction,^{17,18} might result in reduced plasticity.¹⁹ Thus, progressive brain volume decline might result from a failure to benefit from the neurotrophic effects of experience,²⁰ including the impact of enriched environments on neurogenesis.²¹ Moreover, dynamic alterations in synaptic architecture implicated in the pathophysiological mechanisms of schizophrenia²²⁻²⁶ may contribute to neuropil reduction over the course of the illness. In addition, reductions²⁷ or abnormalities of oligodendrocytes,²⁸⁻³⁰ including problems with associated genes and proteins^{31,34} may reflect alterations at the cellular level contributing to progressive brain changes in schizophrenia.

While the mechanisms underlying the neuroimaging data showing progression in schizophrenia remain unknown, they may reflect important pathophysiological processes and are worthy of further study. Perhaps the greatest contribution of these data has been to challenge the view of schizophrenia as a static neurodevelopmental encephalopathy. The enthusiasm with which these neuroimaging results have been received does not derive from misguided conclusions about their neurodegenerative nature; rather, it derives from the possibility that the pathophysiological processes responsible for

progressive brain dysmorphology in schizophrenia may be ameliorated or reversed by appropriately targeted treatments.

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In reply

In our article,¹ we argued that changes in measurements on MRI scans over time in patients with schizophrenia should not be interpreted as evidence that neurodegeneration or neurotoxicity is a primary feature of the disease. The points that we raised to support this argument included the paucity of biologically plausible clinical-neuropathologic correlations, the remarkable inconsistency of the data, and the virtual absence of evidence of neurodegeneration in postmortem brain tissue, despite numerous studies. That Mathalon et al now state that concluding otherwise would be "misguided" suggests that our argument was convincing, as these authors in their earlier writings had advocated for a neurodegeneration interpretation (although their current use of the phrase "parenchyma lost" raises concerns that there is still some reluctance). In defending the MRI morphometry literature, they raise an important question: do longitudinal MRI morphometry studies contribute to our understanding of the brain disorder that accounts for the clinical condition? While our article addressed the problems with this literature in terms of a specific interpretation of the findings, we think that the question they now raise invites some additional comment.

Mathalon et al suggest that longitudinal MRI morphometry studies may be useful in identifying meaningful subgroups of patients, or characterizing different stages of illness, or medication effects, or novel phenomena for medi-

cations to affect. The fact that measurements on an MRI scan change over time indicates that these changes (if not technical artifacts) have something to do with the experience of having schizophrenia. Leaving aside the underlying physical basis for the changes (see our prior discussion¹), the problem is that changes in body weight, comorbid drug or alcohol use, smoking, incidental head injury, antipsychotic and other medication use, hormonal change, poor medical care, etc, also may be associated with similar changes in MRI measurements over time. In the best traditions of Karl Popper, studies aimed at falsification, ie, to attempt to show that the changes in patients with schizophrenia are such epiphenomena, are needed.

For the volume changes to be taken as a reflection of the primary illness biology, and not epiphenomena, medication effects, or the like, there should be lawful and consistent relationships between the MRI changes and the clinical course. The problem here is that while one can find an occasional study with volume changes that are biologically plausible and that show a lawful relationship with clinical change (as Mathalon et al illustrate), too many of the studies do not (as we illustrated¹). The suggestion by Mathalon et al that the illogical positive correlation between clinical improvement and brain shrinkage²⁻⁴ is a regression to the mean artifact is not tenable, because, if anything, such systematic effects on one variable (ie, symptom change) would obscure a within-subject correlation between this variable and another (ie, MRI measures). As noted in our article,¹ the problem is not just widespread inconsistency but improbable contradictions (eg, greater sulci increases in one hemisphere but ventricle increases in the other hemisphere in the same people⁵; hippocampal volume decrease in one study of first-episode patients,⁶ yet an increase in another study of a similar population,⁴ and no change in still another⁷; and ventricular volume that literally bounces up and down from one clinical episode to another¹). Is it plausible that patients with schizophrenia would have more than twice the rate of "parenchyma loss" in their first year of illness⁸ than patients with primary progressive multiple sclerosis?⁹

The notion of Mathalon et al that "parenchyma lost" during treatment might represent a salubrious dissolution of noxious parenchyma is a creative proposal, but is there an example in central nervous system therapeutics of such a possibility (other than antineoplastic therapy)? The noxious parenchyma hypothesis implies that brain shrinkage is a desirable outcome for many patients. While it might be of clinical value if the MRI changes were potential targets for tracking the effects of treatments, the literature is very clear that clinical parameters are much more reliable as indications of clinical status than are MRI measurements.

As we stated in our article,¹ the argument is not about whether some MRI studies show progressive changes in measurements; the debate is about what is actually progressing, what causes it, and how important it is. Mathalon et al now concur with our suggestion that the changes may be physiologic, perhaps related at least in part to neuroplastic remodeling of cellular processes (or, as we also suggested, to changes in vascular volume, lipid compartments, or other magnetic properties¹). However, we would reiterate a caution here, as it is not clear that such cellular neuroplastic adaptations would translate into gross MRI volume changes (viz, the largely negative epilepsy literature^{1,10}). It also is