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Neuroanatomy of Down Syndrome *in vivo*: A Model of Preclinical Alzheimer's Disease

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Aging in Down syndrome (DS) is accompanied by neuropathological features of Alzheimer's disease (AD). Therefore, DS has been proposed as a model to study predementia stages of AD. MRI-based measurement of grey matter atrophy is an *in vivo* surrogate marker of regional neuronal density. A range of neuroimaging studies have described the macroscopic neuroanatomy of DS. Recent studies using sensitive quantitative measures of region-specific atrophy based on high-resolution MRI suggest that age-related atrophy in DS resembles the pattern of brain atrophy in early stages of AD. The pattern of atrophy determined in predementia DS supports the notion that AD-type pathology leads to neuronal degeneration not only in allocortical, but also in neocortical brain areas before onset of clinical dementia. This has major implications for our understanding of the onset and progression of AD-type pathology both in DS and in sporadic AD.

KEY WORDS: Alzheimer's disease; atrophy; cerebral cortex; down syndrome; morphometry; MRI.

THE NEUROPATHOLOGY OF DS AS A MODEL FOR PRECLINICAL ALZHEIMER'S DISEASE

Subjects with Down syndrome (DS) older than 40 years show an age-related cognitive impairment with early memory involvement followed by a linear decline in non-memory cognitive function (Alexander *et al*., 1997; Lai and Williams, 1989; Schapiro, *et al*., 1992). Cognitive impairment progresses to a dementia syndrome resembling Alzheimer's disease (AD) (Alexander *et al*., 1997; Evenhuis, 1990; Lai and Williams, 1989; Schapiro, *et al*., 1992). Prevalence of dementia has been estimated to reach 5% to 10% until the fifth decade of life and 40% to 50% by the sixth decade of life in DS (Evenhuis, 1990; Lai and Williams, 1989). Postmortem studies show that at 40 years of age virtually all DS subjects have neuropathological lesions that meet the pathological criteria for AD (Mann *et al*., 1984; Wisniewski *et al*., 1985a, b). Similar to patients with sporadic AD, elderly DS subjects show cerebral atrophy, deposition of Aβ protein in extracellular senile plaques and perivascular amyloid (amyloid angiopathy), intraneuronal neurofibrillary tangles (NFT) and extracellular neuritic plaques and neuropil threads (Jellinger and Bancher, 1998; Mann, 1988). Aβ protein derives from atypical splicing of an ubiquitous transmembrane protein, the amyloid precursor protein, which is coded on chromosome 21 (Vassar, 2005). Neuritic changes arise from the formation of paired helical filaments (PHF) containing polymerized hyperphosphorylated tau protein triplets and cause disruption of the neuronal cytoskeleton with loss of synapses and neurons and altered cortico-cortical connectivity, leading to disconnection of the cerebral cortex (Morrison *et al*., 1986). Neuropathological changes in sporadic AD follow a specific sequence starting in transentorhinal and entorhinal cortex in preclinical stages, later spreading to the hippocampus and involving neocortical association regions in more advanced stages of disease. Primary sensorimotor areas are relatively spared even at severe stages of AD

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(Braak *et al*., 1997). A subcortical area typically affected is the cholinergic nucleus basalis Meynert in the basal forebrain (Mesulam, 2004; Teipel *et al*., 2005). Although the role of plaques and NFT in the pathogenesis of AD remains undetermined, clinicopathological studies have shown that both lesions, if present in sufficient numbers, particularly in the neocortex, are the best morphological marker for AD. Recent studies on neuronal death in AD have indicated only an indirect relationship between neuronal loss and both Aβ deposition and NFTs. Therefore, both AD markers appear to increase the risk of cells to degenerate, but are not the sole cause of the degenerative process in AD.

DS subjects can exhibit significant amyloid deposition in the cerebral cortex already in their third or fourth decade of life (Ikeda *et al*., 1989; Rumble *et al*., 1989). Earliest pathological changes are thought to occur in the medial temporal lobe, after which they are found in neocortical association regions by age of 40 (Hof *et al*., 1995; Hyman *et al*., 1995; Mann and Esiri, 1989; Sadowski *et al*., 1999). An important factor for the development of the neuropathological and clinical phenotype of AD in elderly DS subjects is an increased amyloid burden due to an extra copy of the amyloid precursor protein gene on chromosome 21 (Rumble *et al*., 1989). The laminar and regional cortical distribution of amyloid and neurofibrillary pathology and neuronal loss closely resembles that of AD. On this basis, DS has been proposed as a model to study the predementia stages of AD (Mann, 1988). There are, however, dissimilarities between both pathologies. Pyramidal neuron abnormalities with reduced dendritic arborization, decreased numbers of spines, spine atrophy and anomalies of spine orientation are already present in infancy and fetal stages of DS (Becker *et al*., 1991b). Additionally, there are cytoskeletal abnormalities in DS (Mann *et al*., 1989). These developmental abnormalities make the brain of DS subjects vulnerable for any type of lesions and might contribute to the early onset of dementia in DS subjects. Therefore, the use of DS as a predementia model of AD has to take into account that developmental abnormalities and DS-specific degenerative processes contribute to the neuropathological substrate of dementia in DS.

METHODOLOGICAL BASIS OF MRI ANALYSIS TECHNIQUES

MRI-based measurement of regional brain atrophy can provide an *in vivo* estimate of neuronal loss in neurodegenerative disease. This has specifically been shown for hippocampus atrophy as a measure of allocortical neuronal loss in AD (Bobinski *et al*., 2000; Jack *et al*., 2002; Nagy *et al*., 1996). There are no clinical–pathological correlational studies for other MRI-based volumetric measurements, such as entorhinal cortex, cortical gray matter volume or corpus callosum, but *in vivo* estimates of atrophy derived from MRI-based measurements in areas other than the hippocampus agree with the distribution of neuronal loss and neurofibrillary pathology in postmortem studies in AD (Chetelat and Baron, 2003; Nagy *et al*., 1999; Smith, 2002; Weis *et al*., 1991a). Therefore, MRI-based measurement of regional brain atrophy may also be useful in elderly DS subjects to determine brain atrophy related to AD-type pathology. Based on the evidence from neuropathological studies these changes can be interpreted as *in vivo* marker of progressive AD-related neuron loss. As structural MRI has no known side effects in patients without ferromagnetic implants, it allows repeated examinations over time to study the progression of regional atrophy. Volumetric assessments are based on three-dimensional T1 weighted MRI sequences with a spatial resolution of about 1 mm in all three axes. Acquisition of such a sequence takes about 10–15 min on a 1.5 Tesla scanner. In recent years, 3-T scanners became more widely available so that in the near future volumetric studies will use T1 weighted sequences at 3-T with higher resolution and higher signal to noise ratio.

A wide array of techniques has been developed to determine the extent of regional brain atrophy from volumetric MRI data: (i) visual rating scales, (ii) observer-driven manual volumetry (Fig. 1) and (iii) automated voxel-based techniques (Fig. 2).

Visual rating scales are easily applicable at the cost of relatively low inter-rater reliability (Frisoni *et al*., 2003). Moreover, they are limited to few anatomical features, like gross brain atrophy, ventricular enlargement or hippocampus atrophy. They are useful for the assessment of individual brain atrophy in clinical routine. Manual volumetric measures are time-consuming, but provide much higher inter-rater reliability. Like visual ratings, manual volumetric measures are limited to few anatomical features. In contrast, automated morphometric techniques provide fast and reliable segmentation of a multitude of anatomical features within a spatial resolution at voxel-level (Ashburner and Friston, 2000). However, all automated techniques are prone to artifacts induced by differences in image quality leading to

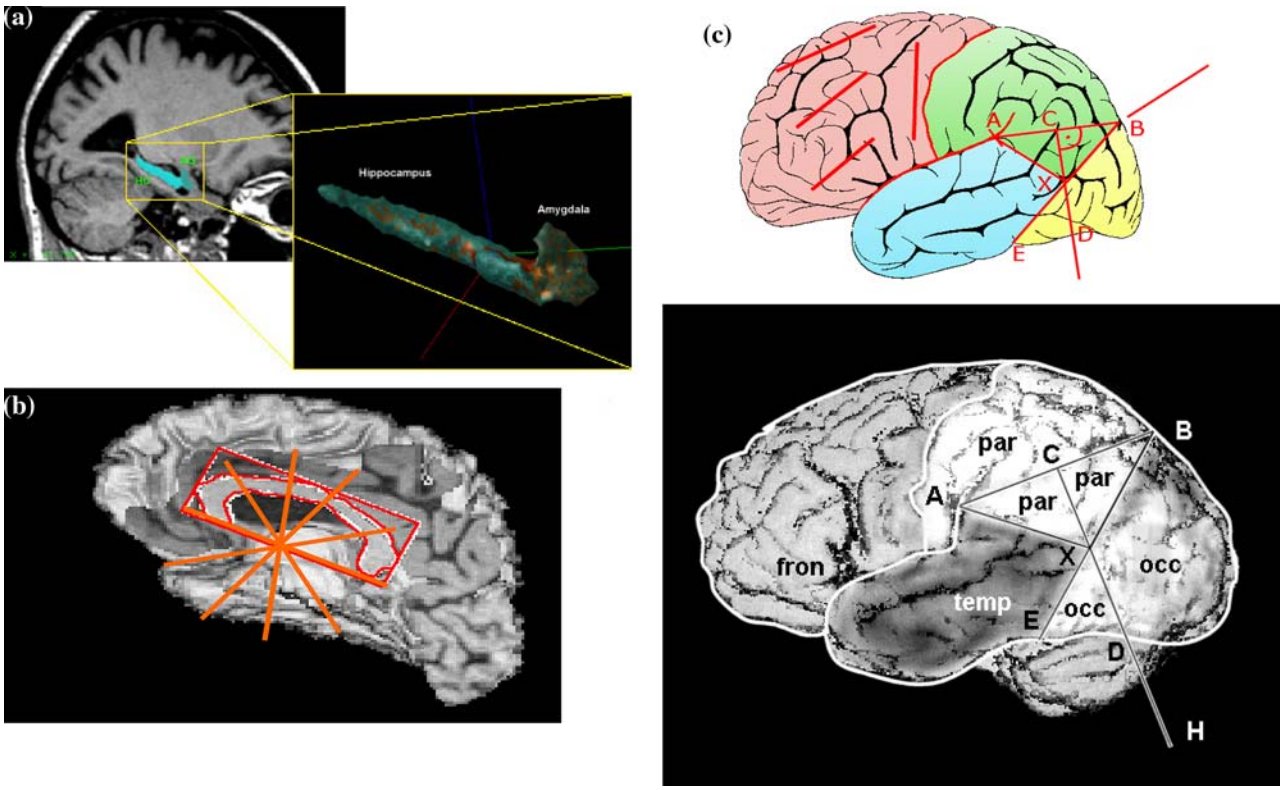

Fig. 1. Manual volumetric measures. (a) Hippocampus/amygdala volumetry. Left: sagittal MRI section through the right hippocampus with the hippocampus (light blue) and the amygdala (turquoise, anterior to hippocampus) manually labeled. Right: three-dimensional reconstruction of the hippocampus and amygdala from manually labeled volumetric MRI scans (Hampel *et al.*, 2002b). (b) Corpus callosum. Midsagittal MRI section through the brain with the corpus callosum and five corpus callosum subregions manually outlined (Teipel *et al.*, 2002a). C1 – Rostrum; C2 – anterior truncus; C3 – middle truncus; C4 – posterior truncus and isthmus; C5 – Splenium. (c) Lobar volumes. Upper row: Schematic drawing of lobar borders on the sagittal surface of the brain: central sulcus between frontal and parietal lobes; lateral sulcus between frontal and temporal lobes; geometrical construction based on the sulcus parieto–occipitalis and the most posterior point of the lateral sulcus between parietal, temporal and occipital lobes. Lower row: Lobar borders projected on the lateral surface projection of the brain from a volumetric MRI scan (Bokde *et al.*, 2002).

local misregistration (Bookstein, 2001). This is particularly true for multicenter data, so that few studies so far have tried to pool MRI data from several centers for automated morphometric analysis. Results from automated analysis always should be compared with findings from manual volumetric studies and results from independent samples to assess their validity.

MRI SHOWS THE NEUROANATOMY OF DS *IN VIVO*

The neuroanatomy of DS has two dimensions: (i) the developmental abnormality of the brain constituting an important part of the DS phenotype and (ii) the progressive brain atrophy with advancing age in DS adults that is superimposed on the developmental abnormality and is believed to result partly from AD-type pathological changes. In recent years, autopsy data on the neuroanatomy of DS have been complemented by an increasing body of evidence from *in vivo* structural imaging using CT and to a larger extent MRI.

MRI Shows the Developmental Abnormalities of the DS Brain

The brain of DS subjects is characterized by several postmortem macroscopic features which are related to pre- and post-natal abnormalities in synaptogenesis leading to retardation of brain growth (Schmidt-Sidor *et al.*, 1990): lower brain weight and brachycephaly, with a small cerebellum, frontal and temporal lobes, reduced number and depth of the cerebral sulci, and a narrow superior temporal gyrus

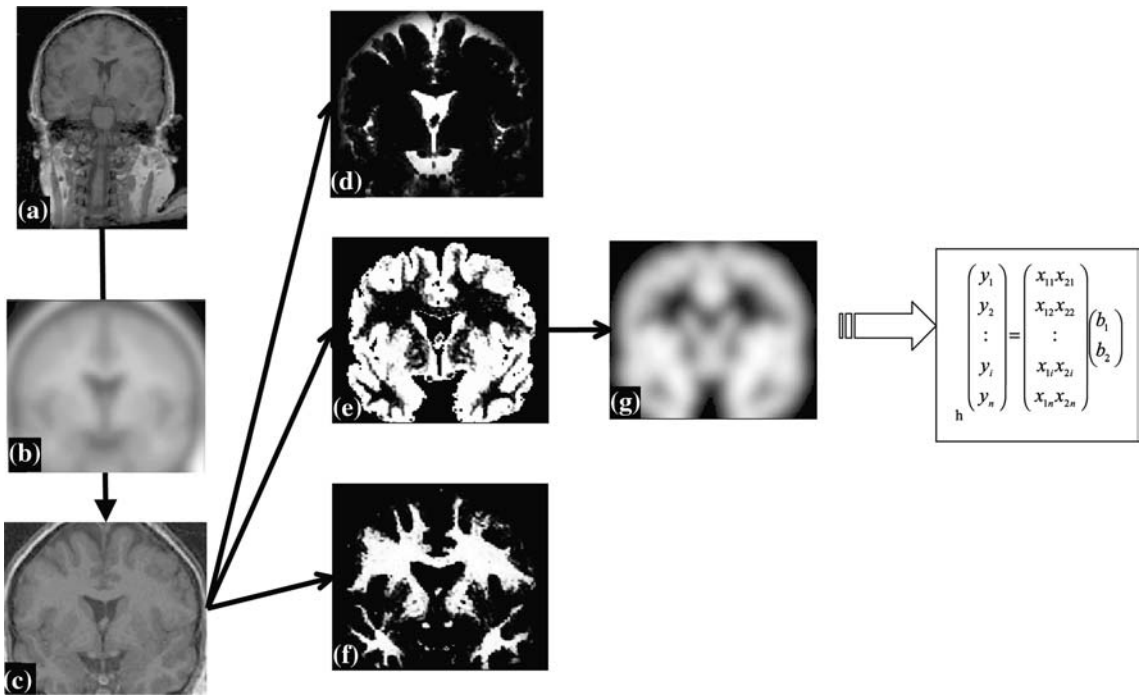

Fig. 2. The processing stream of classical VBM An MRI volume of the brain in native space (a) is transformed into standard space according to the Talairach and Tournoux coordinate system (Talairach and Tournoux, 1988) using a non-linear transformation algorithm in reference to a standard brain template (b), resulting in an MRI brain volume in standard space (c). This volume is segmented into cerebrospinal fluid (d), gray matter (e) and white matter (f) maps. After smoothing with a Gaussian kernel (g), MRI volumes in standard space are pooled across several subjects and can be subjected to statistical analysis on a voxel by voxel basis, typically using the general linear model framework (matrix h).

(Becker *et al.*, 1991a; Coyle *et al.*, 1986; Wisniewski, 1990). Even after controlling for body size, brain volume is smaller in DS subjects compared to age-matched normal controls (Raz *et al.*, 1995; Yoshimura *et al.*, 1990). MRI studies show a consistent phenotype of regional brain abnormalities compared to age-matched non-DS subjects. Table I gives an overview on MRI volumetric findings in young and non-demented adult DS subjects compared to age-matched non-DS controls.

Consistent with postmortem data, overall brain volume is reduced in DS subjects, including cerebellum and cerebral gray and white matter. Hippocampus volume is disproportionally reduced, whereas amygdala volume reductions do not exceed the overall reduction of brain size. Interestingly, parahippocampal gyrus volume is relatively larger in DS (Kesslak *et al.*, 1994; Raz *et al.*, 1995). This might be related to developmental abnormalities in neurogenesis. Only one study investigated the relative reductions of cerebral lobe volumes in DS (Pinter *et al.*, 2001b), one study investigated volumes of anterior and posterior cortex (Jernigan, *et al.*, 1993). Cerebral volume reductions were predominant in frontal and occipital lobes, as well as in planum temporale and superior temporal gyrus. Absolute volumes of temporal and parietal lobes were reduced, but these effects were no more significant after adjustment for overall brain size. The relative preservation of temporal lobe volume was related to a significantly larger white matter volume after adjustment for brain size. The authors speculated that this might reflect a selective abnormality in white matter maturation. An additional factor, however, may be methodological difficulties in determining the posterior borders of the temporal lobes on MRI scans, as their method relied on a semi-automated parcellation of the brain using a pediatric template. It is not clear from the study whether the use of a normal pediatric brain template might have introduced a bias in defining the lobe borders on the differently proportioned brains of the DS subjects. In two previous studies, subcortical gray matter structures (basal ganglia, thalamus) were normal in DS (Jernigan *et al.*, 1993; Pinter *et al.*, 2001b).

Table I. MRI Findings on Developmental Abnormalities of the Brain in DS

Region	Effect	Reference
Total brain volume	↓	Pinter *et al.* (2001b), Weis *et al.*, (1991b)
Gray matter	↓	
White matter	↓	
Total cerebral volume	↓	Pinter *et al.* (2001b), Weis *et al.* (1991b)
Gray matter	↓	
White matter	↓	
Cerebellar volume	↓	Pinter *et al.* (2001b)
Hippocampus	↓ after adjustment for overall brain volume	Pinter *et al.* (2001a), Pearlson *et al.* (1998), Aylward *et al.* (1999), Raz *et al.* (1995)
Amygdala	↓ not different after adjustment for overall brain volume	Pinter *et al.* (2001a), Aylward *et al.* (1999)
Parahippocampal gyrus	↑ after adjustment for overall brain volume	Raz *et al.* (1995), Kesslak *et al.* (1994)
Frontal lobe	↔ after adjustment for overall brain volume	Pinter *et al.* (2001b)
	↓ Anterior cortex, including frontal and anterior temporal lobe, after adjustment for total cerebral gray matter volume	Jernigan *et al.* (1993)
Parietal lobe	↑ after adjustment for overall brain	Pinter *et al.* (2001b)
	↑ Posterior cortex, including superior parietal lobes, after adjustment for total cerebral gray matter volume	Jernigan *et al.* (1993)
Temporal lobe	↑ after adjustment for overall brain volume	Pinter *et al.* (2001b)
Occipital lobe	↔ after adjustment for overall brain volume	Pinter *et al.* (2001b)
Superior temporal gyrus	↔ after adjustment for overall brain volume	Pinter *et al.* (2001b), Frangou *et al.* (1997)
Planum temporale	↓ after adjustment for overall brain volume	Frangou *et al.* (1997)
Lenticular nucleus	↑ after adjustment for total cerebral gray matter volume, ↔ absolute volumes	Jernigan *et al.* (1993), Pinter *et al.* (2001b)
Diencephalon (thalamus and hypothalamus)	↑ after adjustment for total cerebral gray matter volume, ↔ absolute volumes	Jernigan *et al.* (1993), Pinter *et al.* (2001b)
Ventricles	↑	Pearlson *et al.* (1998)
Corpus callosum	↓ (Rostrum)	Wang *et al.* (1992)

Summary of MRI findings in different brain areas:
↑ – increase of volume
↓ – decrease of volume
↔ – no volume change.

MRI Shows Effects of Aging on the DS Brain

Potential Study Designs

Age-related changes of brain morphometry in elderly non-demented DS subjects are thought to represent the effect of preclinical AD-type pathology. However, the effects of aging are superimposed on preexisting developmental brain abnormalities in DS. Therefore, the design of an MRI study may depend upon the specific question to be answered. Not every design is able to differentiate between developmental abnormalities and age-related changes of the brain in DS. Three basic designs can be distinguished:

(i) studies comparing elderly DS subjects with elderly non-DS subjects are suitable for the description of correlations between regional brain measurements and cognitive abnormalities, but not the differentiation between the contribution of developmental and age-related alterations.

(ii) studies comparing elderly DS subjects with younger DS subjects can describe age-related alterations in brain morphology possibly linked to AD-type pathology. However, they cannot distinguish between the effects of age and AD-type pathology.

(iii) studies providing an intra-individual timeline of regional brain atrophy are often difficult to perform due to methodological limitations (changes in scanner hardware over time, selection bias over time due to non-randomly missing subjects), but are the gold standard to determine the effect of AD-type pathology on the DS brain.

MRI Findings on Age Effects in the Medial Temporal Lobes

In recent years, *in vivo* studies using magnetic resonance imaging (MRI) have investigated age-related brain atrophy in DS. Several computer assisted tomography (CT) and MRI studies have reported significantly reduced volumes of the hippocampus and adjacent medial temporal lobe structures with advancing age in non-demented DS subjects (Kesslak *et al*., 1994; Krasuski *et al*., 2002; Lawlor *et al*., 2001). Hippocampus and amygdala volumes are significantly correlated with decline of memory function, even after controlling for overall cognitive performance and age (Krasuski *et al*., 2002). These findings agree with neuropathological evidence of extensive tangle pathology and neuronal loss in entorhinal cortex and hippocampus (Hof *et al*., 1995; Sadowski *et al*., 1999) as well as the early decline of memory function in elderly DS subjects.

Two studies found no atrophy of hippocampus and parahippocampal gyrus before onset of dementia. Both studies, however, together with others showed reductions of hippocampus and parahippocampal gyrus volumes in elderly demented DS subjects compared to non-demented, younger DS subjects (Aylward *et al*., 1999; Pearlson *et al*., 1998; Raz *et al*., 1995). In summary, hippocampus volume declines with age, most likely even before onset of dementia. This decline is superimposed on developmental reductions of hippocampus volume. Parahippocampal gyrus volume declines with age in DS, this decline, however, seems to start from a developmentally relatively spared or even increased parahippocampal volume.

MRI Findings on Age Effects in Neocortical Areas

The most consistent age-related finding in DS subjects outside of the medial temporal lobe in cross-sectional studies was an increase of ventricular volume with age in demented elderly DS subjects (Ikeda and Arai, 2002; Kesslak *et al*., 1994). There are only few studies focusing on the onset and progression of neocortical atrophy in DS adults. Manual measures of total brain and gray matter volumes showed no significant atrophy before the onset of dementia (Kesslak *et al*., 1994; Pearlson *et al*., 1998; Raz, *et al*., 1995; Schapiro *et al*., 1989; 1992). However, demented DS subjects showed progressive atrophy of brain gray matter predominantly in temporal lobes, and widening of cerebrospinal fluid spaces in serial CT examinations (Ikeda and Arai, 2002; Lai and Williams, 1989; Schapiro *et al*., 1989). It has been suggested that significant brain atrophy occurs only when dementia becomes manifest in older DS subjects (Schapiro *et al*., 1989). Evidence from AD, however, suggests that regional atrophy precedes onset of clinical dementia not only in the hippocampus, but also neocortical brain regions (Fox *et al*., 2001; Karas *et al*., 2004; Pennanen *et al*., 2005). The lack of predementia neocortical atrophy in DS found in these earlier studies might be related to low sensitivity of the measures employed, particularly CT-based volumetry and visual ratings, a relatively narrow age-range, and small sample sizes.

Recent studies have employed more sensitive markers to detect neocortical atrophy in predementia stages of DS. A potential marker of neocortical degeneration is the corpus callosum (Hampel *et al*., 2002a). The corpus callosum fibers originate from layer III and V pyramidal neurons in the cerebral cortex (Innocenti, 1986), which are early and specifically affected by AD-type pathology (Morrison *et al*., 1986; Pearson *et al*., 1985). Corpus callosum area is reduced both in postmortem examination (Weis *et al*., 1991a) and in *in-vivo* MRI studies (Hampel *et al*., 1998) in AD patients. Corpus callosum area correlates with measures of cortical dysfunction derived from PET and EEG, supporting the notion that corpus callosum atrophy can be used as a marker of neocortical neuronal degeneration in AD (Hampel *et al*., 2002a; Janowsky *et al*., 1996; Teipel *et al*., 1998, 1999, 2002b; Yamauchi, *et al*., 1993). On this basis, we determined corpus callosum atrophy in 34 DS subjects and 32 healthy control subjects. We found significant atrophy of the corpus callosum even before onset of dementia in DS adults (Teipel *et al*., 2003). The extent of corpus callosum atrophy in elder compared to younger DS subjects was comparable to that of hippocampus atrophy. The age-related decrease of corpus callosum was most pronounced in the splenium area, representing projections from posterior temporal, superior parietal and occipital cortex (De Lacoste *et al*., 1985). These findings suggest that loss of inter-hemispheric projecting neurons in posterior association cortex precedes the clinical onset of dementia in DS. Corpus callosum atrophy is a specific marker for the loss of intra-cortical projecting neurons, but has limited spatial resolution. Therefore, in a subsequent study, we used an automated voxel-based approach to determine the extent of regional cortical gray matter loss in predementia stages of DS (Teipel *et al*., 2004). In recent years,

voxel-based morphometry (VBM) has been developed to search the entire brain for morphological changes (Ashburner and Friston, 2000). VBM is observer independent and automated, and therefore highly replicable. It allows for processing of a high number of scans within a relatively short time, and can detect morphological changes throughout the entire brain. Using VBM, we investigated age-related changes of gray matter volume within a DS group (Teipel *et al.*, 2004). Gray matter maps were determined from volumetric T1 weighted MRI scans obtained in coronal orientation on a 1.5-T scanner (General Electric Signa II, Milwaukee). The protocol followed a modification of the previously established processing stream of VBM (Fig. 2) (Good *et al.*, 2001). In a group of 32 DS subjects, age was significantly correlated with decline of cortical gray matter in parietal, frontal and occipital cortex (mainly lingual cortex), as well as temporal lobe and parahippocampal gyrus. The effects were most pronounced in superior parietal lobes, which agrees with the findings of predominant corpus callosum atrophy in the splenium receiving major projections from superior parietal lobes (Fig. 3).

This study only included subjects without dementia, from 25 up to 62 years of age. When cortical gray matter volumes were correlated with a test of verbal memory, decline in memory performance was correlated with reduced gray matter volume in left superior and middle temporal gyrus, bilateral precuneus, left hippocampus, right middle temporal gyrus, and right middle frontal gyrus. Therefore, even after controlling for age and general cognitive function, correlations between episodic memory and gray matter volume revealed brain areas which are thought to be associated with visual attention (precuneus) (Corbetta *et al.*, 1995), episodic memory encoding (hippocampus) (Greicius *et al.*, 2003; Squire and Zola-Morgan, 1991), episodic memory retrieval (right prefrontal cortex) (Lee, *et al.*, 2000; Rugg *et al.*, 2002) and language (left temporal pole, left lateral temporal cortex, including Wernike's area) (Benson, 1988; Cabeza and Nyberg, 2000). These findings may indicate that impaired memory performance in the DS subjects is related to local morphological brain changes, most likely on the basis of developmental abnormalities or neurodegenerative changes or both. One has, however, to take into account that only non-demented subjects were included which led to a ceiling effect in the memory scores.

MRI findings on age-related brain changes in DS are summarized in Table II.

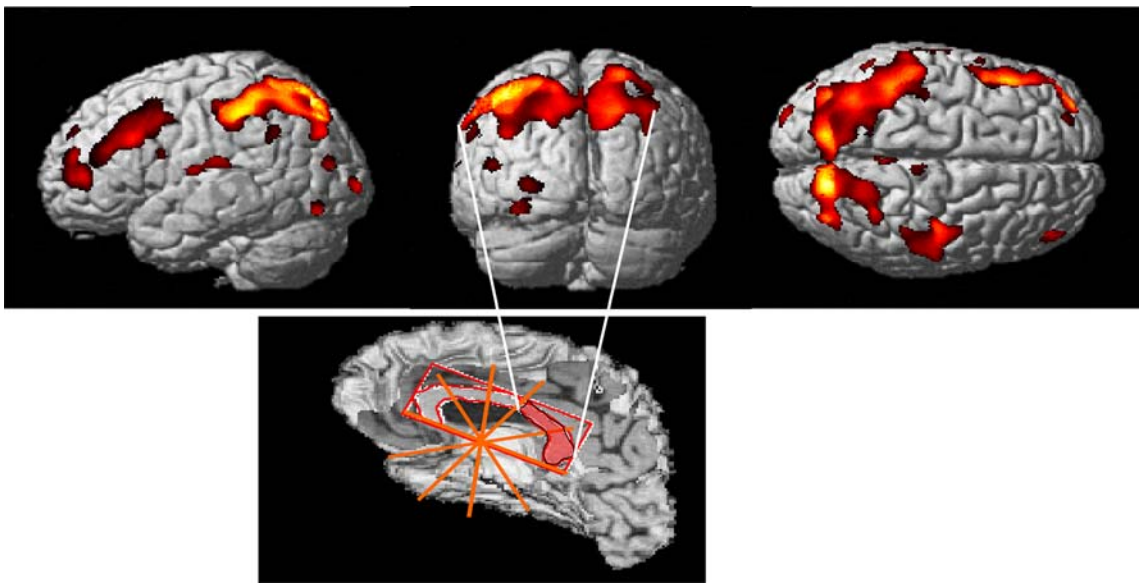

Fig. 3. Age-related reduction of cortical gray matter and corpus callosum area in non-demented DS subjects Upper row: Color coded map of significant negative correlations between gray matter and age projected on the normalized rendered brain surface from the MRI scan of a DS subject. Gray matter is significantly reduced with age in bilateral superior parietal lobes, prefrontal cortex and lateral temporal lobes, as well as medial temporal lobes (not shown) (Teipel *et al.*, 2004). Lower row: Midsagittal section, outlining the corpus callosum. Age-related reductions are most pronounced in posterior corpus callosum (splenium) (Teipel *et al.*, 2003). This area is known to receive major projections from posterior association cortex, particularly superior parietal lobes (De Lacoste *et al.*, 1985).

Table II. MRI Shows Age-related Brain Atrophy in DS

Region	Effect	Reference
Non-demented elderly DS subjects versus young DS subjects		
Hippocampus	↓	Krasuski *et al.* (2002) (Kesslak *et al.*, (1994
Parahippocampal gyrus	↓	Krasuski *et al.* (2002)
Corpus callosum	↓ (Splenium)	Teipel *et al.* (2003)
Total brain volume	↔	Kesslak *et al.* (1994), Pearlson *et al.* (1998), Raz *et al.* (1995), Schapiro *et al.* (1989, 1992)
Total gray matter volume	↔	Kesslak *et al.* (1994), Pearlson *et al.* (1998), Raz *et al.* (1995), Schapiro *et al.* (1989, 1992)
Demented DS subjects versus non-demented DS subjects		
Total brain volume	↓	Kesslak *et al.* (1994), Pearlson *et al.* (1998), Raz *et al.* (1995), Schapiro *et al.* (1989, 1992)
Total gray matter volume	↓	Kesslak *et al.* (1994), Pearlson, *et al.* (1998), Raz *et al.* (1995), Schapiro *et al.* (1989, 1992)
Frontal cortex	↓	Teipel *et al.* (2004)
Temporal lobes	↓	Lai and Williams, (1989), Teipel *et al.* (2004)
Parietal cortex	↓	Teipel *et al.* (2004)
Hippocampus	↓	Lawlor *et al.* (2001)
Parahippocampal gyrus	↓	Krasuski *et al.* (2002), Teipel *et al.* (2004)
Ventricles	↑	Kesslak *et al.* (1994), Ikeda and Arai, (2002)

Summary of MRI findings in different brain areas:
↑ – increase of volume
↓ – decrease of volume
↔ – no volume change

Interpretation of MRI Findings and Their Limitations

These findings suggest that, like in AD, regional brain atrophy, including hippocampus, parahippocampus, but also neocortical association areas, accompanies aging in DS and can be detected even before the onset of clinical dementia. The most likely substrate of these macroscopic changes are progressive AD-related pathological changes in the DS brain composed of tangle and plaque accumulation as well as synaptic and neuronal loss. These changes precede the onset of dementia in DS and can be detected *in vivo* using high resolution imaging techniques like hippocampus and corpus callosum volumetry as well as VBM.

There are, however, two caveats to be taken into account for the interpretation of these findings: First, DS is a developmental disorder and therefore any age related changes are superimposed on developmental abnormalities. This is well illustrated by a recent study (White *et al.*, 2003) demonstrating morphological differences between adult non-demented DS subjects and healthy age matched controls using MRI and VBM. DS subjects had reduced gray matter volume in cerebellum, left medial frontal lobe, right superior and middle temporal lobe, and anterior and middle cingulated gyrus. This regional pattern of gray matter changes is clearly distinct from the age effects we found in the non-demented DS subjects using VBM (Teipel *et al.*, 2004). It can, however, not be excluded that age effects are masked by higher variability of brain morphology in brain areas which are severely affected by developmental abnormalities. Second, the resemblance between DS and AD neuropathology is close, but not perfect. Plaque density was found to be higher in many DS subjects compared to AD patients and more widely distributed throughout the cortex (Hof *et al.*, 1995). Additionally, results of several studies suggest cytoskeletal abnormalities in DS (Mann *et al.*, 1989), and overexpression of proteins other than amyloid which may contribute to neurodegeneration (De La Torre *et al.*, 1996; Engidawork and Lubec, 2001). Therefore, the possibility cannot be excluded that age-effects on cortical gray matter in non-demented DS subjects reflect at least partially DS-specific degenerative processes other than AD.

SUMMARY AND PERSPECTIVES

There is conclusive evidence for both, developmental abnormality of neuroanatomy and age

associated brain atrophy in DS. An important task for future studies is the quantitative analysis of serial MRI examinations in non-demented elderly DS subjects followed over several years, some of them until conversion into dementia. These data would be very important to distinguish between developmental and age-associated (degenerative) alterations of brain morphology in DS. A wide range of cross-sectional studies, however, provides strong evidence for an independent contribution of age-associated neurodegeneration to progressive brain atrophy, particular in medial temporal lobes and posterior association cortex, the typical predilection areas of sporadic AD. Therefore, MRI investigation of brain aging in DS not only gives new insight in the onset and progression of neurodegenerative changes in DS, but also opens a window into the preclinical stages of AD. The finding of allocortical and neocortical brain atrophy in non-demented elderly DS subjects suggests that both allocortical and neocortical neuronal loss precedes the onset of clinical dementia in AD-type pathology. This has implications for our understanding of the onset of allocortical and neocortical neurodegeneration in AD. In particular, it supports the notion that treatment in AD should be initiated early in the course of the disease in order to rely on intact neuronal systems and even suggests that treatment should precede onset of clinical dementia. This will be even more important once disease modifying treatment approaches become available. From the diagnostic perspective, the findings on neocortical atrophy in predementia stages of DS-related AD suggest that structural MRI analysis should not only involve hippocampal, but also neocortical measures for the early detection of AD-related pattern of brain atrophy.

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