

**ALZHEIMER'S DISEASE IN DOWN SYNDROME**E. HEAD<sup>1</sup>, D. POWELL<sup>2</sup>, B. T. GOLD<sup>3</sup>, F.A. SCHMITT<sup>4</sup>*Sanders-Brown Center on Aging<sup>1,3,4</sup>**Department of Molecular and Biomedical Pharmacology<sup>1</sup>**Magnetic Resonance Imaging and Spectroscopy Center<sup>2</sup>**Department of Anatomy and Neurobiology<sup>3</sup>**Department of Neurology<sup>4</sup> University of Kentucky Lexington, KY, USA*

**A key challenge to adults with Down syndrome (DS) as they age is an increased risk for cognitive decline, dementia, and Alzheimer disease (AD). In DS persons ranging from 40-49 years of age, 5.7-55% may be clinically demented and between 50-59 years, dementia prevalence ranges from 4-55% (reviewed in (Head et al, 2012)). Despite the wide ranges reported for dementia prevalence, a consistent feature of aging in DS is the progressive accumulation of AD brain pathologies. By the age of 40 years, virtually all have sufficient senile plaques and neurofibrillary tangles for a neuropathological diagnosis of AD (Wisniewski et al, 1985). Thus, there is dissociation between the age of onset of AD neuropathology (40 years) and increasing signs of clinical dementia. We discuss the hypothesis that frontal impairments are a critical factor affecting cognitive function and are associated with white matter (WM) and AD neuropathology. While these may be an early sign of conversion to dementia, we also review several other clinical comorbidities that may also contribute to dementia onset.**

Down syndrome (DS) was initially described by J. Langdon Down in 1866 (Down, 1866) and identified as a chromosome 21 trisomy by Lejeune in 1959 (Lejeune et al, 1959). DS or trisomy 21 is one of the most common causes of intellectual disability and recent national prevalence estimates suggest that 13.65 per 10,000 live births are infants with DS leading to 5,429, on average, annual DS births (Center, 2006). DS is associated with characteristic facial features, deficits in the immune and endocrine systems and delayed cognitive development (Roizen and Patterson, 2003). Improvements in medical care for children and adults with DS, have led to significant extensions in lifespan and enhanced quality of life (Glasson et al, 2002, Bittles et al, 2006). As a consequence, up to age 35 years, mortality rates

are comparable in adults with DS to individuals with intellectual disability from other causes (Strauss and Eyman, 1996). However, after age 35, mortality rates double every 6.4 years in DS as compared to every 9.6 years for people without DS (Strauss and Eyman, 1996).

*Dementia in Adults with DS*

A key challenge for adults with DS as they age is the increasing risk for developing clinical symptoms of AD. A recent report suggests that 75% of adults with Down syndrome survive to 50 years of age and 25% over 60 years of age (Glasson et al, 2002). The proportion of these surviving individuals that develop clinical dementia can vary considerably. Between the ages of 20-29, two studies consistently

*Keywords: beta-amyloid, dementia, neurofibrillary tangles, oxidative damage, Trisomy 21*

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report that no individuals with DS were demented (Franceschi et al, 1990; Prasher and Filer, 1995). Between the ages of 30 and 39 years, reports of prevalence range between 0 to 33% of individuals being clinically demented (reviewed in (Head et al, 2012)). From 40-49 years of age, 5.7-55% may be demented and between 50-59 years prevalence ranges from 4-55% (reviewed in (Head et al, 2012)). Although based on smaller sample sizes, the range of individuals affected by dementia over the age of 60 years is between 15-77% (Lai and Williams 1989; Prasher and Filer, 1995; Zigman et al, 1996; Visser, 1997; Holland, 2000; Tyrrell et al, 2001). Further, estimated ages of onset in those individuals with dementia also appear to range from 48 to 56 years (Lai and Williams, 1989; Evenhuis, 1990; Prasher and Krishnan, 1993; Visser, 1997; Burt et al, 1998; Oliver et al, 1998; Devenny et al, 2000; Janicki and Dalton, 2000; Tyrrell et al, 2001; Zigman, 2002) with a subset of individuals showing an earlier age of onset (e.g. 46 years (Devenny et al, 2005)). Interestingly, AD neuropathology appears in virtually all adults with DS older than 40 years of age. A consistent observation in all of these studies, however, is that there is a subset of aged DS persons who do not appear to develop clinical signs of dementia at any age.

Decline in function in specific cognitive domains may be sensitive to early dysfunction and may occur at a younger age than a diagnosis of dementia. The pattern and sequence of cognitive impairments, distinct from a diagnosis of dementia, in adults with DS exhibit characteristics similar to AD in the general population (Owens et al, 1971; Dalton et al, 1974; Wisniewski et al, 1978; Thase et al, 1982; Lai and Williams, 1989; Oliver et al, 1998). Severe cognitive deterioration, such as acquired apraxia and agnosia, has been reported in 28% of individuals with DS at age 30 years with a higher prevalence of these impairments in subsequent years (Lai and Williams, 1989; Oliver et al, 1998). As reviewed by Carr, individuals with DS show a larger percentage decline in verbal ability (crystallized intelligence or verbal IQ) with a greater percentage deterioration in performance skills (performance IQ scores) throughout the aging process, in comparison to individuals with intellectual disability who do not have DS and in contrast to the general population

(Carr, 2005). The earliest manifestations of dementia in DS appear to involve changes in personality and behavior (Aylward et al, 1997; Cooper and Prasher, 1998; Holland et al, 2000), which are likely frontal-dependent. Pragmatics or socially deficient communication may be an early sign of frontal lobe dysfunction in DS and may represent a striking change from previous well developed social capacities in the disorder (Nelson et al, 1995). Thus, executive dysfunction may be an early sign of aging and progression to dementia in DS (Ball et al, 2008; Krinsky-McHale et al, 2008).

#### *Alzheimer's disease neuropathology in Down syndrome*

In parallel with the age-dependent increased risk for developing dementia virtually all adults with DS over the age of 40 years have sufficient neuritic plaques and neurofibrillary tangles for a neuropathologically based diagnosis of AD (Wisniewski, 1978; Wisniewski et al, 1985; Mann and Esiri, 1989). Senile plaques contain the b-amyloid (Ab) peptide that is derived from a longer precursor protein, b-amyloid precursor protein (APP), the gene for which is on chromosome 21. The most common form of DS, trisomy 21, leads to the overexpression of APP (Rumble et al, 1989). Thus, a primary focus of neurobiological studies in aged DS cases has been on APP processing and the temporal events in Ab pathogenesis (Head and Lott, 2004) reflecting the general hypothesis that Ab is thought to be a causative factor in AD pathogenesis and that overexpression of APP may lead to the elevated levels of Ab in DS (Hardy and Selkoe, 2002; Rovelet-Lecrux et al, 2006; Theuns et al, 2006). Extracellular Ab accumulation in diffuse plaques does not typically begin until after the age of 30 years (Mann and Esiri, 1989). Between the ages of 30 and 40 years, neuropathology rapidly accumulates until it reaches levels sufficient for a diagnosis of AD by 40 years (Wisniewski et al, 1985). Our own work also shows that there is an exponential rise in AD pathology, and specifically A $\beta$  measured biochemically after the age of 40 years (Nistor et al, 2007), suggesting an acceleration phase to disease development. There are reports of younger individuals with AD pathology although typically, not of sufficient extent for a neuropathology diagnosis of the disease (Lemere

**Table 1.** *Dementia health risks and Down syndrome dementia*

Dementia Health risk factor	Risk and Putative Mechanism	Down syndrome
Hypertension	Stroke; cerebrovascular disease; protein extravasation	Individuals with DS have lower resting heart rates and lower blood pressure than general population
Obesity	High BMI is associated with a 59% increased risk for AD; also a risk for sleep apnea syndrome (see below)	45-79% of males; 56-96% of females are reported to be overweight
Diabetes	May alter A $\beta$ clearance in brain; may promote inflammation	Age of onset ~22 years for Type 1 diabetes is comparable to general population's; Preliminary data on Type 2 diabetes suggests a lower rate, however.
Cardiovascular disease	Promotion of cerebrovascular disease; associated dyslipidemia increases risk of brain plaque pathology	Rate of mitral valve prolapse is high. However, lower risk for cardiovascular disease in adults with DS compared to general population; this includes lower rates of hypercholesterolemia and heart disease compared to adults with other Intellectual Disabilities
Cerebrovascular disease	Direct injury to brain regions involved in cognition; inflammation; hypoperfusion; increased A $\beta$ production	Lower risk for cerebrovascular disease observed in adults with DS compared to general population
Head injury	A $\beta$ and tau pathologies are increased in brain; increased APP production	No available epidemiological reports
Sleep apnea	Lowered oxygen during sleep impacting brain	An estimated 94% of persons with DS, ages 17-56 have obstructive sleep apnea of varying severity
Thyroid dysfunction	May reflect thyroid stimulating hormone on A $\beta$ processing; a cofactor for vascular dementia risk	Seen in 35 to 40% of adults with incidence increasing with advancing age; Hashimoto's thyroiditis may be mistaken for dementia
Seizures	Seen with neurodegeneration, early onset, and ApoE $\epsilon$ 4 in ~2 to 8% of persons with AD	Possible link to myoclonus epilepsy gene on chromosome 21; rate increases with age in DS from 7% to 46% (over age 50) up to 84% of persons with DS and dementia

*Cited from: (Bittles et al, 2007, Esbensen, 2010, Profenno et al, 2010, Barnes and Yaffe, 2011, Daviglus et al, 2011, Reitz et al, 2011)*

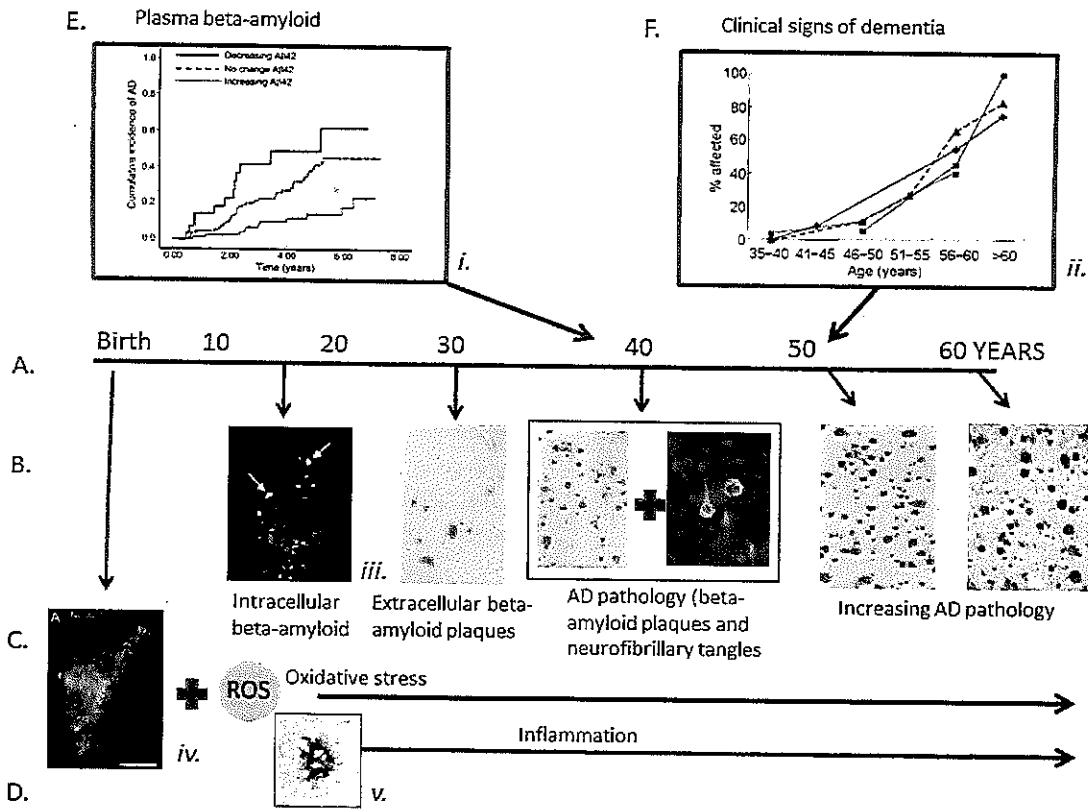


Fig. 1. Hypothetical sequence of neuropathological events as a function of age in Down syndrome.

et al, 1996; Leverenz and Raskind, 1998; Stoltzner, 2000). The source of extracellular A $\beta$  is neuronal and in autopsy studies of younger individuals with DS shows that as young as 15 years, intracellular A $\beta$  can be observed (Mori et al, 2002; Cataldo et al, 2004). Intracellular A $\beta$  is localized to endosomes, intracellular organelles responsible for degrading and turning over proteins within cells (Cataldo, 2000; Cataldo et al, 2004). A $\beta$  can also be measured in plasma and may be a very useful biomarker for conversion to dementia in DS (Schupf et al, 2010). Schupf and colleagues show that decreasing plasma A $\beta$ 42, increasing A $\beta$ 40 and a decline in the ratio of A $\beta$  42/A $\beta$  40 may indicate conversion. Interestingly, longitudinal changes in plasma A $\beta$  may be far more sensitive than a single-time measure, which does not discriminate between DS with and without dementia (Head et al, 2011).

In addition to A $\beta$  and NFT neuropathology, several other types of pathology have been reported at different ages that may contribute to the

development of dementia either early in the disease or possibly exacerbate cognitive symptoms later in disease. People with DS show higher levels of oxidative stress at all ages than people in the general population. For example, oxidative damage is increased in prenatal DS brains compared to non-DS controls (Brooksbank et al, 1985; Odetti et al, 1998) and is higher in adult DS brain compared to similarly aged individuals without DS (Cenini et al, 2012). Early increases in lipid peroxidation measured by 8,12-iso-iPF2 $\alpha$ -VI, is observed in the urine of young subjects (1-15 years) with DS, as compared to age-matched controls (Pratico et al, 2000). Mitochondria in DS, responsible for producing cellular energy but also for producing reactive oxygen species (ROS), are dysfunctional and in turn lead to abnormalities in APP processing and enhanced A $\beta$  production (Busciglio et al, 2002). Indeed mitochondrial dysfunction has been observed in fetal DS cells (Busciglio et al, 2002). Interestingly, the extent of protein carbonyl accumulation, 3-nitrotyrosine and

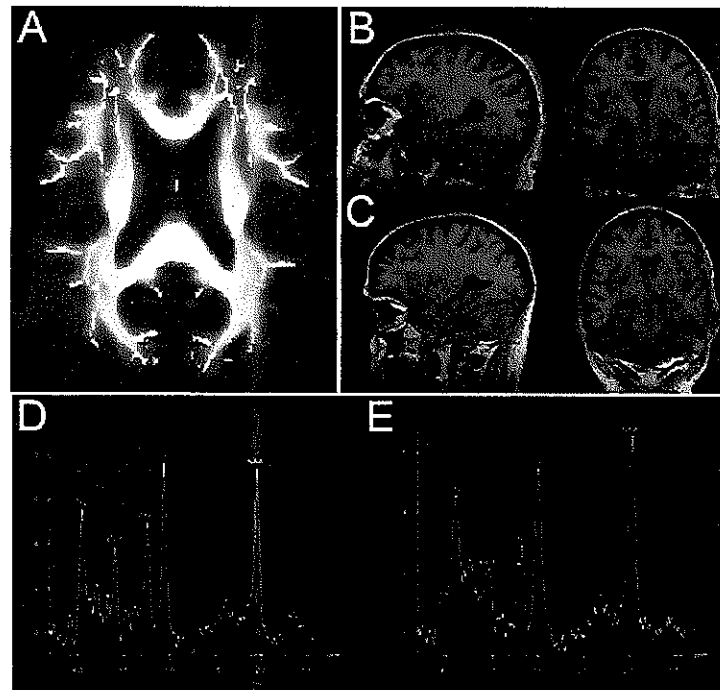


Fig. 2. Imaging in Down syndrome as a function of dementia

4-hydroxy-2-trans-noneal (HNE) (all indicators of oxidative damage) does not appear to increase with age *per se* in DS but HNE levels were higher overall in DS (Cenini et al, 2012). However, oxidized DNA/RNA is higher in DS and increases in the teens and twenties and is further exacerbated by the presence of A $\beta$  (Nunomura, 2000). Thus, some types of oxidative damage increase with age in DS prior to the development of AD neuropathology.

Neuroinflammation has been implicated in AD in the general population and the brains of people with AD show signs of microglial engagement, gliosis and upregulation of numerous cytokines and chemokines (Akiyama et al, 2000). Recently several genome wide array studies have shown that several genetic risk factors are associated with inflammation genes (Di Bona et al, 2008). There are inflammation genes on chromosome 21 that are overexpressed in DS (Wilcock, 2012). Although whether inflammation is a life-long phenomenon in DS and/or whether it is exacerbated with age and AD has yet to be fully explored (Wilcock, 2012). For example, complement (C1q) activation has been reported in a 15 year old

person with DS (Stoltzner, 2000) (although this person also had A $\beta$  deposition) but C1q activation is more consistently observed after 29 years of age (Stoltzner, 2000; Head et al, 2001) in parallel with the deposition of A $\beta$ . Microglial cells, key mediators of inflammation in the brain, also show pathology in people over the age of 40 years with DS and may be tightly linked to NFT accumulation (Xue and Streit, 2011). Interestingly, a lack of microglial activation was also reported in this study suggesting that the neuroinflammation theory be reconsidered both in DS and in AD (Xue and Streit, 2011).

#### *White Matter Degeneration in DS*

In addition to AD cortical pathology, there is some evidence of white matter (WM) degeneration that is more extensive in DS relative to non-DS autopsy cases or that increase with age and disease. Further, diffusion tensor imaging (DTI) studies have shown white matter degradation in non-DS women with a family history of dementia and at least one apolipoprotein E4 allele. While structural imaging studies have suggested a greater AD risk in non-DS

individuals with WM degeneration (Gold et al, 2012), there are few systematic studies of large collections of DS autopsy samples or DTI. Therefore, there are many gaps in our knowledge regarding the role of WM pathology and dementia.

A $\beta$  deposits and APP accumulation has been observed in the WM of the frontal cortex in DS (Ikeda et al, 1994; Tokuda et al, 1994). Ubiquitin positive punctuate deposits, that correspond to WM degeneration in the frontal cortex, increases after 21 years of age in DS (Mattiace et al, 1991). Interestingly, this pattern was virtually identical to non-DS autopsy cases. Corpora amylacea, thought to reflect swollen glial processes has also been observed in the frontal WM of a 32 year old DS case (Nishimura et al, 2000). The most recent study of WM pathology in DS showed that  $\alpha$ B-crystallin, which is a member of the heat shock protein family, was increased as a function of age up to 23 years in DS (older ages were not included in the study) (Palminiello et al, 2009). Given the role of  $\alpha$ B-crystallin in acting as a molecular chaperone to prevent aggregation of proteins and maintaining proteins in a folding-competent state under stress conditions, this suggests that the DS brain is under potentially chronic levels of stress and that WM is particularly vulnerable. Indeed, DRYK1a (a gene on chromosome 21), is expressed at higher levels in DS compared to controls when WM of the corpus callosum was examined (Dowjat et al, 2007) and may be a contributor to WM vulnerability to stress. Thus, in combination, there are small studies over the past two decades suggesting frontal cortex WM pathology and degeneration with age in DS.

WM degeneration may be caused by the development of AD or the aging process but is also strongly associated with cerebrovascular disease and associated risks (see Table 1). Although the risk of cerebrovascular accident in aging persons with intellectual disability is not different from the general population, the number of people with DS included in this study was small (Draheim et al, 2010; Jansen et al, 2012). In several ways, people with DS may be protected from cerebrovascular incidents given reports of generally lower blood pressure (Morrison et al, 1996) and lower incidence of atherosclerosis (Murdoch, 1977; Pueschel, 1992, Draheim et al, 2010). However, A $\beta$  is deposited along blood vessel

walls in people with DS in older ages and this can lead to cerebrovascular compromise and hemorrhage (Mendel et al, 2010).

Diffusion tensor imaging (DTI) is a magnetic resonance imaging technique (MRI) which represents a non-invasive in vivo method for characterizing the microstructural properties of WM connecting distributed cortical networks, by measuring the rate and direction of diffusion of water molecules in neural tissue (Basser et al, 2000; Beaulieu, 2002; Moseley, 2002; Le Bihan, 2003). Consequently, we are currently using DTI to evaluate white matter integrity changes in adults with DS (Figure 2A). DTI work in the process of being published by our lab suggests that similar regions are degraded in DS with AD subjects compared to DS subjects. Furthermore, some cognitive tests correlate with this loss of white matter integrity.

*Brain imaging functional and structural declines as a function of age and AD in DS.*

Age-associated impairments in DS may be linked to structural (e.g. MRI – Figure 2B,C) and functional brain changes observable by in vivo imaging approaches (e.g. PET). However, only a few functional brain imaging studies of DS have been reported. These are characterized by small samples and a variety of scanning tasks and imaging resolutions, so the results are sometimes inconsistent. For example, early reports on a small number of people with DS studied with FDG-PET showed higher cerebral glucose metabolic rate (GMR) than in non-trisomic individuals (Schwartz et al, 1983; Cutler, 1986). This was consistent with reports of cases of DS where higher than normal rates of synaptic density (and therefore more presumed neuronal activity) were found at autopsy (Cragg, 1975; Huttenlocher, 1979). Although these findings could be interpreted as consistent with some compensatory response, a larger PET study (Schapiro et al, 1988) failed to find any global or regional cerebral glucose metabolic rate differences (lower or higher) between DS (N=14) and non-trisomic controls (N=13). Other PET studies of DS showed inconsistent results (Schapiro et al, 1988; Schapiro et al, 1990; Dani et al, 1996; Pietrini et al, 1997), potentially due to methodological and sample differences.

Middle-aged people with DS (N=17) with no clinical signs of dementia, showed lower GMR compared with controls in several areas including the frontal lobe (BA47, BA11 - see (Haier et al, 2003) for a complete list) and the temporal lobe (BA38, BA22, BA37, BA39). In addition several areas of increased GMR relative to controls in DS included regions of the frontal and temporal cortex (Haier et al, 2003). Specifically, increased entorhinal cortex GMR compared to controls was seen. This suggests that increased GMR in the DS group could reflect early compensatory neural responses to dementia neuropathology such that regional GMR increases and decreases would predict subsequent clinical signs of dementia.

This hypothesis is supported by DS subjects' cognitive evaluations (e.g., Dementia Questionnaire for Persons with Intellectual Disability (DMR) (Evenhuis, 1996)). Although none of the DS subjects showed evidence of clinical dementia at the time, there was a range of DMR scores that correlated to increased GMR, consistent with a compensatory hypothesis (Haier et al, 2008). Further, structural MRI revealed areas where decreased grey matter (GM) volumes correlated with the DMR score. Based on the imaging data in DS so far, there is a critical need for longitudinal studies in adults with DS to track changes in the pre-dementia stage through the development of dementia. These studies could then link clinical decline to structural and functional *in vivo* imaging outcomes to help predict who is vulnerable to an earlier age of onset of dementia.

Another area of research involves magnetic resonance spectroscopy (MRS). In a recent report, Lamar and colleagues investigated the contribution of myo-inositol (mI) using *in vivo* proton MRS in persons with DS with and without dementia (Lamar et al, 2011). Hippocampal mI levels were higher in DS with dementia when compared to DS without dementia and age-matched controls. Further, differences were seen for N-acetylaspartate (NAA) as an index of mitochondrial function and neuronal density between the DS groups such that DS with dementia had lower NAA levels in hippocampus. As the myo-inositol transporter gene is located on chromosome 21, this study may provide a useful marker of the presence of dementia in DS and could eventually provide evidence for dementia risk if used

longitudinally.

Earlier <sup>1</sup>H-MRS research done on aging DS persons described a significant age-related increase in mI concentrations in the occipital lobe. This age related rise in mI was speculated to be ascribed to an early sign of dementia similar to that seen AD (Huang et al, 1999). Preliminary work using proton spectroscopy in our lab using a single 2cm x 2cm x 2cm voxel in the posterior cingulate gyrus (PCG) similarly suggests that the NAA/mI ratio is smaller in DS with dementia compared to DS alone (Figure 2D,E). These results are consistent with published results by Ross, et al using an identical spectroscopy voxel comparing AD patients to controls (Lin et al, 2005).

#### *Conclusions and Future Directions*

Clinical dementia is more commonly observed in individuals with DS with an age of onset between 48 and 56 years, which is over 10 years after the initial signs of AD neuropathology begin to accumulate (see Figure 1). Thus, there is a prodromal or asymptomatic phase in DS when AD pathology progressively accumulates (30-40 years) but clinical signs of dementia may be delayed by up to a decade if not longer (>10 years) (Lai, 1989), similar to estimates of 10-20 years for AD in the general population (Morris et al, 1996; Amieva et al, 2005). This provides a therapeutic window or an opportunity for prevention that is unique to adults with Down syndrome and that could target specific pathological pathways given the age of the individual (Figure 1).

#### ACKNOWLEDGEMENTS

The authors were supported by NIH/NICHHD R01 HD064993.

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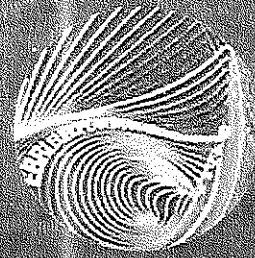
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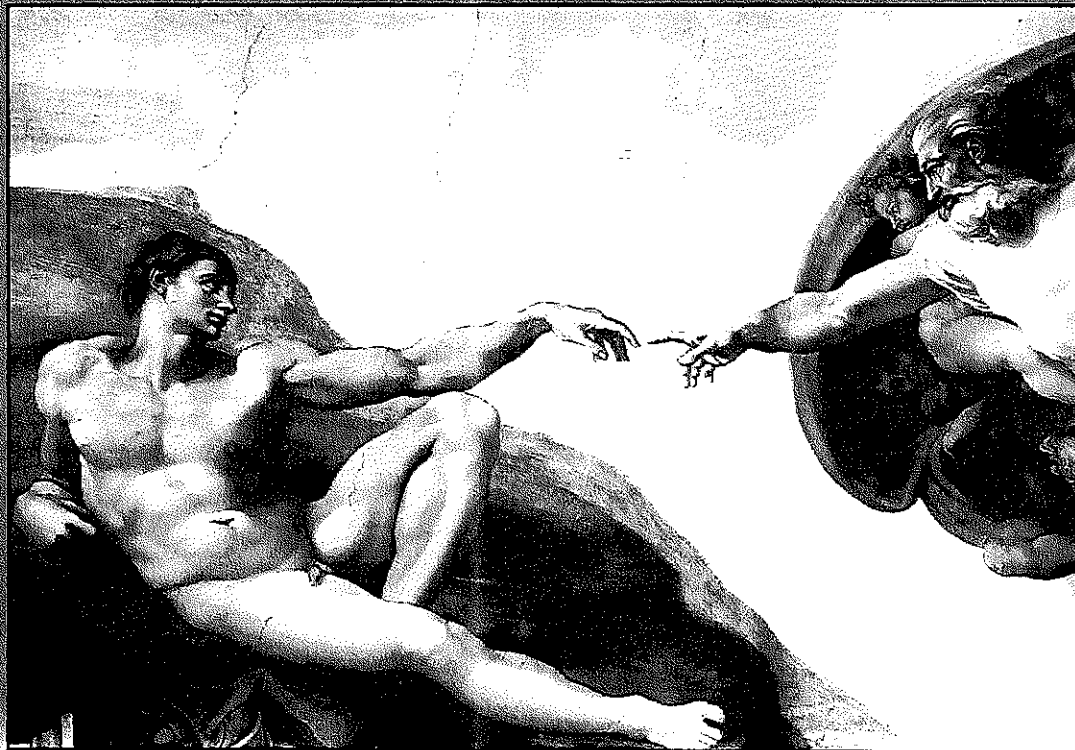
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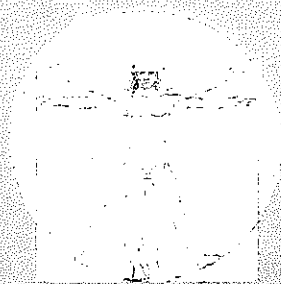


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