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The Comparison of Cognitive and Functional Performance in Children and Alzheimer's Disease Supports the Retrogenesis Model

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Abstract. The retrogenesis model states that the progression of brain aging and Alzheimer's disease (AD) deterioration proceeds inversely to human ontogenic acquisition patterns. Our aim was to assess if the progressive decline of cognitive abilities and functional capacity in AD follows an inverse sequence of acquisition compared to normal developmental patterns. One hundred eighty one children ranging in age from 4 to 12 years and 148 adults (cognitively normal, subjects with mild cognitive impairment, and mild-moderately severe AD) were assessed with the same cognitive and functional tools. The statistical analyses showed a progressive and inverse distribution on cognitive, functional, and mental age scores when comparing results of children classified by chronological age and patients by dementia staging. The pattern of cognitive acquisition in children showed a progressive development of overall cognitive function along all age ranges, in addition to a simultaneous acquisition of instrumental and basic daily living activities in the functional domain. AD patients showed a progressive decline in cognitive and functional domains, which concurs with the sequence of impairment reported in this dementia. Our findings provide support to the inverse and progressive pattern of functional and cognitive decline observed in AD patients compared to the developmental acquisition of these capacities in children, as stated by the retrogenesis model. Nonetheless, certain differences should be considered when comparing the sequence of acquisition during ontogenic development with that of progressive loss during the course of AD. Retrogenesis may account for the progressive loss of neocortical-related functions in AD.

Keywords: Activities of daily living, aging, Alzheimer's disease, child development, cognition, dementia

Supplementary data available online: http://www.j-alz.com/issues/33/vol33-1.html#supplementarydata06

INTRODUCTION

Alzheimer's disease (AD) is the most frequent neurodegenerative disease worldwide [1], with epidemiological studies estimating that 18 to 22 million people were living with AD dementia in 2010 [2–4].

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The characteristic clinical signs are insidious onset, a relentlessly course, progressive and irreversible cognitive impairment (in particular memory loss), functional decline on daily living activities, and behavioral disturbance [5–7]. These manifestations are related to a broad spectrum of pathological changes: neurofibrillary tangles, loss of synapses, neuronal degeneration, and progressive atrophy of the brain [8, 9].

Several theories were developed in the last century which attempted to define the progressive pattern of degenerative AD symptomatology and its relationship with the normal maturational course of human development. Barraquer Bordas [10] and de Ajuriaguerra's group reported important analogies between cognitive decline in dementia [11–14] and the inverse sequence of Piaget's hierarchy of developmental stages [15]. More recently several studies have provided evidence of a significant concordance between cognitive acquisition according to Piaget developmental stages and the progressive cognitive and functional decline in AD [16–21]. Building upon a previous body of work [22] and on the integration of clinical evidence provided by several sources, Reisberg and associates postulated the retrogenesis model, as a new model which explained different aspects of AD etiopathogenesis [23, 24]. Retrogenesis was defined as the process by which degenerative mechanisms reverse the order of acquisition in normal development.

Several neuropathological findings give support to the phenomenon of retrogenesis in AD. There is neuropathological evidence that extracellular deposits of amyloid-β which in aged persons accumulate in senile plaques in the cerebral cortex, believed to represent an early event in AD, may play an important physiological role modulating the elimination of glutamate synapses during brain development. It is speculated that this process becomes pathogenically activated in AD, which may contribute to explaining the progressive deterioration of cognitive functions observed in this dementia (for a review, see [25]). Based upon previous research [22], Reisberg and co-workers stated that white matter changes in AD follow a reverse pattern of myelogenesis. Recent neuroimaging studies with structural MRI have found a pattern of white matter degeneration in AD consistent with this hypothesis [26–28]. For example, significant abnormalities in late-myelinating white matter fiber pathways (neocortical association and allocortical fibers) but not in early-myelinating pathways (primary motor and sensitive fibers) have been observed in AD patients compared to elderly controls [27]. Moreover, microstructural white matter alterations in corticocortical projecting tracts with relative preservation of extracortical projecting fibers have been reported in moderate stages of AD [28], in addition to reduced white matter microstructural integrity in the frontal cortex of early AD patients (known to be one of the regions with latter maturation) [26]. However, findings reported by various studies on the neuropathological mechanisms of white matter changes in AD are not consistent, providing at the present time mixed support for the retrogenesis model. In addition, several studies mapping human cortical development through several periods of lifespan, have reported that the cortical neurodegenerative trajectory seen in AD [29] proceeds in a pattern opposite to the normal maturational sequence of human development [30].

Few studies have investigated the concordance between functional and cognitive deterioration in AD with the converse developmental cognitive and functional acquisition in children, in order to support the retrogenesis model. Most of these studies have applied cognitive tools designed for assessment in children to elderly people or vice versa, in order to compare AD progression with normal developmental acquisition. Shimada et al. [31] found significant positive associations between mental age (measure derived from intelligence quotient) and cognitive status in moderate to severe AD patients. Shoji et al. [32] showed that children acquire cognitive and basic and instrumental daily living skills (ADL) in early childhood (between 3 and 11 years of age), whereas AD patients experience a regression in cognitive and functional domains to the level of kindergarten students, that is between 4 and 5 years of childhood age. Overall, the latter studies indicate that the progression of functional and cognitive impairment in AD mirrors reverse human developmental acquisition.

In the present study, the authors endeavored to examine cognitive and functional acquisition in children and the progressive loss of these capacities in normal aging elderly persons, subjects with mild cognitive impairment (MCI), and AD patients, by means of functional and cognitive tools extensively used in clinical practice for AD diagnosis and a standardized test for measuring intellectual ability. The main aim of this study was to assess the validity of the retrogenesis model of AD in terms of the following: that the progressive decline of cognitive and functional capacities in AD follows an inverse sequence of acquisition compared to normal developmental patterns. Therefore, we attempted to: i) study the evolution of children's performance with cognitive and functional tools conceived for the assessment of adult population, and compare it with the regression shown by elderly healthy controls,

MCI, and AD patients in the same tests and scales; ii) analyze the changes in adults' performance (healthy controls, MCI, and AD patients) and children's intellectual capacity with an intelligence test designed for the assessment of both children and the adult population. In accordance with the retrogenesis model, we predicted that the regression in cognitive, functional, and intellectual scores showed by AD patients would mirror an inverse sequence compared to normal developmental patterns shown by children in these domains.

MATERIALS AND METHODS

Study population

The total sample comprised 329 participants: 181 children and 148 elderly volunteers. A total of 181 children ranging in age from 4 to 12 years participated in the study. Results on our preliminary study conducted on this child population by our research group have already been reported [33]. All children were recruited in a subsidized private school in Barcelona of medium socioeconomic status. In collaboration with the school committees, parents were informed of the study protocol and gave their written consent prior to the participation of all children in this investigation. This study was approved by and conducted in accordance with the local Ethics Committee of Hospital Universitari del Mar of Barcelona, and with the ethical standards laid down in the Declaration of Helsinki. The inclusion criteria were regular school attendance and absence of learning disabilities. Children with a previous medical history of CNS impairment, psychiatric disorder, developmental disturbance, or any sensory deficit that could interfere with the test execution or influence cognitive function were excluded. In each grade, 20 children were selected at random and examined in order to divide the sample into 9 age groups, with the purpose of including 20 subjects within each category of age range. Therefore, each age group comprises 20 subjects except: 5 year old students ($n = 21$), 10 year old students ($n = 21$), and 12 year old students ($n = 19$). All children completed all tests in a quiet and comfortable room in the school facilities during the regular school schedule.

For comparison, a total of 148 elderly volunteers were examined. The elderly group included healthy controls, subjects reporting subjective memory failures, and individuals diagnosed with MCI and probable AD. Elderly participants were incidentally selected for this study from a large cohort of outpatients from the Behavioural Neurology and Dementia Section of Hospital del Mar, Barcelona, and Maria Wolff Foundation, Madrid, whereas elderly healthy controls were recruited from family relatives of the outpatients and other volunteers. Upon arrival at the research center, elderly volunteers were informed of the ensuing protocol and gave their written informed consent before participating in the study. AD patients received a diagnosis of probable AD by two senior staff neurologists, according to criteria of the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association [34]. Subjects were neuropsychologically assessed with specific measures which have shown a high sensitivity to AD cognitive impairment. Individuals were excluded from the study if they had causes of dementia other than AD (e.g., Parkinson's disease, cerebrovascular disease), a history of drug abuse, psychiatric disturbance, or neurologically relevant disorders that could interfere with the neuropsychological assessment. All patients included in the study received annual neurological, medical, and neuropsychological examinations. Patients were classified according to their functional loss and cognitive status. These were assessed utilizing the Global Deterioration Scale (GDS) [35] and the Functional Assessment Staging procedure (FAST) [36]. Among the 148 elderly volunteers, 30 were controls subjects free of subjective or objective cognitive deficits (GDS1), or subjects who reported subjective cognitive failures but who were free of objective cognition related deficits (GDS2), 30 were diagnosed with mild cognitive impairment without dementia (GDS3), 30 with mild dementia (GDS4), 30 with moderate dementia (GDS5), and 28 with moderately severe dementia (GDS6, FAST 6a and 6b). No GDS or FAST stage 7 patients participated in the study, due to the difficulties in assessing cognitive capacities in these subjects with the test battery employed. FAST 6a and 6b patients were included, due to the cognitive and functional correspondence reported between acquisition and loss in 4 year old children and early FAST 6 substages [24]. All participants underwent a single neuropsychological assessment session. An adequate quality control of all environmental conditions necessary for carrying out the ensuing protocol was instituted in all cases. Total administration time was approximately 40 to 60 min.

At the end of the study period, functional scores were not available for 43 children: 3 subjects of 4 years, 1 subject of 6 years, 11 subjects of 7 years, 5 subjects of 8 years, 8 subjects of 9 years, 2 subjects of 10 years, 5 subjects of 11 years, and 8 of 12 years. The functional scales from these participants were not delivered to the

research team. Nonetheless, because these 43 children completed all other cognitive testing, their results were not excluded from the analyses.

Neuropsychological assessment

The neuropsychological battery consisted of the Mini-Mental Status Examination (MMSE) [37] NORMACODEM version [38], the Kaufman Brief Intelligence Test (K-BIT) [39], the GDS [35], the FAST [36], and the Interview for Deterioration in Daily Living Activities in Dementia (IDDD) [40].

Global neuropsychological assessment of all patients was performed using the GDS and the FAST. The GDS incorporates both cognitive and functional aspects of aging and dementia, whereas the FAST focuses on functional aspects. The GDS classifies subjects on a scale starting with stage 1 (GDS 1: absence of cognitive decline) and ending with stage 7 (GDS 7: very severe cognitive decline). The FAST instrument contains 16 successive functional stages and substages which describe the progressive deterioration of functional capacity in AD. Stage 1 designates no difficulties for the patient while Stage 7(f) describes the most handicapped status.

The MMSE NORMACODEM version was administered as a measure of basic cognitive status. This brief test is the most widely used cognitive test for the detection of cognitive impairment in clinical settings and in epidemiological studies. The MMSE NORMACODEM version included in this project was adapted following the original version. Age and formal education were clearly related to the performance obtained by controls; therefore all scores were adjusted according to these two variables. On this scale, higher scores indicates better performance.

Patients were functionally assessed by means of the IDDD. This is a functional scale which measures functional disability in self care (16 items) and complex activities (17 items). On this disability scale, a higher score indicates greater impairment. The range of the total score is 33, indicating no performance deficit, to 99, indicating complete dependence in the performance of assessed activities and the recommended cut-off for dementia is 37. Recommended cut-off score for dementia in Spanish speaking communities studied by the NORMACODEM validation study was 36 [41]. For the purpose of the present study, the original IDDD scale was adapted for administration to a pediatric population. The entire IDDD scale was administered to the children: no items from the original scale were omitted although a total of 7 items out of 33 from the original IDDD scale were rewritten (1 item regarding basic activities [self-care] and 6 items related to complex activities). All modifications performed in the original scale were exclusively content-related: space orientation at home was substituted for school environment, frequency was deleted from all items, and allusion to several specific daily items was replaced with a general category that included the same type of objects. In all cases the rewritten items met equivalent functional demand requirements in comparison with those from the original IDDD. The modifications continued to permit a high degree of correspondence between the functional status in children and elderly persons. No validation of the IDDD-child adapted scale was performed prior to study onset. However, the latter modifications were thought to have a limited impact on the reliability of the functional outcome rated in children compared to that provided by the original instrument in the adult population. Answers on the IDDD scale referring to children were reported by parents, whereas family members and/or caregivers provided answers for elderly participants. The adapted IDDD scale for children used in the present study has been translated into the English language and is appended in Supplementary Table 1, in order to allow the comparison with the original IDDD.

Intelligence quotient (IQ) was assessed with the K-BIT, as this tool meets the need of evaluating the intellectual status of children and adults covering a wide range of age, from 4 to 90 years, and correlates significantly with the Wechsler Intelligence Scale for Children-Third edition (WISC-III) [42]. The K-BIT consists of two subtests: Expressive Vocabulary (word definition and vocabulary knowledge) and Matrices, providing three overall scores: total, verbal, and manipulative. In the present study, IQ corresponds to K-BIT total standardized score. IQ was assessed to ensure all healthy participants included in the study were within the standard norms and to assess the relationship between IQ, MMSE, and IDDD scores.

Statistical analyses

The first step consisted of a descriptive analysis of the sociodemographic characteristics of both adults and children. Secondly, boxplots were plotted for the key neuropsychological variables (MMSE, IDDD, and K-BIT total scores), providing measures of median, interquartile range (IQR), maximum and minimum values for each age range in the group of children, and for each GDS stage in the elderly population group. With reference to the elderly population, the reader

should be aware that the subjects within this group are healthy controls, MCI, and AD patients. In addition, 95% confidence intervals for the population means of MMSE, IDDD, and K-BIT total scores were calculated according to age (among children) and GDS staging (adults), respectively. Finally, linear regression analyses were carried to analyze the association between cognitive and functional capacities in the elderly and child groups. For this analysis, MMSE and IDDD scores were adjusted for IQ values (K-BIT total score). In addition, linear regression models with a quadratic term were fitted for the MMSE, IDDD, and K-BIT verbal and manipulative raw scores, respectively, in order to quantify the proportion of variability explained by the intellectual status in the elderly and child groups. The quadratic term consisted of a variable whose values were the quadratic differences between 5.5 and values 1 to 5 among children (1 : 4 years; 2 : 5 years; 3 : 6–7 years; 4 : 8–9 years; 5 : 10–12 years), and 6 to 10 among the elderly (6: GDS 1&2; 7: GDS 3; 8: GDS 4; 9: GDS 5; 10: GDS 6). Statistical analyses were performed using the statistical software packages SPSS, version 15.0, and R Statistical Software, version 2.11.1 [43].

RESULTS

Demographic data

Sociodemographics of elderly participants are provided in Table 1. Of the 148 elderly participants, 60 were males (40.5%) and 88 were females (59.5%). One hundred forty-five individuals (97.9%) were right-handed and 3 (2.02%) were left-handed. Only 79 subjects (53.02%) had achieved at least the elementary degree, equivalent to more than six years of formal education. Table 2 summarizes the sociodemographics of the children studied. Of the 181 children who participated in the study, 83 were boys (45.9%) and 98 were girls (54.1%). In this group, 164 (90.6%) were right-handed and 17 (9.4%) left-handed.

Neurocognitive data: cognition, functional ability, and intelligence quotient

Tables 1 and 2 display sociodemographics from the participants and results obtained on the MMSE, IDDD, and K-BIT (IQ).

Table 1
Sociodemographic data, MMSE, IDDD, and K-BIT scores of elderly participants according to GDS staging

GDS	*n*	Gender (male)[a]	Age[b]	Education[b]	MMSE[b,c]	IDDD[b,c]	K-BIT[b,c]
1+2	30	15 (50.0%)	73.2 ± 4.6 (65–84)	8.7 ± 4.7	28.7 ± 1.1; [28.3, 29.1]	33.4 ± 0.6; [33.2, 33.6]	96.7 ± 15.7; [90.9, 102.5]
3	30	18 (60.0%)	74.2 ± 5.2 (65–85)	7.6 ± 4.1	26.3 ± 1.9; [25.6, 27.0]	35.3 ± 1.7; [34.7, 35.9]	84.5 ± 13.4; [79.5, 89.5]
4	30	14 (46.7%)	76.4 ± 5.3 (65–87)	7.6 ± 3.8	21.6 ± 2.7; [20.6, 22.6]	45.3 ± 6.2; [43.0, 47.6]	71.0 ± 14.7; [65.6, 76.5]
5	30	8 (26.7%)	79.0 ± 5.6 (65–89)	6.0 ± 2.9	17.0 ± 3.3; [15.8, 18.3]	54.0 ± 9.2; [50.5, 57.4]	51.3 ± 10.2; [47.5, 55.1]
6	28	5 (17.9%)	79.9 ± 5.5 (65–89)	7.9 ± 5.2	10.5 ± 3.7; [9.0, 12.0]	74.4 ± 9.6; [70.7, 78.1]	41.3 ± 3.8; [39.9, 42.8]

[a]Data are presented as relative frequency within their GDS group*. [b]Data are presented as the mean + standard deviation. The age ranges are in parenthesis. [c]Confidence Interval for mean at 95% are shown within the brackets. GDS, Global Deterioration Scale; MMSE, Mini-Mental Status Examination; IDDD, Interview for Deterioration in Daily Living Activities in Dementia; K-BIT total score, Kaufman Brief Intelligence Test (K-BIT). *It should be noted that because of the selection criteria of a FAST stage of 6a or 6b only, the GDS stage 6 subjects are selectively relatively mildly impaired in comparison with the full severity spectrum of this stage. This is because the GDS and FAST stages are highly correlated and FAST stage 6 is comprised of 5 substages, 6a to 6e, with 6e being the most impaired. Hence, the most impaired subjects in GDS stage 6 were likely to be excluded.

Table 2
Sociodemographic data, MMSE, IDDD, and K-BIT scores of children according to age ranges.

Age	*n*	Gender (male)[a]	MMSE[b,c]	IDDD[b,c,d]	K-BIT[b,c]
4	20	6 (30.0%)	14.2 ± 2.7; [12.9, 15.5]	55.8 ± 10.4; [50.5, 61.2]	107.6 ± 8.7; [103.5, 111.7]
5	21	12 (57.1%)	17.8 ± 3.5; [16.2, 19.4]	51.9 ± 7.3; [48.5, 55.2]	110.6 ± 8.1; [106.9, 114.3]
6	20	10 (50.0%)	24.2 ± 2.2; [23.1, 25.2]	47.0 ± 5.4; [44.4, 49.6]	107.8 ± 10.4; [102.9, 112.6]
7	20	8 (40.0%)	27.2 ± 1.6; [26.4, 28.0]	43.1 ± 3.8; [40.2, 46.0]	101.7 ± 10.0; [97.0, 106.4]
8	20	9 (42.9%)	27.7 ± 1.4; [27.0, 28.4]	41.0 ± 5.8; [37.8, 44.2]	109.0 ± 11.5; [103.6, 114.4]
9	20	11 (55.0%)	28.1 ± 1.3; [27.5, 28.7]	38.7 ± 4.7; [35.7, 41.6]	102.3 ± 10.0; [97.7, 107.0]
10	21	8 (38.1%)	29.1 ± 0.8; [28.7, 29.4]	36.0 ± 3.9; [34.1, 37.9]	100.9 ± 8.6; [96.9, 104.8]
11	20	10 (50.0%)	29.1 ± 0.9; [28.6, 29.6]	35.1 ± 3.3; [33.3, 37.0]	102.3 ± 6.9; [99.1, 105.5]
12	19	9 (47.4%)	28.7 ± 1.2; [28.1, 29.3]	33.5 ± 1.0; [32.8, 34.2]	107.6 ± 10.9; [102.4, 112.9]

[a]Data are presented as relative frequency within their group of age. [b]Data are presented as the mean + standard deviation. The age ranges are in parenthesis. [c]Confidence Interval for mean at 95% are shown within the brackets. MMSE, Mini-Mental Status Examination; IDDD, Interview for Deterioration in Daily Living Activities in Dementia; K-BIT total score, Kaufman Brief Intelligence Test (K-BIT). [d]Functional data (i.e., IDDD score) are presented for $n = 138$.

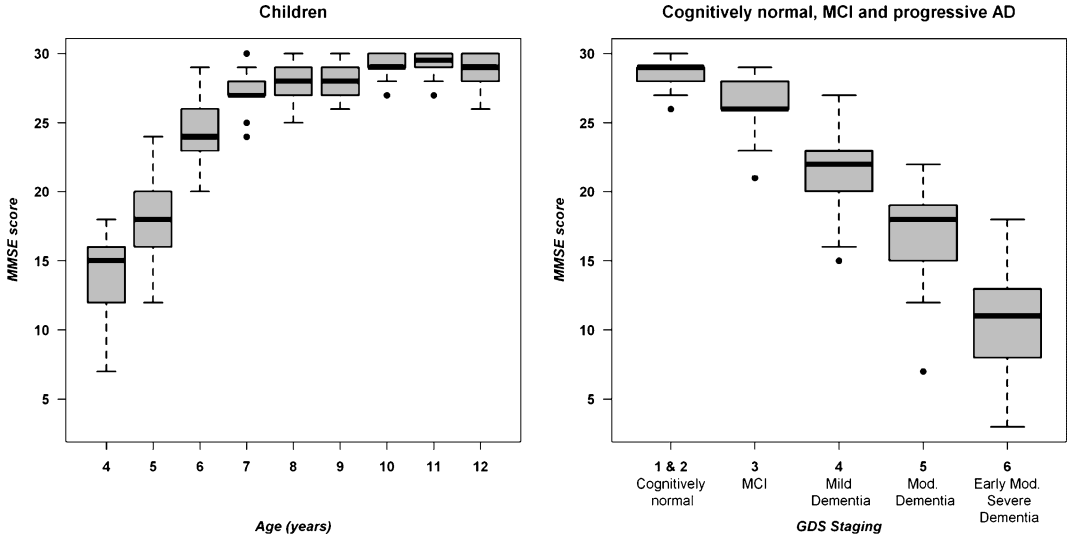

Fig. 1. Box-plot diagrams of total Mini-Mental Status Examination (MMSE) scores obtained by mentally and physically healthy children aged 4 to 12 years and elderly participants with normal cognition (GDS [Global Deterioration Scale] stages 1 and 2), mild cognitive impairment (MCI) (GDS stage 3), mild dementia (GDS stage 4), moderate dementia (GDS stage 5), and early moderately severe dementia (GDS stage 6 and Functional Assessment Staging stage 6a and 6b) symptomatology. All dementia subjects had probable AD.

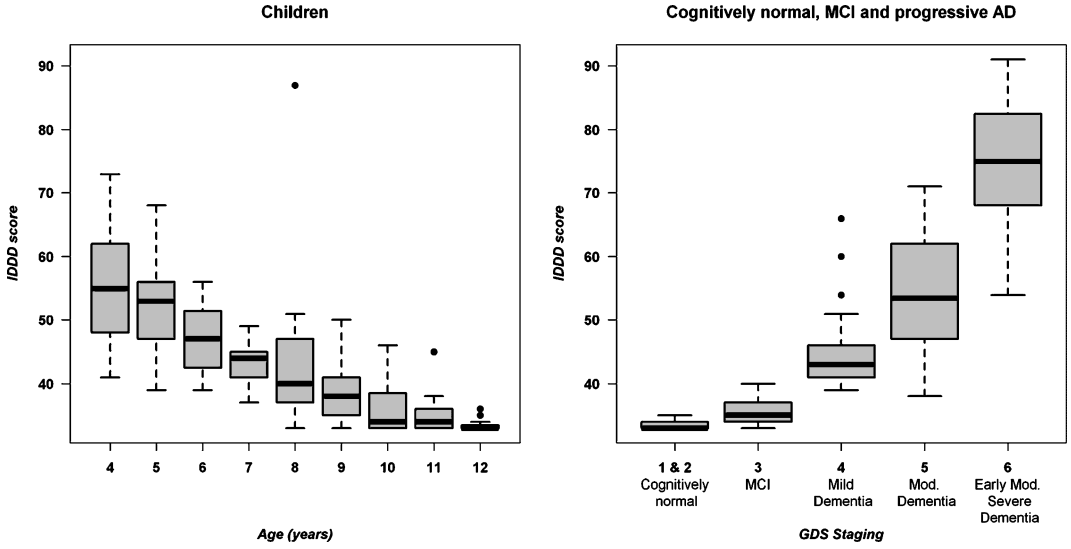

Fig. 2. Box-plot diagrams of total Interview for Deterioration in Daily Living Activities in Dementia (IDDD) scores obtained by mentally and physically healthy children aged 4 to 12 years and elderly participants with normal cognition (GDS [Global Deterioration Scale] stages 1 and 2), mild cognitive impairment (MCI) (GDS stage 3), mild dementia (GDS stage 4), moderate dementia (GDS stage 5), and early moderately severe dementia (GDS stage 6 and Functional Assessment Staging stage 6a and 6b) symptomatology. All dementia subjects had probable AD.

Descriptive analyses and confidence intervals (95% CI) on MMSE scores in the elderly and the child populations are reported in Tables 1 and 2, respectively. Figure 1 shows box-plot diagrams with median, IQR, and minimum and maximum values for total MMSE scores for each range of age in children and for each GDS stage (2 to 6) in elderly participants. Comparative measures of the cognitive performance in this test between the children and the elderly participants revealed an "inverted-U" shape. Children showed a positive trend, with scores gradually increasing from the age of 4 years until the age of 10, when total

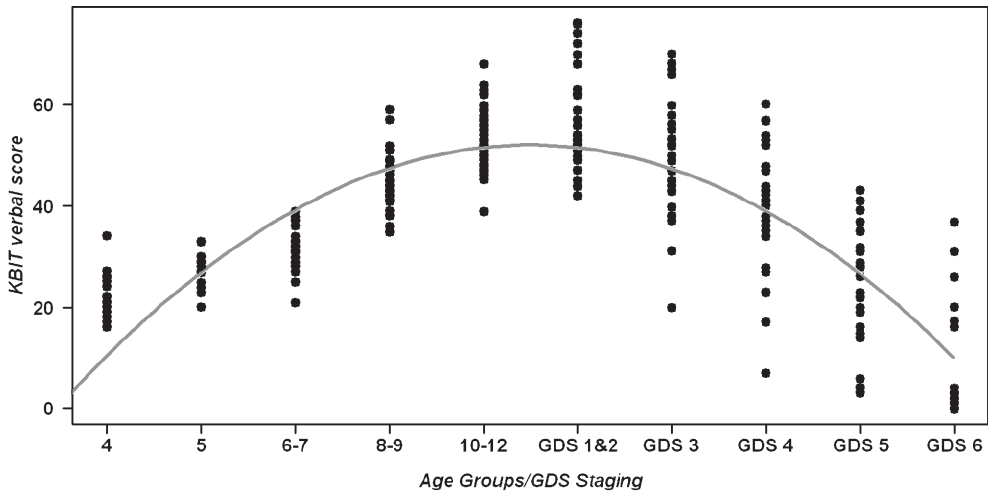

Fig. 3. Total raw scores in vocabulary used for the calculation of intellectual status obtained by mentally and physically healthy children aged 4 to 12 years and elderly participants with normal cognition (GDS [Global Deterioration Scale] stages 1 and 2), mild cognitive impairment (GDS stage 3), mild dementia (GDS stage 4), moderate dementia (GDS stage 5), and early moderately severe dementia (GDS stage 6 and Functional Assessment Staging stage 6a and 6b) symptomatology. All dementia subjects had probable AD. Results indicate a substantial correspondence in the verbal component of IQ (vocabulary raw score) as a function of age (children) and GDS staging (adults), respectively. The curve represents the fit of a linear regression model with a quadratic term ($R^2 = 0.69$). KBIT, Kaufman Brief Intelligence Test.

performance seems to reach a plateau. Conversely, results obtained by elderly volunteers showed a continuous decrease on total test scores related with the progressive advancement of GDS staging.

Descriptive data and confidence intervals (95% CI) with respect to IDDD total scores achieved by the elderly population and children are provided in Tables 1 and 2. Box-plot diagrams with median, IQR, and minimum and maximum values for total IDDD scores obtained by children within each age range (4 to 12 years old) and for the GDS staging (1–6), in the elderly participants are shown in Fig. 2. Descriptive statistics performed on functional ability in this scale between both groups revealed a "U" shape pattern: children experience a continuous decrease of total score in this scale with increasing age, indicating continuous functional acquisition inverse to the gradual increase of total score shown by elderly participants with the progressive advancement of GDS staging. A box-plot diagram on the performance obtained by children and elderly participants on IDDD items, grouped as basic and instrumental/advanced daily living activities is provided in Supplementary Figure 1.

Descriptive analyses and confidence intervals (95% CI) of K-BIT total scores for elderly and child population appear in Tables 1 and 2. K-BIT verbal and manipulative raw scores for both children classified by age and patients classified by dementia staging are shown in Figs. 3 and 4.

Regression analysis between cognitive and functional scores in the overall sample

Linear regression analyses applied between functional and cognitive data within the overall sample and adjusting for IQ values, revealed a strong association between MMSE and IDDD total scores ($R^2 = 0.7$). As expected, this association showed a negative correlation (higher MMSE scores indicating better cognition were associated with lower IDDD scores, indicating better functioning). In addition, the linear regression models with a quadratic term of the test scores on age and GDS staging on healthy children and elderly participants respectively, yielded R^2 values of 0.83 and 0.71 for MMSE and IDDD total scores (Supplementary Figures 2 and 3), and R^2 values of 0.69 and 0.64 for K-BIT verbal and manipulative total raw scores used for the calculation of the IQ (Figs. 3 and 4). These results indicate that an important proportion of the variability observed in test scores for cognitive, functional and intellectual status (between 64% and 83%) was accounted for by the models.

DISCUSSION

The results showed a progressive cognitive and functional decline in AD patients on measures of mental status and functional ability, which was the inverse of the progressive acquisition of these capacities

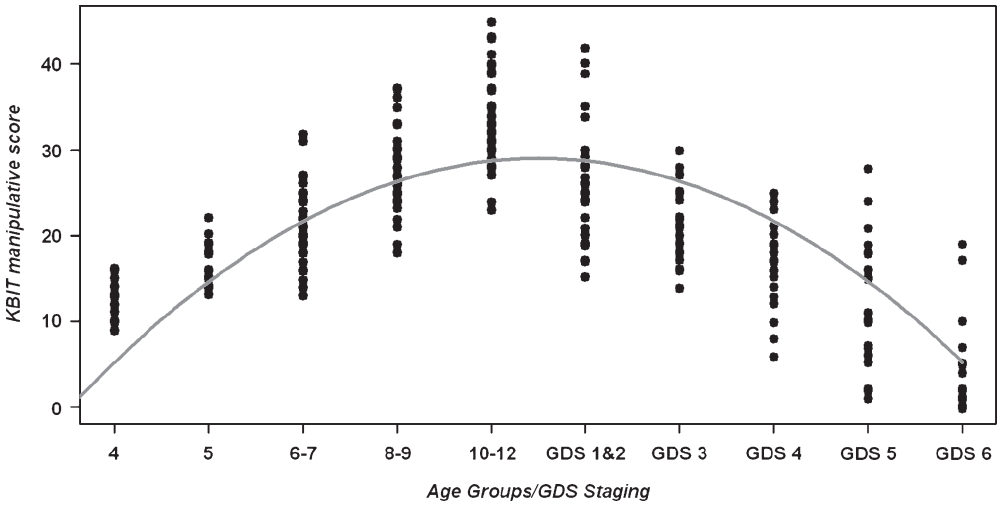

Fig. 4. Kaufman Brief Intelligence Test (KBIT) total raw scores in matrices used for the calculation of intellectual status obtained by mentally and physically healthy children aged 4 to 12 years and elderly participants with normal cognition (GDS [Global Deterioration Scale] stages 1 and 2), mild cognitive impairment (GDS stage 3), mild dementia (GDS stage 4), moderate dementia (GDS stage 5), and early moderately severe dementia (GDS stage 6 and Functional Assessment Staging stage 6a and 6b) symptomatology. All dementia subjects had probable AD. Results indicate a substantial correspondence in the manipulative component of IQ (matrices raw score) as a function of age (children) and GDS staging (adults), respectively. The curve represents the fit of a linear regression model with a quadratic term ($R^2 = 0.64$).

experienced by children during normal development. In this group, total scores in both MMSE and IDDD reached a plateau around the age of 10, suggesting an optimal cognitive and functional status on these measures at this age. Cognitive performance exhibited by elderly persons (healthy, MCI, and the progressively-impaired AD population) mirrored a reverse pattern compared to that obtained by the progressively older children. As expected, the pattern of functional loss in AD patients was progressively limited first in complex (advanced and instrumental) daily living activities in early stages (GDS 4) of AD dementia, whereas basic ADLs (self care) were related to more severe GDS stages (5 and 6). In contrast, children showed a pattern of simultaneous and progressive acquisition for both basic and complex daily living activities with increasing age. Furthermore, a significant relationship was found between cognitive and functional total outcomes in the overall sample after statistically controlling for the intelligence quotient, suggesting that the observed association between cognition and functioning cannot be entirely attributed to formal education. Changes in IQ in the overall sample are illustrated by a progressive loss in the elderly group parallel with the advancement of GDS stages, whereas in children a stable trend is observed with increasing age. This is because, by definition and design, IQ is a ratio of mental age to chronological age and hence, the IQ can remain constant despite the advances in cognition and functioning which occur in the course of development. In the aged subjects, chronologic age remains relatively constant while, with the advance of MCI and AD, cognition and functioning decline. Hence, an IQ score is not an appropriate comparator for development and dementia relationships.

The first aim of the present study was to analyze and compare changes in children's performance on cognitive and functional tools (MMSE, IDDD) with the regression showed by elderly controls and AD patients. As expected, regression analyses revealed a strong negative association between overall cognitive and functional outcomes within the cognitively normal, MCI, and progressively demented persons and the progressively older child population, indicating a consistent linkage between both capacities in all individuals, after statistically controlling for IQ. Thus, higher cognitive status is a predictor of higher functional ability in our sample and vice versa.

Concerning cognitive capacity, the analyses showed an "inverted-U" shape performance-pattern, when comparing progressively older children's results on the MMSE with those obtained by the healthy and progressively impaired AD elderly population. Children at the age of 6 years surpassed 24 points on average in the MMSE [33], considered the cutoff to distinguish normal adults from those with mild or more moderately severe dementia [37, 38]. MMSE scores achieved by children around the age of 6 and 7 were comparable to

those obtained by MCI adults (GDS 3), and at the age of 10 to scores obtained by healthy adults (GDS 1 and 2). As for cognitive status in the most severe AD patients studied (GDS 5 and the early GDS stage 6 persons, with FAST stages of 6a or 6b), GDS 5 stage individuals were equivalent in score to those obtained by children at the age of 5 years, whereas GDS 6 staging individuals were lower than those observed in 4 year old children on the MMSE. These results would be in line with those reported by Shoji et al. [32], suggesting similar cognitive capacities in moderate and severe AD patients and kindergarten students. Using the MMSE cognitive screening test, the present results are in agreement with those reported by previous studies that support the observation that the progression of cognitive decline in AD mirrors reverse human developmental acquisition.

Neuroimaging studies have revealed a wide spectrum of changes in cortical maturation and the myelination process during childhood. All of these changes have been significantly associated with the improvement of overall cognitive capacities in normal children, relating brain maturation with cognitive developmental acquisition [44–48]. Cortical gray matter development appears to follow a well-defined sequence of functional maturation, with primary sensoriomotor cortices along with frontal and occipital poles maturing first, followed next by all other cortical areas which develop from a parietal-to-frontal direction [30]. Parallel to these changes, a progressive pattern of gray-matter thinning has also been observed through childhood and adolescence, appearing first in dorsal parietal and sensoriomotor primary cortices implicated in the processing of senses and movement, spreading into temporal and dorsolateral prefrontal areas, and finally into higher order association cortices in all brain lobes. Thus, the sequence in which the cortex matures concurs with cognitive ontogenic acquisition patterns. Additionally, neuroimage time lapse-maps that have charted the dynamic trajectory of cortical development during childhood and early adulthood indicate that this process is far from being homogenous, but that particular subregions follow temporally distinct maturational trajectories. A ten year follow up study with this technique has revealed that recently evolved/higher-order association cortices mature later than phylogenetically older cortices (e.g., somatosensory and visual cortices), once that the cognitive functions they integrate are consolidated [30]. In AD, a characteristic progression of neuropathology, mainly neurofibrillary tangles, have been described as follows: first, limbic (entorhinal); second, paralimbic (fusiform inferotemporal); third, prefrontal-parietal posterior (homotypical cortex); and fourth, primary sensory and motor areas (idiotypic cortex). [49, 50]. Thus, after the initial involvement of limbic structures, maps have demonstrated the spatio-temporal pattern of neocortical degeneration, spreading and following a temporal to frontal to sensoriomotor sequence. The time-lapse maps have also pointed to phylogenetically younger and more plastic neocortical areas (e.g., higher association cortices) as the most vulnerable to degeneration in the first stages of AD in comparison with phylogenetically older cortical areas [29]. Related to this, cortical thinning has been recorded in frontal areas in MCI, and this has been associated with a poorer outcome in executive neuropsychological measures [51–55]. Such evidence would also be partially in accord with the retrogenesis model, as the frontal cortex is known to be one of the latest cortices to maturate along the course of phylogenetic evolution and ontogenic development. In sum, all of these findings are consistent with the hypothesis that the maturational sequence of brain during human development proceeds in a pattern in several aspects opposite to the neurodegenerative sequence of AD. Probably, the retrogenesis model explains the correspondence in the pattern of acquisition/loss in neocortical related cognitive functions observed in normal development and the AD neurodegenerative process.

Regarding functional capacity, statistical analyses revealed an inverted "U" shape performance-pattern when comparing progressively older children's results on the IDDD with the results obtained by the healthy and the progressively impaired AD elderly population on the same scale. As expected, mean scores obtained in the IDDD by elderly healthy cognitively normal subjects (GDS 1-2) and MCI patients (GD3) denote a preserved functional status, with results under the cutoff value of 36 points [41]. Similar functional ability was observed in children at the age of 10 years in the study sample, with IDDD total mean scores under the cutoff of 36 points. The latter suggest that performance levels in instrumental and basic daily living activities are achieved in childhood during elementary school. In contrast, AD patients with mild to moderate dementia (GDS 4 and 5 stages) in all cases obtained mean scores above 36 points, indicating functional regression. Therefore, functional status in these GDS groups would be similar to that shown by children approximately 7 to 4 years of age, whereas in the most severe stages of AD studied (GDS 6, FAST stages 6a and 6b), daily living skills are regressed below the level observed in 4 year old children. These findings are consistent with those of previous studies that have

reported a significant relationship between progressive cognitive development in children and cognitive impairment in AD, as well as a significant relationship between functional acquisition in children with progressive functional disability in AD patients [31, 32].

At the same time, the present data suggests a non-exact correspondence between the ordinal sequence of functional acquisition in children and the progressive functional loss in the elderly AD population. Children showed with increasing age a progressive improvement of overall functional ability, developing simultaneously their personal autonomy in basic and complex daily living activities. They experienced the most notable advances in the age range from 4 to 9 years old, achieving at the age of 10 an optimal functional ability on the IDDD. This pattern of functional acquisition slightly differs from the sequence of functional loss shown by AD patients [7]. In AD the course of functional disability is highly predictable and has been consistently associated with the loss of cognitive status [55]. In AD, the course of progressive functional decline is circumscribed to advanced and instrumental daily living activities during first stages of the disease (GDS 4), whereas impairment of basic ADLs is related to more severe stages of dementia (GDS 5 and 6) [7, 56]. Our results are congruent with the extensive body of work which has demonstrated this hierarchical pattern of functional loss in AD. Such staging of functional loss would partly diverge from the sequence of simultaneous acquisition in instrumental and basic ADLs shown by the children of our sample during normal development.

We also explored changes in IQ shown by progressively older children, related with the progressive course of AD. As illustrated by the analyses, a clear tendency was shown toward a progressive decline in IQ (K-BIT verbal and manipulative scores) parallel to the progressive course of AD. In contrast, children's K-BIT raw scores showed a positive trend, and IQ stood within standard norms for all groups of age, as expected in normal development. In elderly subjects, cognitive decline related to normal aging cannot explain the steep IQ regression exhibited by AD patients due to the following reasons: a) K-BIT standardization was performed in a sample of 1,341 Spanish healthy subjects with an age range of 4 to 90 years old after adjusting for age and schooling [38], two variables that have extensively demonstrated a relevant influence upon IQ and cognitive performance; b) the elderly participants in the present study were very homogeneous in terms of schooling (years of education), therefore this variable cannot be considered a probable confounder that can explain the progressive decline of K-BIT scores and cognitive performance shown by AD patients. Thus, K-BIT raw and standardized scores must reflect IQ distribution according to the normal aging in elderly population, whereas the progressive decline of intellectual status with the severity of dementia should respond to a marked cognitive impairment secondary to the progressive brain degeneration inherent to AD. We must also consider that executive functioning in addition to memory is one of the cognitive domains more vulnerable not only to normal age-related impairment [55, 57], but to the prodromal AD stage [58–60] and AD onset [61]. Recent studies using volumetric neuroimaging techniques and neuropsychological testing have reported a close association between executive disturbances and gradual signs of cortical thinning in frontal lobe areas in MCI and AD individuals [53, 62, 63], in addition to deep grey matter structures in AD patients [64]. Abstract reasoning is considered a high order component of executive functioning (an accepted measure of high analytical reasoning, problem solving, and fluid intelligence) and a key component of intellectual status determined with the K-BIT. As such, executive decline may exert a significant negative and progressive impact on IQ estimation, particularly in AD patients. Furthermore, in this study cognitive status provided by MMSE score was adjusted in accordance with age and formal education, in order to counterbalance the effects of these possible confounders. Brain structural differences related to the decline of cognitive status have also been reported in AD patients and healthy controls [29]. In the AD patients, the regression of cognitive status over time was found to be highly significant compared to the stable trend showed by healthy controls in MMSE scores. Moreover, significant positive associations were found in AD patients between the decline of MMSE scores and gray matter reduction in most regions of the neocortex, in particular in the temporoparietal, limbic, and frontal cortices, but not in sensory and motor cortices. Overall, significant negative deviations from average IQ score and the progressive deterioration of cognitive status exhibited by AD patients in comparison with that shown by healthy aged persons support the existence of a differentiated cognitive pathological process in AD in comparison with normal aging. In contrast, children's stable trend in IQ within standard norms for all groups of age mirrors the progressive improvement of overall intellectual status inherent to the dynamic course of normal development and brain maturation. Such findings contribute once more to support the retrogenesis model of cognitive and intellectual decline in AD.

Several caveats should be considered when interpreting the results of this study. The first is that the MMSE is considered a tool which provides an overall estimation of cognitive status. Therefore cognitive capacity should be investigated in the future by means of a more comprehensive battery of neuropsychological testing, focused on the detailed assessment of all key areas (e.g., attention, language, memory, praxis, and executive functioning) involved in developmental maturation and AD progressive impairment across the relevant severity range. Second, we recognize that longitudinal models would certainly help to supply additional relevant data on the precise correspondence between developmental maturation and cognitive decline in AD, when assessing the validity of the retrogenesis model of AD from the perspective of the present study. Third, because no validation of the functional IDDD adapted scale for children was carried before initiating the study, a complete correspondence on functional ability exhibited by children and elderly participants cannot be assured. However, content modifications performed on the original scale were minor; these were restricted to a reduced number of items and in all cases met equivalent basic and complex demanding tasks, involving analogous functional abilities for children. Therefore, no considerable deviations should be expected in the reliability of the functional outcome reported in children using the present IDDD adapted version. Consequently, we were able to perform a reliable comparison on the progressive acquisition/loss of overall functional ability between children and AD patients. The absence of IDDD scores concerning a significant proportion of the child group may have had a substantial impact on functional ability results among the upper age ranges (7, 9, 11, and 12 years of age) where they were mainly distributed. This is a period when the development of complex activities is key. Despite this weakness, the child sample size was big enough to assure the statistical power of our analyses and a high correspondence was found when comparing overall functional trends between both groups. Finally, differences observed in cognitive and functional patterns between children and elderly persons may partly be the result of the comparison of two categories with no methodological correspondence used to contrast our data: age groups (with 9 subgroups) versus GDS staging clinical categories (with 5 subcategories). Certainly, this methodological approach may have contributed to amplifying intrinsic differences between both sequences of acquisition/loss in both populations. Despite this important limitation in our design, a notable concordance was still found for cognitive and functional patterns in normal developmental acquisition in children and AD progression.

In sum, our findings support a remarkable correspondence between progressive deterioration in AD patients and developmental maturation in children: that the sequence of functional and cognitive decline in AD reverses the sequence of human developmental acquisition, as hypothesized in the retrogenesis model of AD. Despite such correspondence, certain fine grained possible differences should be considered when comparing the specific ordinal sequence of cognitive and functional loss observed in AD, with the order with respect to the normal developmental pattern of acquisition.

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