

# Serum BDNF levels and cognitive performance in AD Patients: Influence of apathy and ApoE4 status

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## BACKGROUND

Brain-derived neurotrophic factor (BDNF) deficits seem to influence Alzheimer's disease (AD) pathology and low circulating BDNF may promote cognitive deterioration, but the influence of apathy and APOE4 status on the associations of serum BDNF levels with cognitive performance in AD patients was not previously investigated in longitudinal studies.

## MATERIALS AND METHODS

We investigated serum BDNF levels and its associations with cognition in two sets of mild to moderate AD patients. First, we evaluated baseline BDNF serum levels and cognitive performance in AD patients (n=252) as a function of the presence of apathy and of the APOE4 status. Then, we assessed the influence of apathy and APOE4 status on the associations of cognitive performance with baseline BDNF and changes in BDNF levels induced by Cerebrolysin (n=52), donepezil (n=52) and a combination of both treatments (n=54) in AD patients enrolled in a randomized, double-blind trial. BDNF levels were measured in serum samples obtained at baseline, at week-16 (end of active Cerebrolysin treatment) and at week-28 (endpoint) by using specific ELISA kits.

## RESULTS

Baseline BDNF serum levels and cognitive performance were reduced in AD patients with apathy and in female ApoE4 carriers as compared with patients without apathy and female ApoE4 non-carriers, respectively (Tables 1-2; Figures 1-2). The negative impact of apathy on cognitive performance was particularly evident in patients with moderate to moderately severe AD (Figure 2); while that of ApoE4 was restricted to MMSE (table 2).

Cerebrolysin and donepezil induced a synergistic increase on serum BDNF levels in AD patients (table 3; Figure 3). Drug-induced BDNF increases were greater in patients with apathy/depression and APOE4 than in the rest of AD patients at both week-16 (4.7 vs 0.8 ng/ml; p<0.05) and week-28 (4.8 vs 0.7 ng/ml; p<0.05), irrespectively of the therapy group. In the subgroup of APOE4 patients, baseline BDNF levels correlated negatively with scores of ADAS-cog+ change from baseline to week-16 and to week-28; and these correlations were significant for patients receiving Cerebrolysin (Figure 4), but not for those on donepezil. In APOE4 patients treated with Cerebrolysin, enhanced BDNF levels at week-16 were associated to greater cognitive improvements at the same time point, and predicted a better cognitive performance at endpoint too (Figure 5).

Table 1

	AD patients		Analysis		
	No Apathy (n=83)	Apathy (n=167)	X <sup>2</sup>	df	P
Female gender	66 (79.5)	128 (76.6)	0.26	1	ns
APOE ε4 allele	38 (45.8)	80 (47.9)	0.75	1	ns
Dysphoria	37 (44.6)	98 (58.7)	4.44	1	<0.05
SSRIs treatment	21 (25.3)	67 (40.1)	5.34	1	<0.05
CIBIS+:			18.86	2	<0.001
3 (mild)	38 (45.8)	33 (19.8)			
4 (moderate)	33 (39.8)	91 (54.5)			
5 (moderately severe)	12 (14.5)	43 (25.7)			
Mean ± SD	Mean ± SD	F	df	P	
Age (years)	75.31±7.10	74.83±7.53	0.24	1, 248	ns
Apathy (score)	0.00±0.00	4.34±2.46	258.23	1, 248	<0.001
Dysphoria (score)	1.02±1.67	1.92±2.41	9.30	1, 248	<0.01
BDNF (ng/ml) <sup>a</sup>	17.02±9.55	14.15±9.22	10.09	4, 245	<0.05
ADAS-cog+ (score) <sup>b</sup>	33.93±13.97	42.90±14.89	7.75	6, 243	<0.01
NPI (score) <sup>c</sup>	8.39±8.25	15.99±10.31	18.74	12, 237	<0.001

Apathy was associated with significant reductions in serum BDNF (p<0.05) and ADAS-cog+ (p<0.01) in AD

Table 2

	Female AD patients		Analysis		
	APOE No-E4 (n=98)	APOE E4 (n=98)	X <sup>2</sup>	df	P
	N (%)	N (%)	X <sup>2</sup>	df	P
Apathy	62 (63.9)	66 (68.0)	0.37	1	ns
Dysphoria	54 (55.7)	55 (56.7)	0.02	1	ns
SSRIs treatment	39 (39.8)	30 (30.6)	1.81	1	ns
CIBIS+:			2.57	2	ns
3 (mild)	28 (28.9)	21 (21.6)			
4 (moderate)	44 (45.4)	55 (56.7)			
5 (moderately severe)	25 (25.8)	21 (21.6)			
Mean ± SD	Mean ± SD	F	df	P	
Age (years)	75.14±7.86	75.42±6.28	0.07	1, 192	ns
Apathy (score)	2.85±3.03	2.84±2.76	0.00	1, 192	ns
Dysphoria (score)	1.77±2.26	1.73±2.46	0.02	1, 192	ns
ADAS-cog+ (score)	40.40±16.43	40.85±14.15	0.04	1, 192	ns
NPI (score)	15.02±11.60	13.02±9.92	1.67	1, 192	ns
BDNF (ng/ml) <sup>a</sup>	17.28±9.52	13.44±8.37	9.58	6, 187	<0.01
MMSE (score) <sup>b</sup>	18.11±4.26	16.30±3.58	18.87	9, 184	<0.001

ApoE4 was associated with significant reductions in serum BDNF (p<0.01) and MMSE (p<0.001) in AD women

Table 3

	Cerebrolysin	Donepezil	Combined Therapy
	Mean ± SD	Mean ± SD	Mean ± SD
All patients (N)	52	52	53
Baseline BDNF (ng/ml)	13.76±8.55	16.62±9.10	15.40±10.67
Week-16 BDNF (ng/ml)	16.27±9.37*	16.61±10.25	19.50±12.15**
Week-28 BDNF (ng/ml)	15.31±9.97	17.79±9.89	19.07±10.64*
Baseline ADAS-cog+ (score)	41.15±15.55	40.51±16.21	39.79±17.89
Week-16 ADAS-cog+ (score)	37.57±16.94**	37.22±17.33**	36.02±19.39**
Week-28 ADAS-cog+ (score)	39.47±17.79	39.78±18.29	37.68±19.33*
ApoE4 patients (N)	24	24	21
Baseline BDNF (ng/ml)	10.39±7.08	15.24±8.52	13.04±9.60
Week-16 BDNF (ng/ml)	14.67±9.05**	17.11±8.79	19.26±12.55*
Week-28 BDNF (ng/ml)	15.04±10.25**	18.88±16.56	19.61±13.12*
Baseline ADAS-cog+ (score)	43.49±12.97	43.94±16.49	33.30±12.50
Week-16 ADAS-cog+ (score)	39.41±15.46*	42.04±17.04*	29.04±13.35**
Week-28 ADAS-cog+ (score)	41.76±16.71	43.89±17.66	31.12±14.10

Apathy was associated with significant reductions in serum BDNF (p<0.05) and ADAS-cog+ (p<0.01) in AD

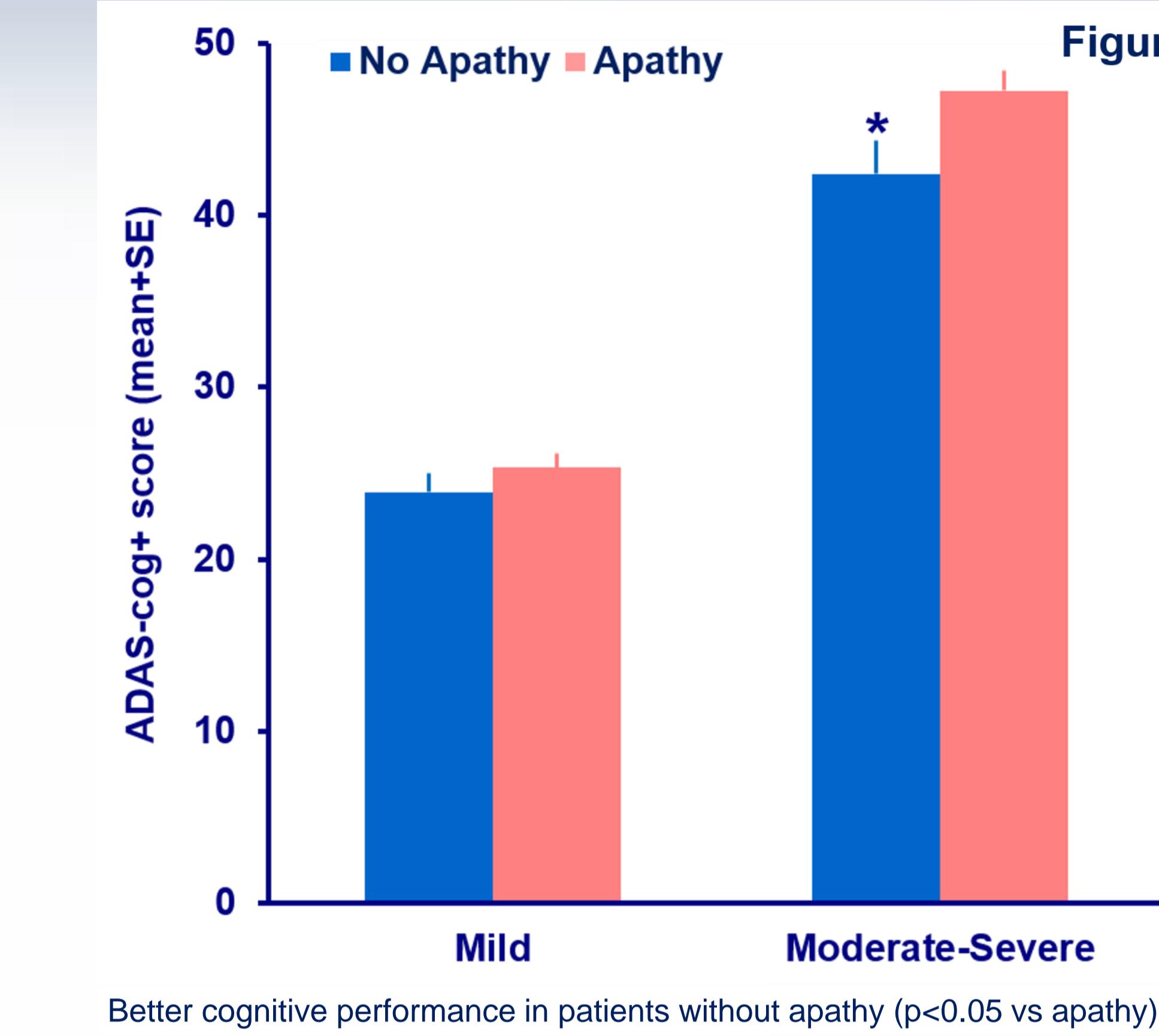


Figure 1  
ADAS-cog+ score (mean+SE)  
Mild vs Moderate-Severe  
No Apathy vs Apathy  
\* indicates significant difference between Mild Apathy and Moderate-Severe No Apathy

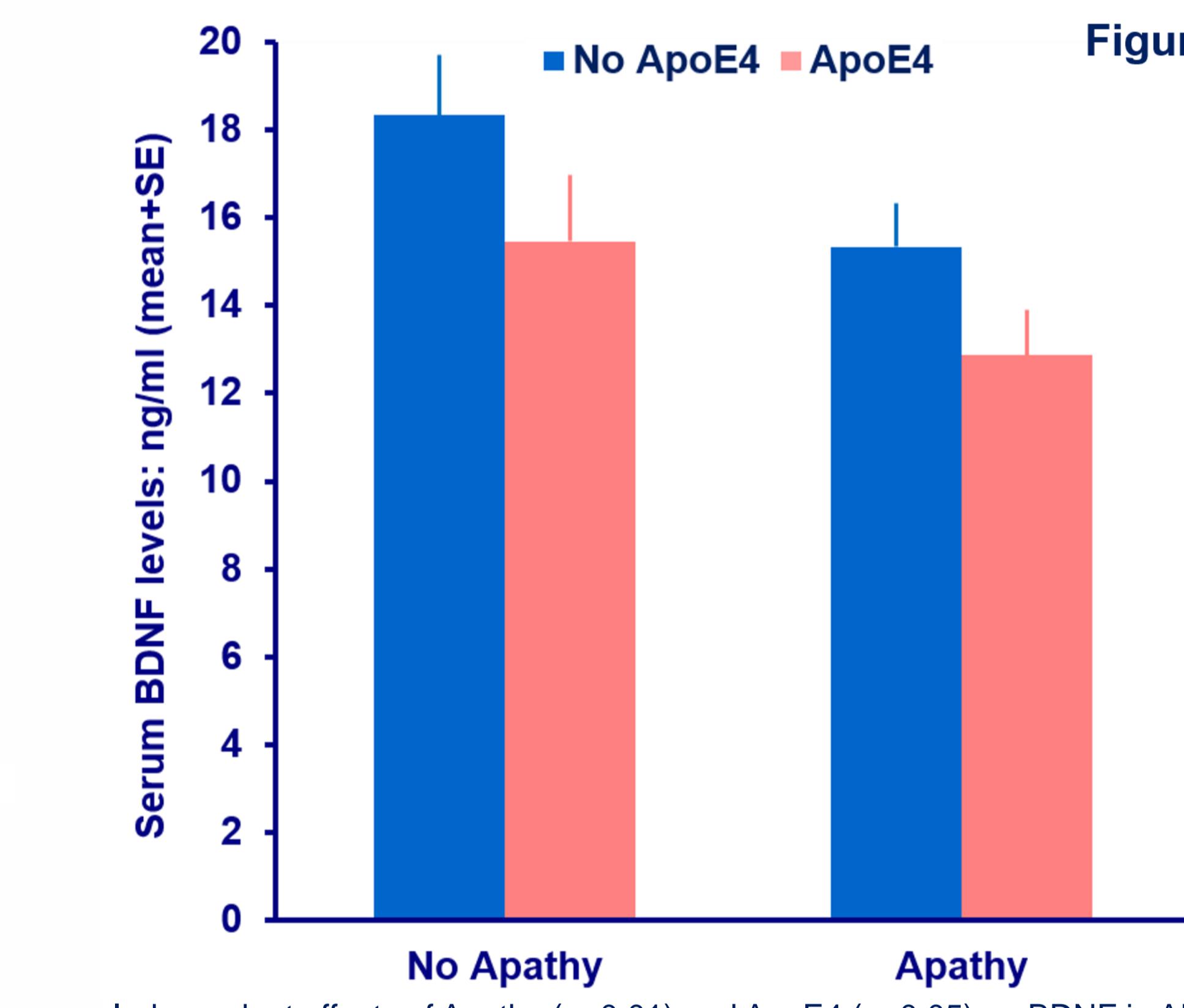


Figure 2  
Serum BDNF levels: ng/ml (mean+SE)  
No Apathy vs Apathy

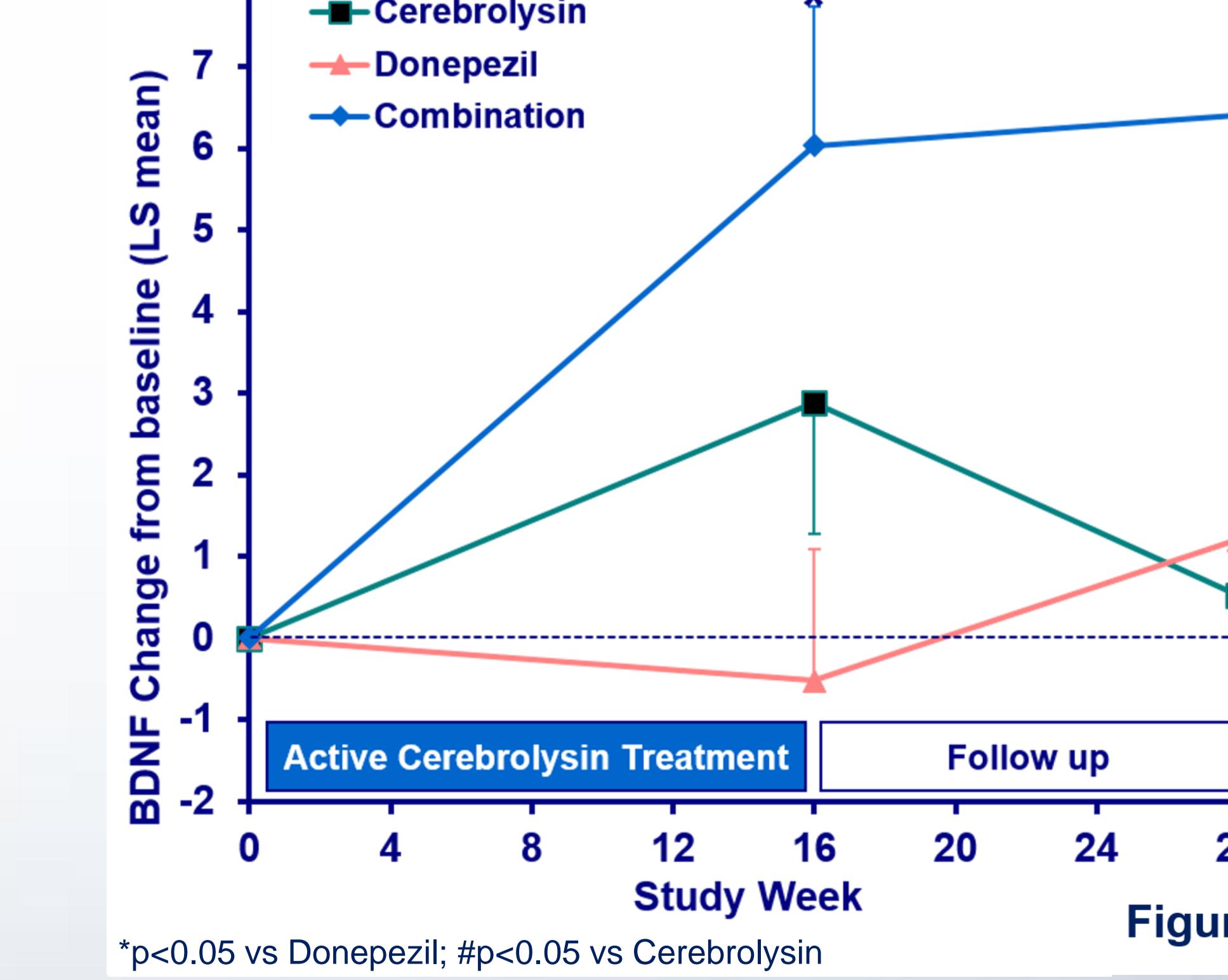


Figure 3  
\*p<0.05 vs Donepezil; #p<0.05 vs Cerebrolysin

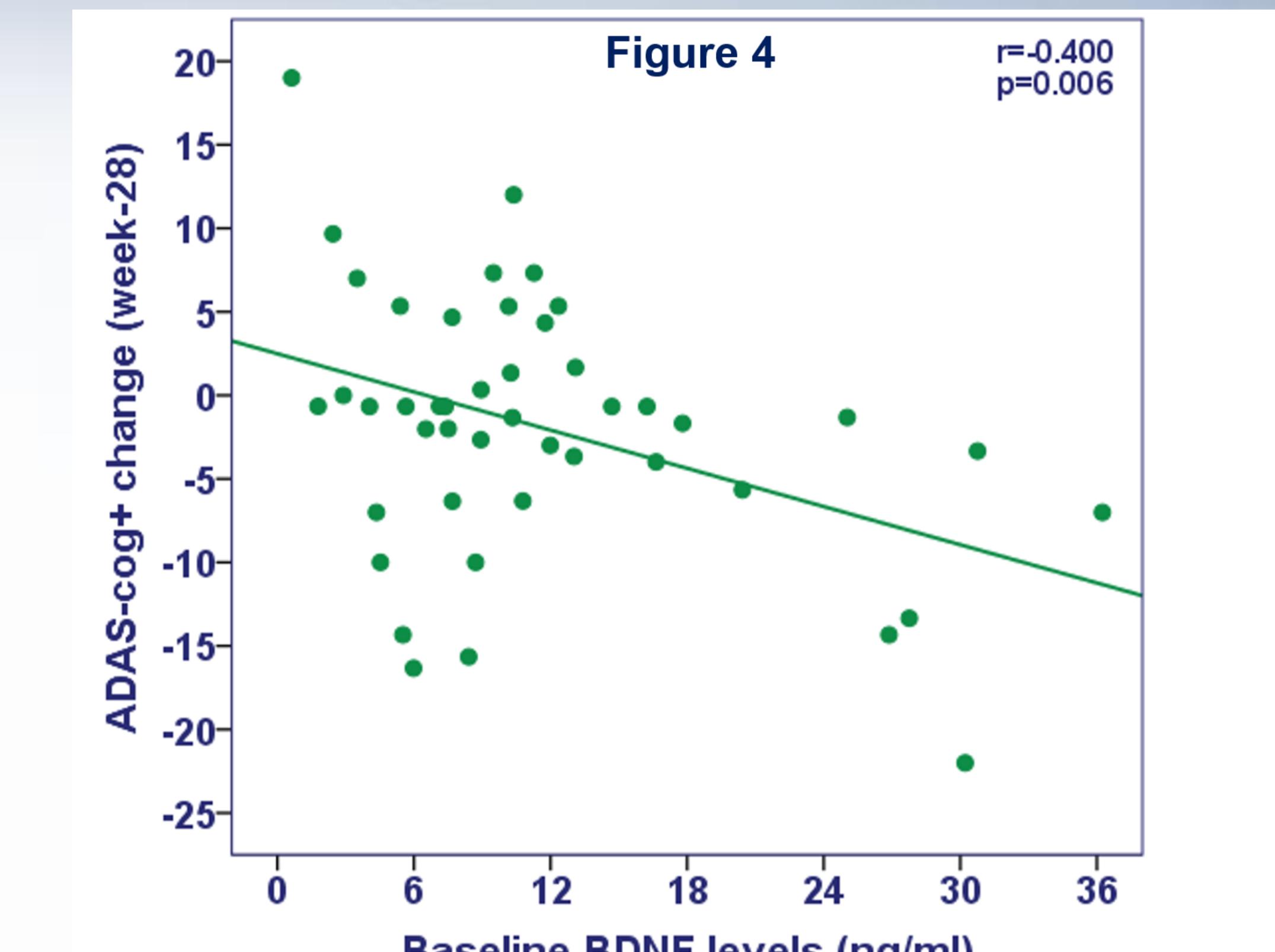


Figure 4  
ADAS-cog+ change (week-28)  
Baseline BDNF levels (ng/ml)  
r=-0.40 p=0.006

