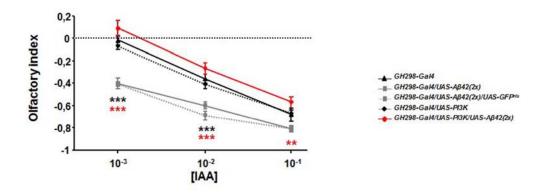
Supplemental Materials Molecular Biology of the Cell

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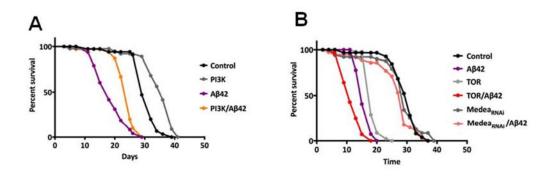
Supplementary Data



Suppl. Fig. S1

Supplementary Figure S1.- PI3K prevents A\u03c342-induced olfactory perception

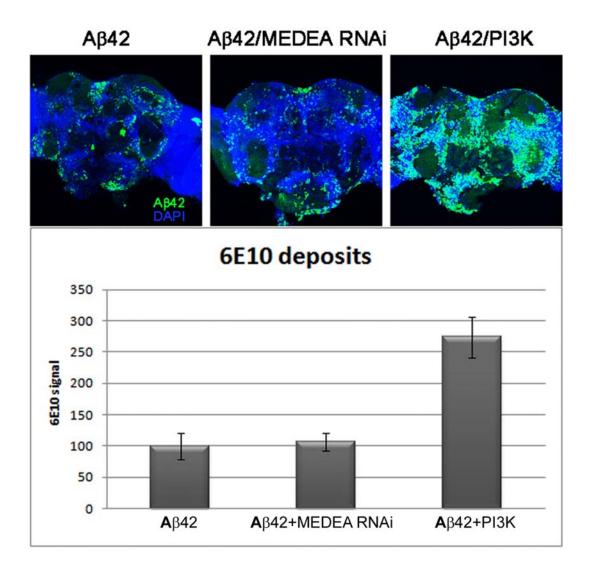
defects to IAA.Adult 5-7 days aged flies were subjected to an olfactory assay for isoamyl acetate (IAA) with three concentrations (v/v). The expression of two different Aβ42 constructs in the GH298-Gal4 domain (genotypes: GH298-Gal4/UAS-Aβ42 and GH298-Gal4/UAS-Aβ42/UAS- GFP^{nls} , full and dotted grey lines respectively) yields more repulsive responses to $[10^{-3}]$ and $[10^{-2}]$ compared to GH298-Gal4 controls (full black line) and GH298-Gal4/UAS-PI3K flies (dotted black line). Theinducible PI3K form (UAS-PI3K) is used in this experiment. However, when PI3K and Aβ42 were co-expressed in GH298 neurons [genotype: GH298-Gal4/UAS-PI3K/UAS-Aβ42(2X)], the olfactory index returned to the normal profile (red line). Black asterisks: comparisons between GH298-Gal4/UAS-Aβ42 and GH298- with respect to control. Red asterisks: comparisons between GH298-Gal4/UAS-Aβ42 and GH298- with respect to control. Red asterisks: comparisons between GH298-Gal4/UAS-Aβ42 and GH298-Gal4/UAS-PI3K/UAS-Aβ42 flies. **p<0.001; ***p<0.0001 (unpaired Student's t test with Welch's correction).



Suppl. Fig. S2

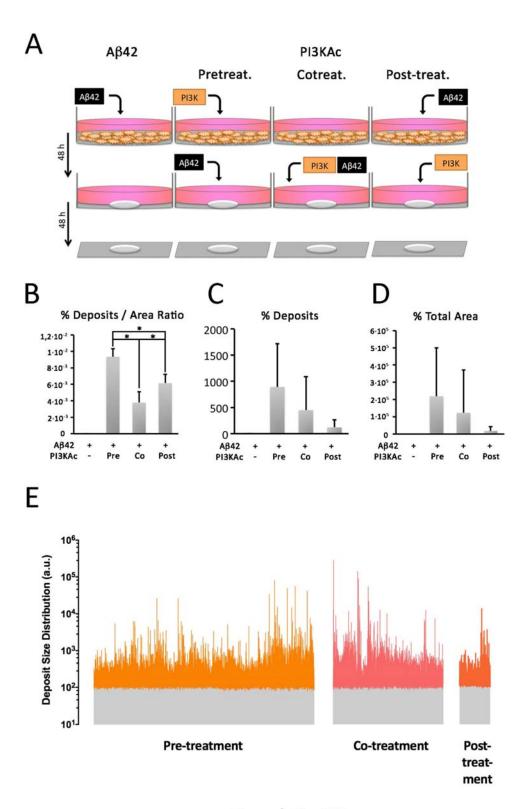
Supplementary Figure S2.- Aβ42-induced reduction of lifespan is prevented by

PI3K synaptogenesis signaling.(A) Longevity profiles of color coded genotypes at 29°C. PI3K activation suppresses the lifespan reduction caused by Aβ42 to a large extent. Numerical data are shown in **Supp. Table S1.(B)** Equivalent profiles for other genotypes including factors that do not participate in the PI3K synaptogenic pathway, mTOR, or included in that signaling, Medea^{RNAi}. Note the full suppression by the later factor and the enhanced lifespan reduction caused by mTOR. Numerical data are shown in **Supp. Table S1**.



Suppl.Fig. S3

Supplementary Figure S3.-Medea downregulation does not increase Aβ42 deposits. Upper panels show confocal images of frontal views of 15 days old adult females expressing UAS-Aβ42 (2X) and UAS-PI3K or $UAS-Medea^{RNAi}$ and stained with 6E10 antibody. Note the increased Aβ deposits in the PI3K brain, but not in the Medea^{RNAi}. Lower panel shows the quantification of the 6E10 signal in the whole stack of brain images in each genotype. A total of three brains per genotype were analyzed. Cell nuclei are marked by DAPI.



Suppl.Fig.S4

Supplementary Figure S4.- PI3K-induced increase in Aβ42 aggregation can be reproduced outside the cell. (A) Cartoon representing the experimental design with SHT-SY5Y differentiated cells treated with Aβ42 oligomers $(36\mu g/ml)$ and PTD-PI3KAc peptide $(50\mu g/ml)$ at different times of administration. Supernatants were stained with 6E10 antibody. Cells treated only with Aβ42 oligomers were used as control. (**B-E**) Histograms representing percentage of deposits/area ratio (**B**), percentage of deposits (**C**), percentage total area (**D**), and deposit size distribution (**E**) of Aβ42 and PI3K/Aβ42 treated cells. Control cells treated only with Aβ42 oligomers did not develop recognizable 6E10 positive deposits.

	Over 4 cm / Pa					_	
Genotypes	Control	PI3	K	Аβ42	РІЗК/АВ42	_	
Control	4000000						
PI3K	0,6588						
Аβ42	< 0,0001****	< 0,000			_		
РІЗК/АВ42	0,0001***	< 0,000	1****	0,0028**			
	Bellow 4 cm / P	aired T te	st (Two-tal	led P value)			
Genotypes	Control	PI3	K	Аβ42	РІЗК/АВ42		
Control PI3K	0,2399						
AB42	0,4581	0,20	16				
РІЗК/АВ42	0,9078	0,75		0.2	074		
Genotypes	Bottom / Pair Control	ed T test		d P value) Aβ42	РІЗК/АВ42	_	
Control	2300000						
PI3K	0,2775	ALCOHOL:					
AB42	0,0194*	0,03					
РІЗК/АВ42	0,136	0,50	57	0,0379*			
		0	A em / Dais	ed T test (Two-	talled Suplus		
Genotypes	Control	AB42	- cm / Pair	mTOR	mTOR/Aβ42	Medea-RNAi	Medea-RNAI/A
Control	The state of the s	***************************************			Commence of the Commence of th		
АВ42	0,031*		- 10				
mTOR mTOR/AB42	0,0082**	0,1537		0,0549	_		
Medea-RNAi	0,0031**	0,1537		0,0549			
Medea-RNAI/Aβ42	0,0031	0,0436				0,3396	
		Dalla	4 cm / Do	red T test (Two	talled Dunluck		
Genotypes	Control	Аβ42	w 4 cm / Pai	mTOR	mTOR/Aβ42	Medea-RNAi	Medea-RNAI/A
Control		-					
Аβ42	0,4831						
mTOR	0,9284						
mTOR/Aβ42	0,7438	0,3288		0,7136			
Medea-RNAi Medea-RNAi/Aβ42	0,0835	0.2204				0,4637	
medea-RNAJ/Ap42	0,2212	0,3384	3			0,4037	
	10-11-11-11-11-11-11-11-11-11-11-11-11-1			d T test (Two-ta		44144	No to a second
Genotypes Control	Control	Αβ42		mTOR	mTOR/Aβ42	Medea-RNAi	Medea-RNAI/A
AB42	0,6361						
mTOR	0,0708						
mTOR/AB42	0,8737	0,0394	. –	0,0665			
Medea-RNAi	0,1166					- Company	A 1
Medea-RNAi/Aβ42	0,1079	0,5755				0,6394	
Genotype		n	Median Surv	Maximum Surv	Mantel-Cox test		
Group VS Control							
Control (UAS-LacZ/+)		30	29	36	0.0001		
		34	36 (+24%)	39 (+8%)	p <0,0001		
PI3K (UAS-PI3K caax/+)		40		24 (-324)	n <0.0001		
PI3K (UAS-PI3K caax/+) Αβ42 (UAS-2xAβ42/+)	ix/UAS-2xAB42)	48 30	18 (-38%) 25 (-14%)	24 (-33%) 27 (-25%)	p <0,0001 p <0,0001		
PI3K (UAS-PI3K caax/+) Αβ42 (UAS-2xAβ42/+) PI3K/Aβ42 (UAS-PI3K cas PI3K/Aβ42 VS Aβ42	ix/UAS-2xAβ42)	30	25 (-14%)	27 (-25%)			
PI3K (UAS-PI3K caax/+) Aβ42 (UAS-2xAβ42/+) PI3K/Aβ42 (UAS-PI3K cas PI3K/Aβ42 VS Aβ42 Aβ42 (UAS-2xAβ42/+)		30	25 (-14%)	27 (-25%)	p <0,0001		
PI3K (UAS-PI3K caax/+) AB42 (UAS-2xAB42/+) PI3K/AB42 (UAS-PI3K cas PI3K/AB42 VS AB42 AB42 (UAS-2xAB42/+) PI3K/AB42 (UAS-PI3K cas		30	25 (-14%)	27 (-25%)			
PI3K (UAS-PI3K cnax/+) ABA2 (UAS-2xAB42/+) PI3K/AB42 (UAS-PI3K ca: PI3K/AB42 VS AB42 AB42 (UAS-2xAB42/+) PI3K/AB42 (UAS-PI3K ca:		30 48 30	25 (-14%) 18 25 (+38%)	27 (-25%) 24 27 (+12%)	p <0,0001 p <0,0001		
PI3K (UAS-PI3K casx/+) AB42 (UAS-2xAB42/+) PI3K/AB42 (UAS-PI3K cas PI3K/AB42 VS AB42 AB42 (UAS-2xAB42/+) PI3K/AB42 (UAS-PI3K cas Genotype		30	25 (-14%) 18 25 (+38%)	27 (-25%) 24 27 (+12%)	p <0,0001		
PISK (UAS-PISK caaw/-) AB42 (UAS-PISK caaw/-) PISK/AB42 (UAS-PISK caa PISK/AB42 (UAS-PISK caa PISK/AB42 (VAS-PISK caa AB42 (UAS-PISK caa PISK/AB42 (UAS-PISK caa Genotype Genotype Gooup VS Control Control (UAS-LacZ/+)		30 48 30 n	25 (-14%) 18 25 (+38%) Median Surv	27 (-25%) 24 27 (+12%) Maximum Surv 35	p <0,0001 p <0,0001 Mantel-Cox test		
PISK (UAS-PISK caaw/+) APA2 (UAS-PISK caaw/+) PISK/APA2 (UAS-PISK caa PISK/APA2 (UAS-PISK caa PISK/APA2 VS APA2 APA22 (UAS-APA24) PISK/APA2 (UAS-PISK caa Genotype Group VS Control Control (UAS-LaCz/+) APA22 (UAS-SZAPA2/+)		30 48 30 n	25 (+14%) 18 25 (+38%) Median Surv 31 15 (-52%)	27 (-25%) 24 27 (+12%) Maximum Surv 35 20 (-43%)	p <0,0001 p <0,0001 Mantel-Cox test p <0,0001		
PISK (UAS-PISK caaw/+) PISK/AB42 (UAS-PISK caaw/+) PISK/AB42 (UAS-PISK caa PISK/AB42 (UAS-PISK caa PISK/AB42 VS AB42 AB42 (UAS-PISK caa Genotype Group VS Control Control (UAS-LacZ/+) AB42 (UAS-ZAB42/+) PISK-AB42 (UAS-ZAB42/+)	tx/UAS-2xAβ42)	30 48 30 n 25 27 45	25 (+14%) 18 25 (+38%) Median Surv 31 15 (-52%) 18 (-42%)	27 (+25%) 24 27 (+12%) Maximum Surv 35 20 (-43%) 23 (-34%)	p <0,0001 p <0,0001 Mantel-Cox test p <0,0001 p <0,0001		
PIBK (UAS-PIBK CanaVr) PIBK/AB42 (UAS-PIBK canaVr) PIBK/AB42 (UAS-PIBK canaVr) PIBK/AB42 (VAS-PIBK canaVr) PIBK/AB42 (VAS-PIBK canaVr) PIBK/AB42 (UAS-PIBK canaVr) PIBK/AB42 (UAS-SAB642/r) PIBK/AB42 (UAS-SAB642/r) PIBK/AB42 (UAS-PIBK canaVr)	ix/UAS-2xAβ42) //UAS-2xAβ42	30 48 30 n 25 27 45 28	25 (-14%) 18 25 (+38%) Median Surv 31 15 (-52%) 18 (-42%) 11 (-64%)	27 (+25%) 24 27 (+12%) Maximum Surv 35 20 (+33%) 23 (-34%) 15 (-57%)	p <0,0001 p <0,0001 Mantel-Cox test p <0,0001 p <0,0001 p <0,0001		
PISK (UAS-PISK caav/+) PISK/AB42 (UAS-PISK caa PISK/AB42 (UAS-PISK ca PISK/AB42 (UAS-PISK ca PISK/AB42 (UAS-PISK ca PISK/AB42 (UAS-PISK ca Genotype Group VS Control Control (UAS-LacZ/+) PISK/AB42 (UAS-MORA)	//UAS-2xAβ42) //UAS-2xAβ42) NAI/+)	30 48 30 n 25 27 45	25 (+14%) 18 25 (+38%) Median Surv 31 15 (-52%) 18 (-42%)	27 (+25%) 24 27 (+12%) Maximum Surv 35 20 (-43%) 23 (-34%)	p <0,0001 p <0,0001 Mantel-Cox test p <0,0001 p <0,0001		
PIBK (UAS-PIBK caav/+) PIBK/ABA2 (UAS-PIBK caa PIBK/ABA2 (UAS-PIBK caa PIBK/ABA2 VAS-PIBK caa PIBK/ABA2 VAS-PIBK caa PIBK/ABA2 VAS-PIBK caa Genotype Group VS Control Control (UAS-LacZ/+) mTOR (UAS-mTOR/-) mTOR (UAS-mTOR/-) mTOR (UAS-mTOR/-) mTOR (UAS-mTOR/-) mTOR (UAS-mTOR/-) mTOR (UAS-mTOR/-)	//UAS-2xAβ42) //UAS-2xAβ42) NAI/+)	30 48 30 n 25 27 45 28 46	25 (-14%) 18 25 (+38%) Median Surv 31 15 (-52%) 18 (-42%) 11 (-64%) 29 (-6%)	27 (-25%) 24 27 (+12%) Maximum Surv 35 20 (-43%) 23 (-34%) 15 (-57%) 37 (+6%)	p <0,0001 p <0,0001 Mantel-Cox test p <0,0001 p <0,0001 p <0,0001 p = 0,0001 p = 0,0001		
PIBK (UAS-PIBK caav/+) PIBK/ABA2 (UAS-PIBK cab/+) PIBK/ABA2 (UAS-PIBK cab PIBK/ABA2 (UAS-PIBK cab PIBK/ABA2 (UAS-PIBK cab PIBK/ABA2 (UAS-PIBK cab Genotype Genotype Genotype Genotype Genotype Genotype Tootrof (UAS-TaaZ/+) ABA2 (UAS-TaaZ/+) ABA2 (UAS-TaaZ/+) Tootrof (UAS-TaaZ/+) Tootrof (UAS-TaaZ/+) Tootrof (UAS-TaaZ/+) MTOR (UAS-TIOS/+) MTOR (UAS-TIOS/+) MTOR (UAS-TIOS/+)	(ν/UAS-2xAβ42) /UAS-2xAβ42) NAU/+) edea RNAI/UAS-2xAβ42) /UAS-2xAβ42)	30 48 30 0 25 27 45 28 46 34	25 (-14%) 18 25 (+38%) Median Surv 31 15 (-52%) 18 (-42%) 11 (-64%) 29 (-6%) 29 (-6%)	27 (-25%) 24 27 (+12%) Maximum Surv 35 20 (-43%) 23 (-34%) 15 (-57%) 37 (+65%) 35 (-)	p <0,0001 p <0,0001 Mantel-Cox test p <0,0001 p <0,0001 p <0,0001 p = 0,0001 p = 0,0001		

Suppl. Table S1

Supplementary Table S1.-Data from climbing and lifespan assays with the corresponding statistical tests. Climbing assay performance is color coded as in main **Figures 2** and **6**.