



68° CONGRESSO NAZIONALE SIGG

Ritorno al futuro

FIRENZE, 13-16 DICEMBRE 2023
PALAZZO DEI CONGRESSI

Impatto di bassi dosaggi di bassi dosaggi di BDNF sulle ricorrenze di Fibrillazione Atriale

Firenze 15 Dicembre 2023

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Università degli Studi Guglielmo Marconi



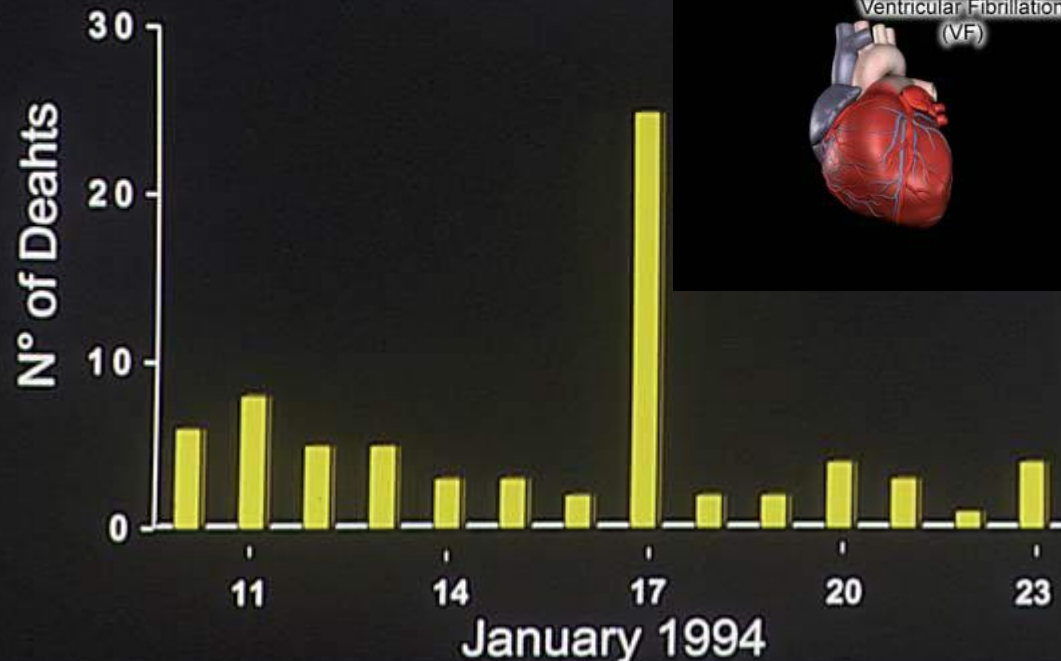
Centro Studi Scienze della Vita



Northridge, Los Angeles Area, 4:31 a.m., January 17, 1994.

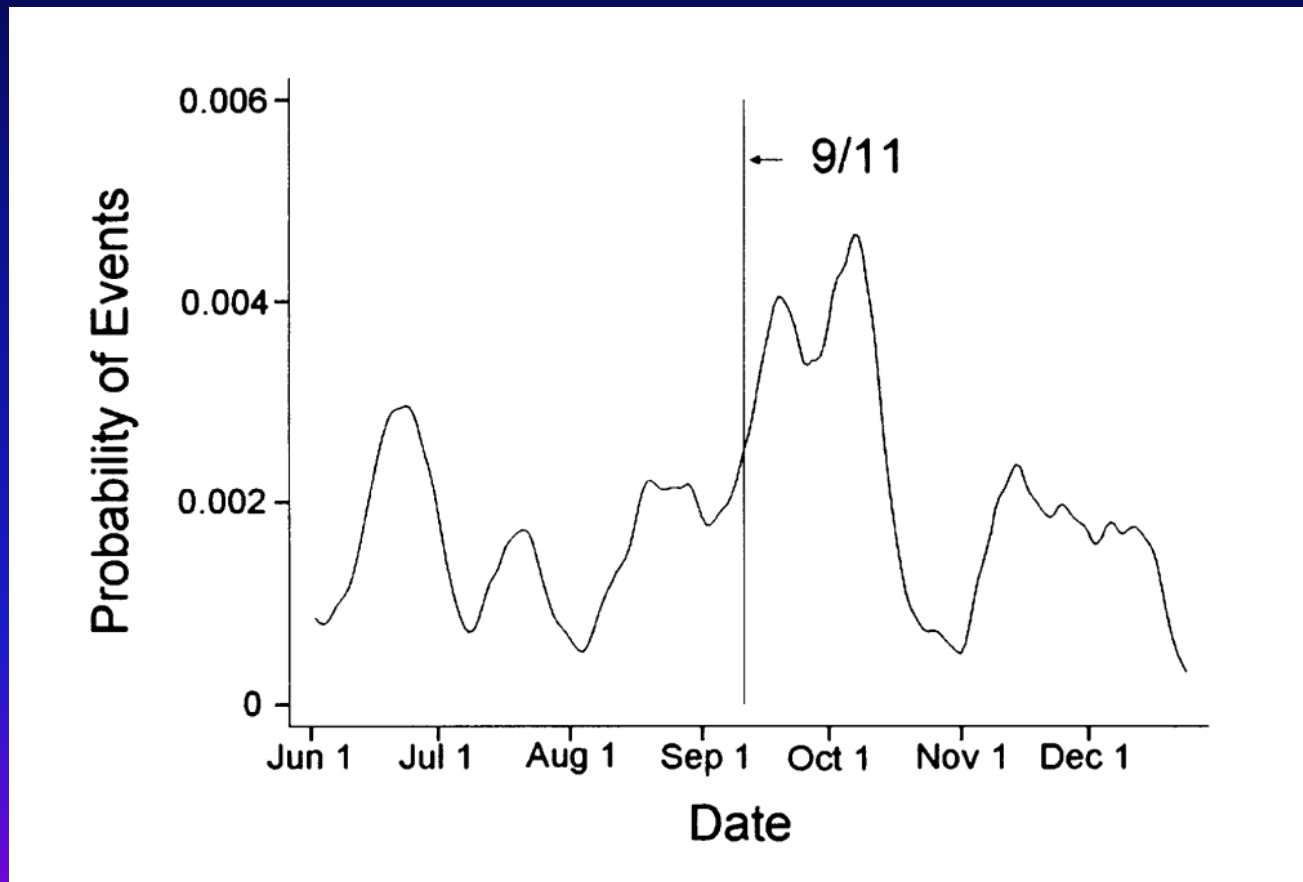
Department
Of Coroner
Los Angeles
County

Sudden Cardiac Death Triggered
by an Earthquake
Leor J et al, N Engl J Med 1996



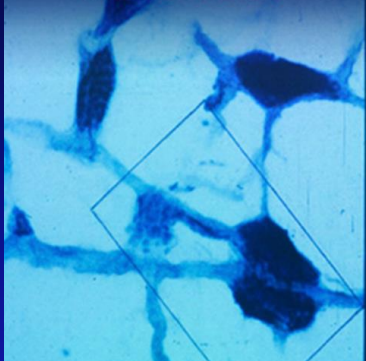
Increased Incidence of Life-Threatening Ventricular Arrhythmias in Implantable Defibrillator Patients After the World Trade Center Attack

JACC Vol. 44,
No. 6, 2004

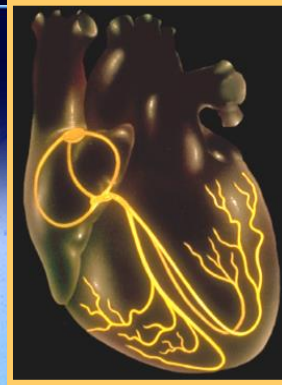
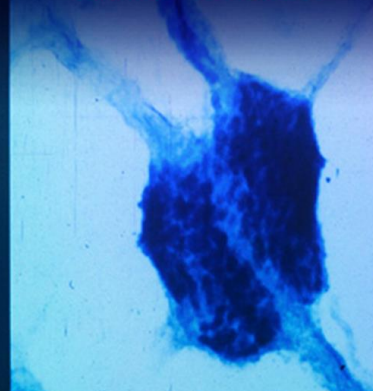


Cardiac Intrinsic Ganglia

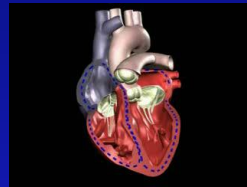
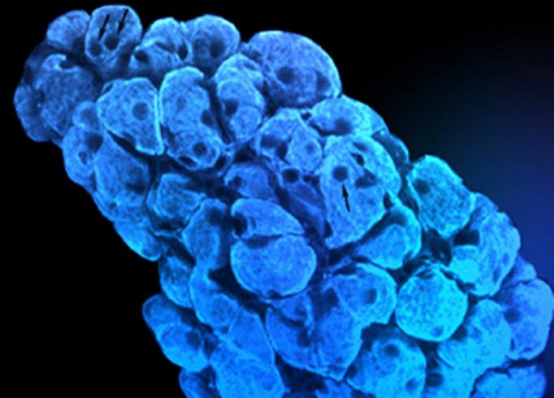
Interconnectivity between Intrinsic Ganglia in the Human Heart



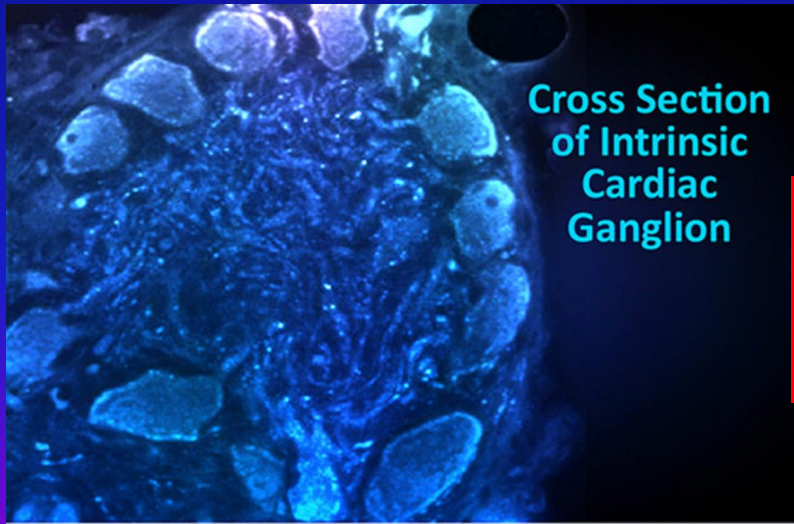
Expanded view of the Intrinsic Cardiac Ganglion



Intrinsic Cardiac Ganglia

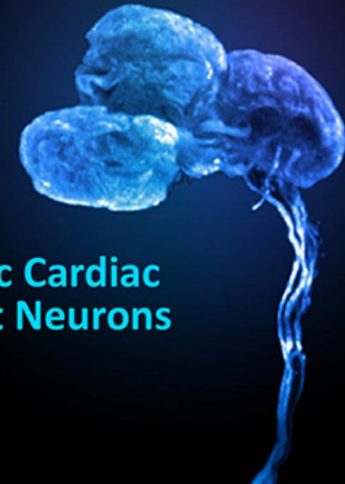


Cross Section of Intrinsic Cardiac Ganglion

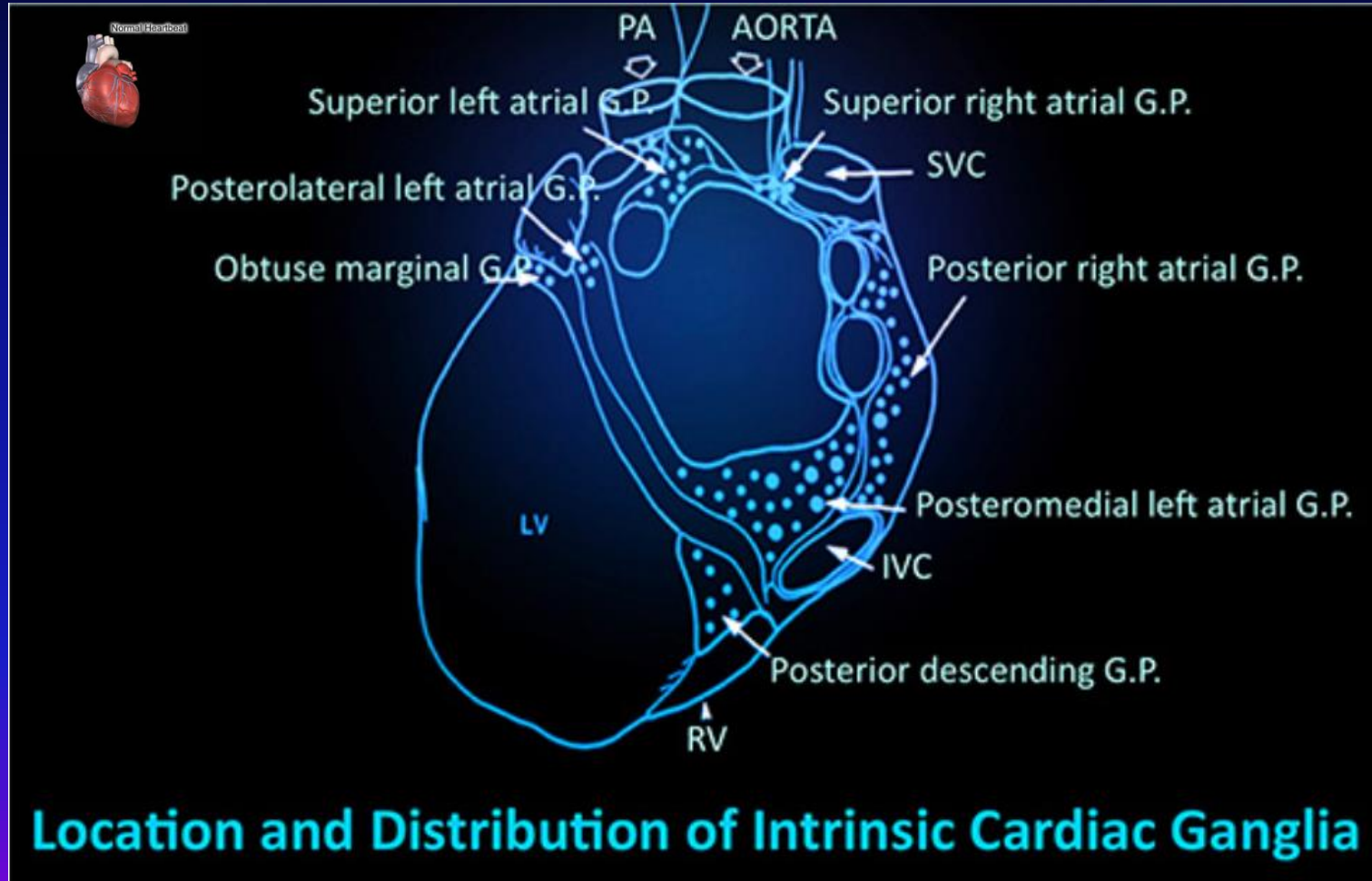


40.000
neurons

Intrinsic Cardiac Afferent Neurons



Location and distribution of Intrinsic Cardiac Ganglia



Hilum Cordis

The cardiac nerves (arrowheads) stained histochemically for acetylcholinesterase in the arterial part of the human *hilum cordis*.

RA Ventral Surface of the Right Atrium

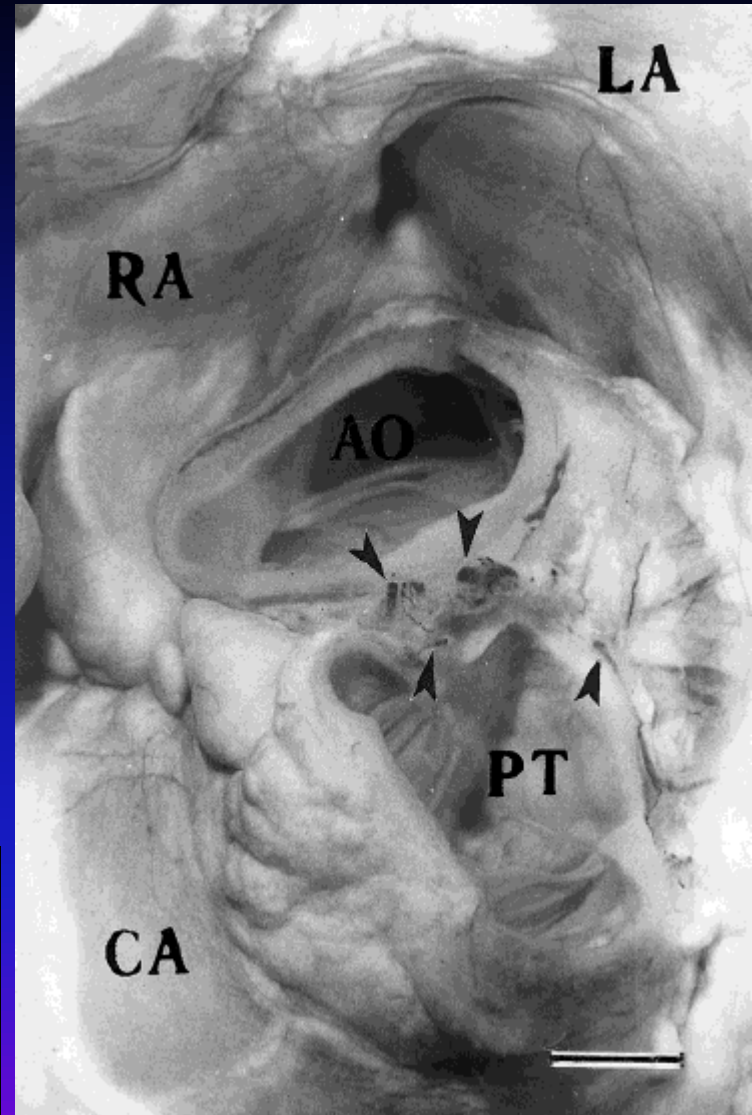
LA Ventral Surface of the Left Atrium

AO Aorta

PT Pulmonary Trunk

CA Conus Arteriosus

Bar = 5 mm.





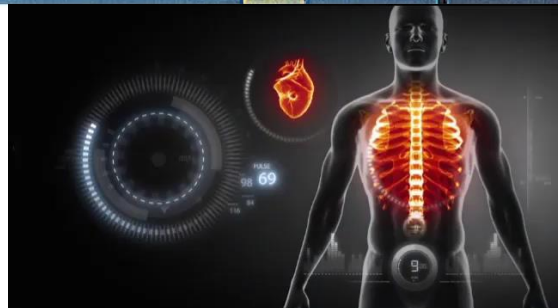
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life



Systematic Review

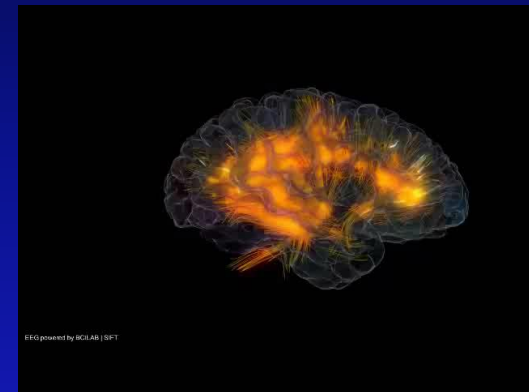
Brain–Heart Axis: Brain-Derived Neurotrophic Factor and Cardiovascular Disease—A Review of Systematic Reviews

Massimo Fioranelli ¹, Maria Luisa Garo ^{2,*} , Maria Grazia Roccia ¹, Bianca Przybylek ²
and Francesca Romana Sconci ²

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- * Correspondence: marilu.garo@gmail.com

Neurotrophins

- **Nerve Growth Factor**
- **Brain-Derived Neurotrophic Factor**
- Neurotrophin-3
- Neurotrophin-4/5
- Neurotrophin-6
- Neurotrophin-7
- Ciliary Neurotrophic Factor
- Glia Maturation Factor
- Glial Cell Line-Derived Neurotrophic Factors
- Neuregulins (NRG-1, 2, 3 and 4)
- Pituitary Adenylate Cyclase-Activating Polypeptide



BDNF

Fattore neurotrofico cerebrale



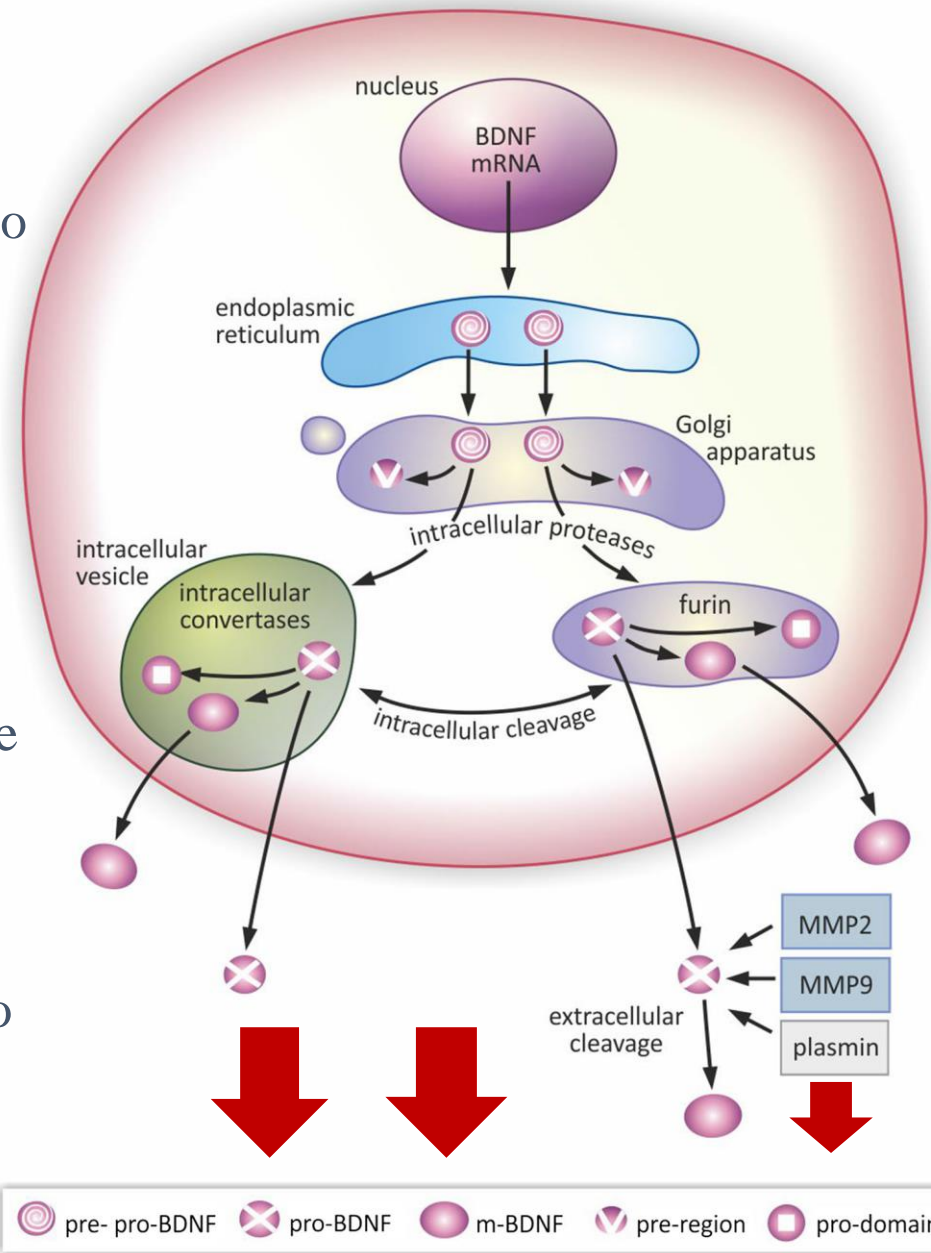
Il fattore neurotrofico cerebrale, o BDNF (da Brain-Derived Neurotrophic Factor), è un polipeptide presente nel cervello dei mammiferi, appartenente alla famiglia delle neurotrofine. BDNF maturo è una proteina costituita da **119 aminoacidi**, massa molare di 14 KDa , il gene è localizzato nel **cromosoma 11, banda p 13**

RUOLI FISIOLGICI DEL BDNF

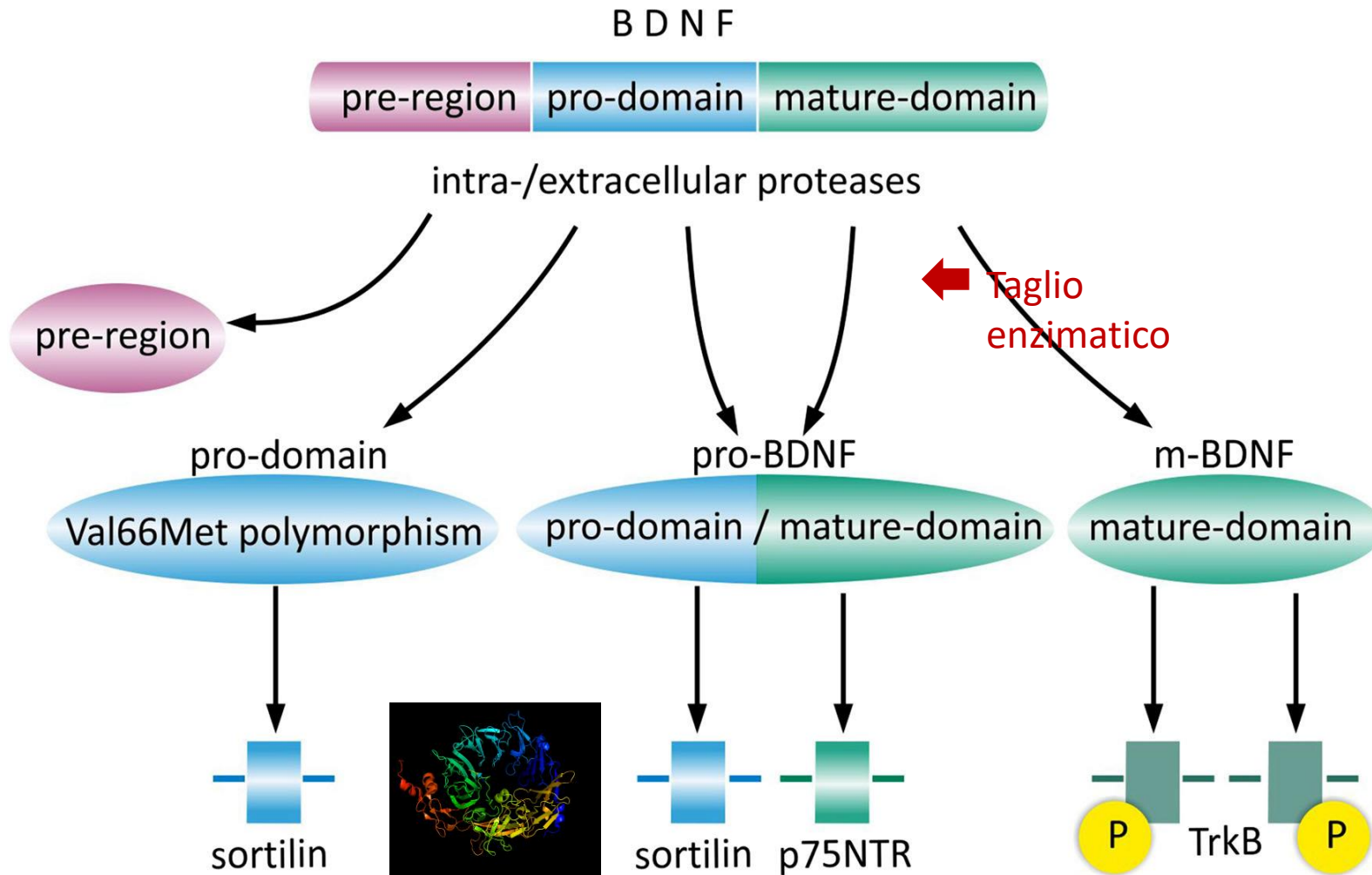
Il Brain-Derived Neurotrophic Factor (BDNF) è una delle neurotrofine del cervello dei mammiferi più studiate e, tra le sue funzioni, tre sono particolarmente importanti per i meccanismi **cognitivi** e di **memoria**:

- Controllo dello sviluppo neuronale e della glia
- Neuro-protezione
- Modulazione delle interazioni sinaptiche sia a breve che lungo termine

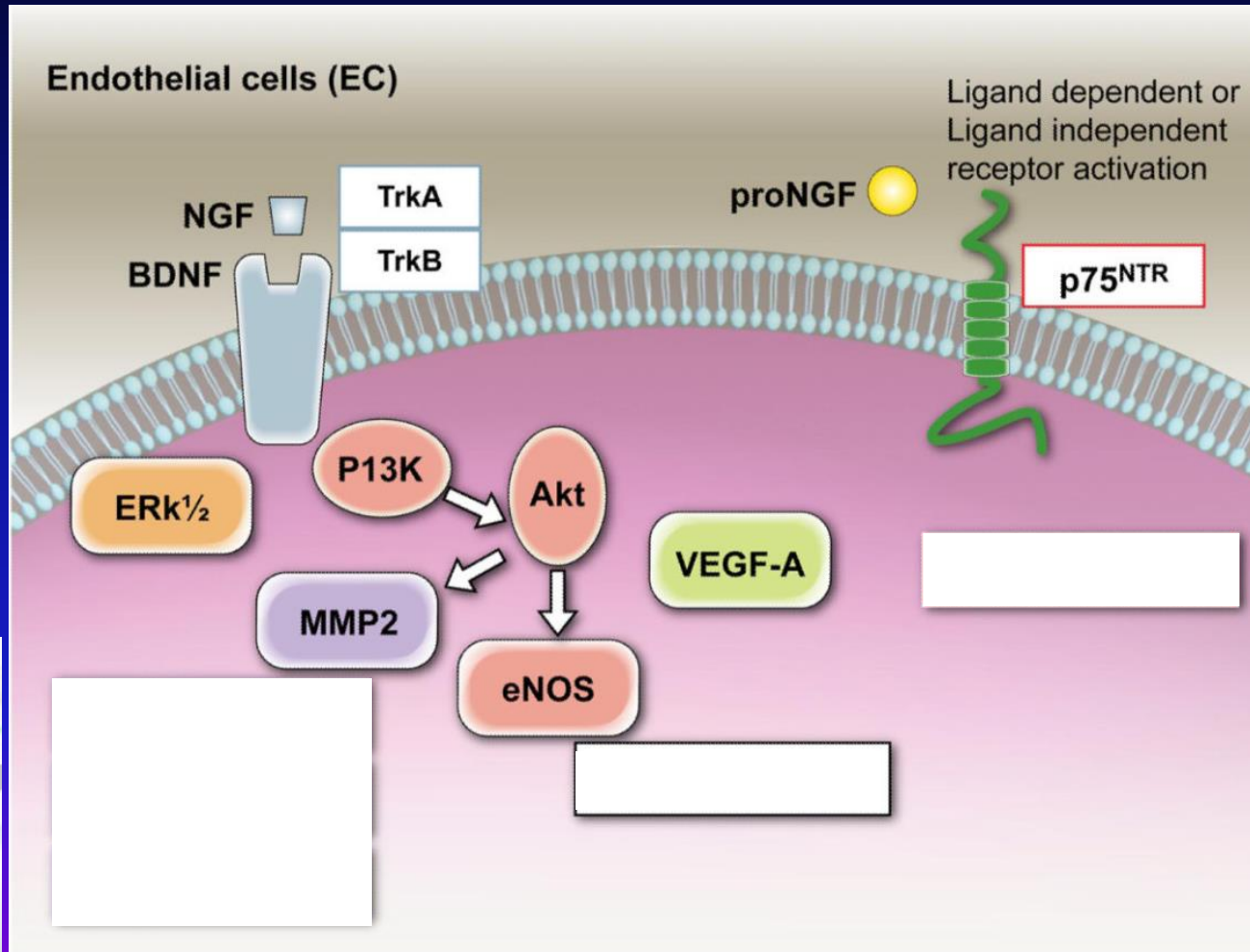
Il BDNF viene sintetizzato attraverso un processo complesso, che genera un numero di isoforme attive in grado di regolare più cascate di segnale



Processi di maturazione del BDNF



Neurotrophin actions on the endothelial cells



BDNF • azioni biologiche



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BDNF

ANTI-
INFIAMMATORIA

Attività antinfiammatoria

- diretta (via down-regolazione di NF- κ B e quindi dei principali mediatori citochinici dell'infiammazione)
- indiretta (via up-regolazione di IL-10)

ANTI-
NEURO-
DEGENERATIVA

Attività anti-neurodegenerativa

freno della formazione dei "gomitoli" di proteina TAU fosforilata che interferiscono sulla comunicazione inter-neuronale

ANTI-
OSSIDANTE

Azione antiossidante

aumento dell'espressione dei geni codificanti per sistemi enzimatici *scavengers* quali superossido dismutasi (SOD) e glutazione ossidasi (GPx)

NEUROTROFICA

Attività neurotrofica

aumento della vitalità dei neuroni corticali e degli astrociti e di quest'ultimi anche della sopravvivenza

- **Ketosis (beta hydroxybutyrate)**

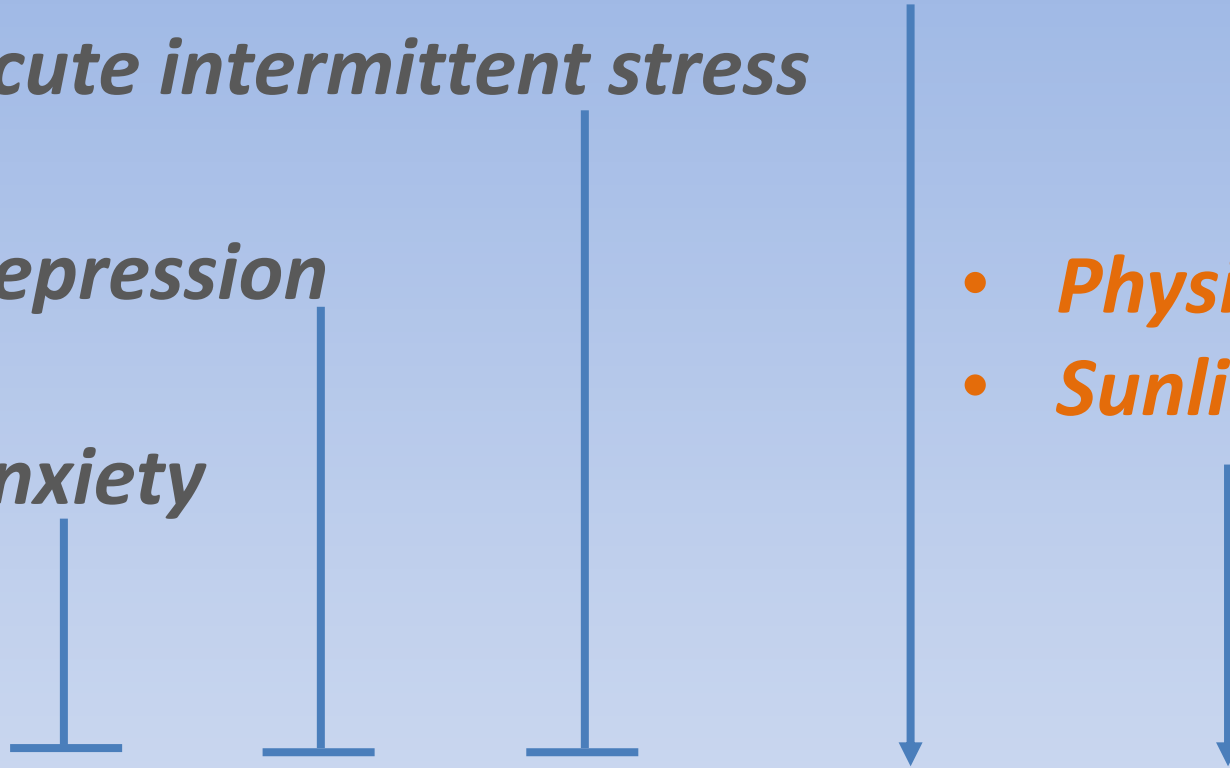
- *Acute intermittent stress*

- *Depression*

- *Anxiety*

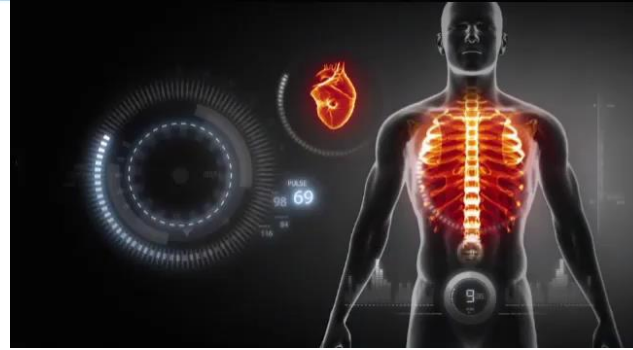
- *Physical exercise*

- *Sunlight exposure*



BDNF codifying mRNA

BDNF 1-7 transcription factors



Systematic Review

The Role of Brain-Derived Neurotrophic Factor (BDNF) in Depression and Cardiovascular Disease: A Systematic Review

Massimo Fioranelli ¹, Maria Grazia Roccia ¹, Bianca Przybylek ² and Maria Luisa Garo ^{3,*}

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Article

The Role of BDNF on Aging-Modulation Markers

Claudio Molinari, Vera Morsanuto, Sara Ruga, Felice Notte, Mahitab Farghali, Rebecca Galla and Francesca Uberti * 

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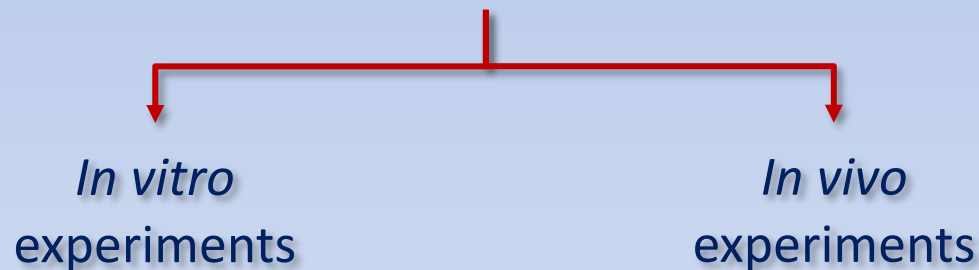
Received: 26 February 2020; Accepted: 4 May 2020; Published: 9 May 2020





Study goal: To demonstrate the effectiveness of low dose SKA BDNF (GUNA-BDNF) in counteracting brain aging induced by oxidative stress

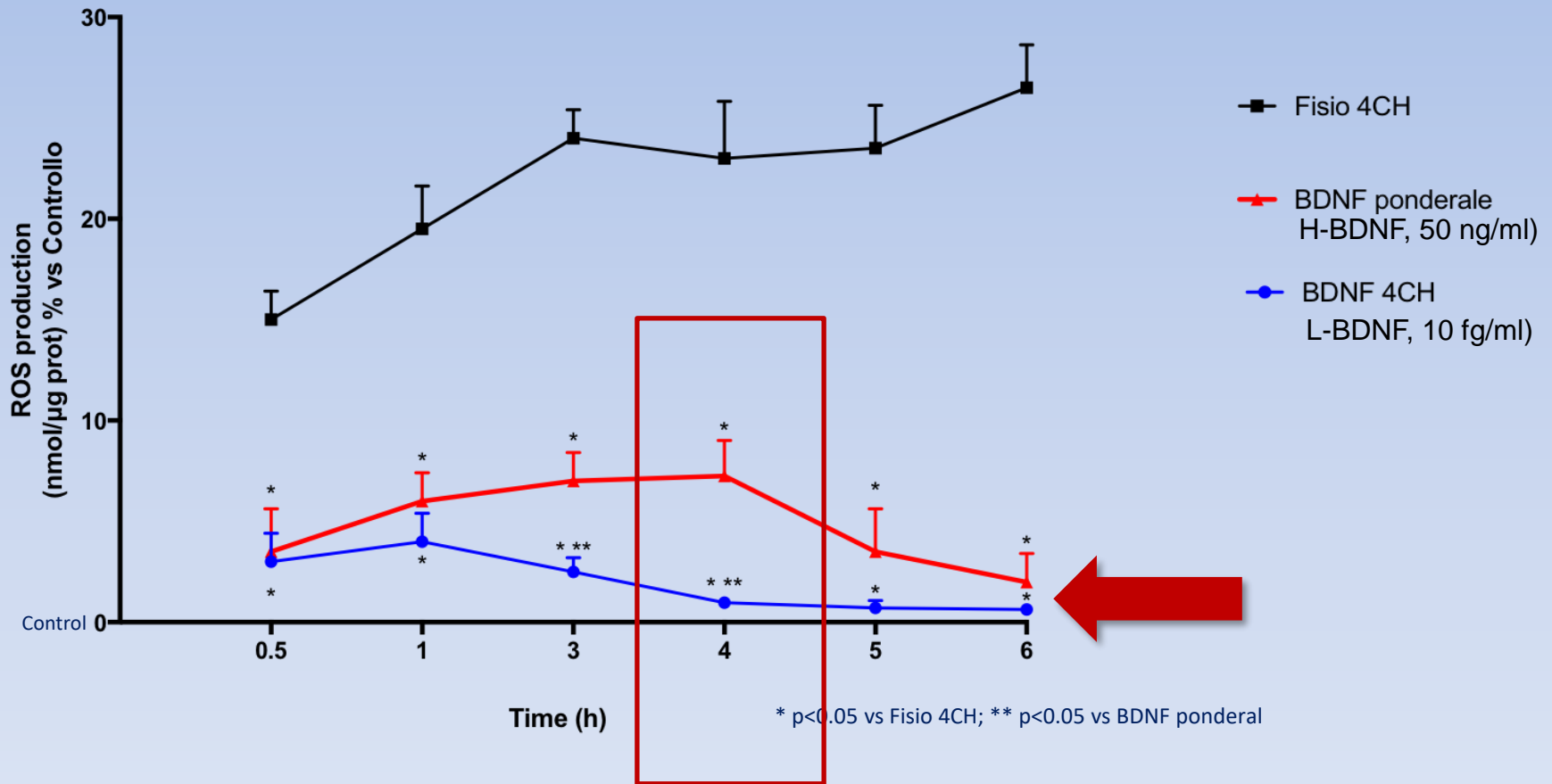
Methods



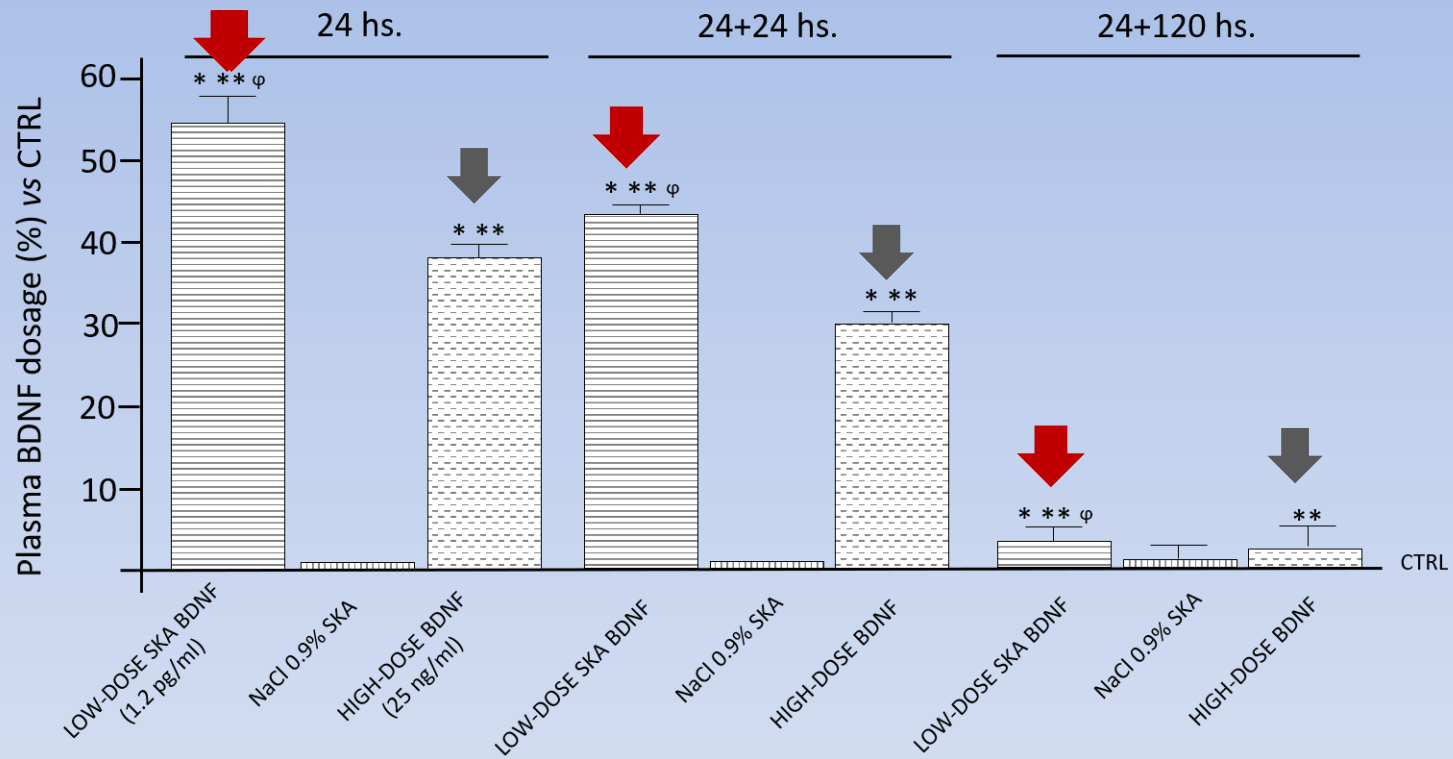
Main outcomes

- ROS REDUCTION
- CELL VIABILITY
- Ability of BDNF low dose to overcome biological barriers

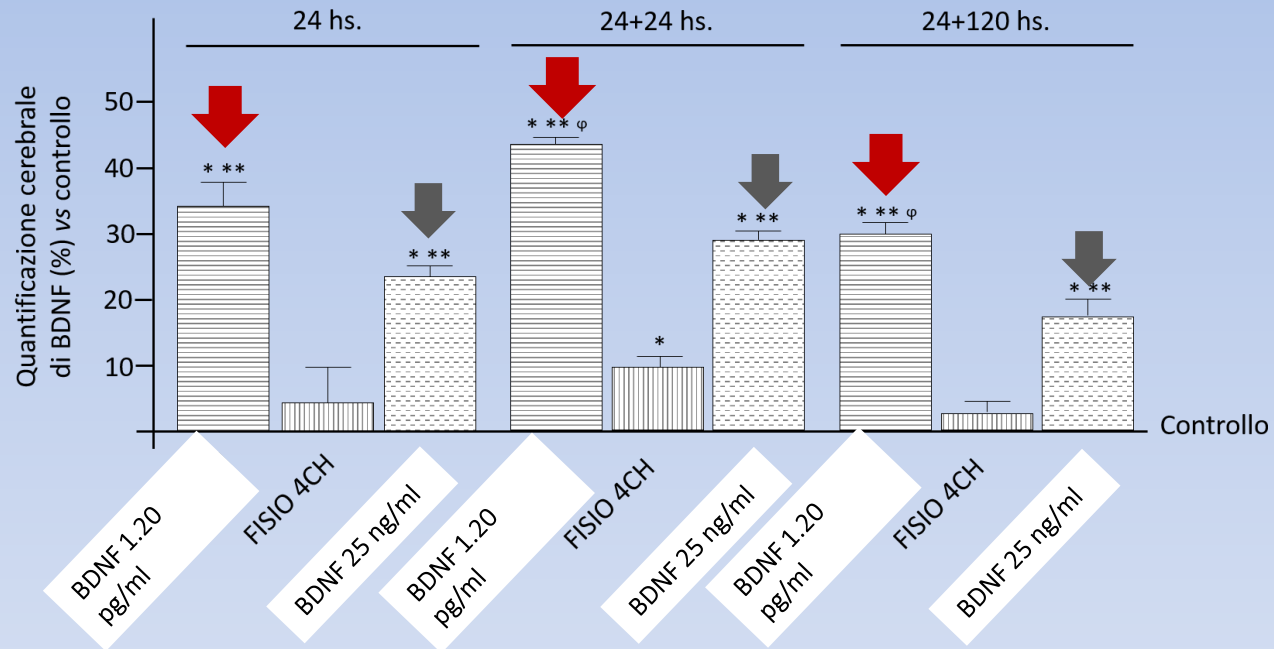
ROS REDUCTION



Plasma BDNF QUANTIFICATION

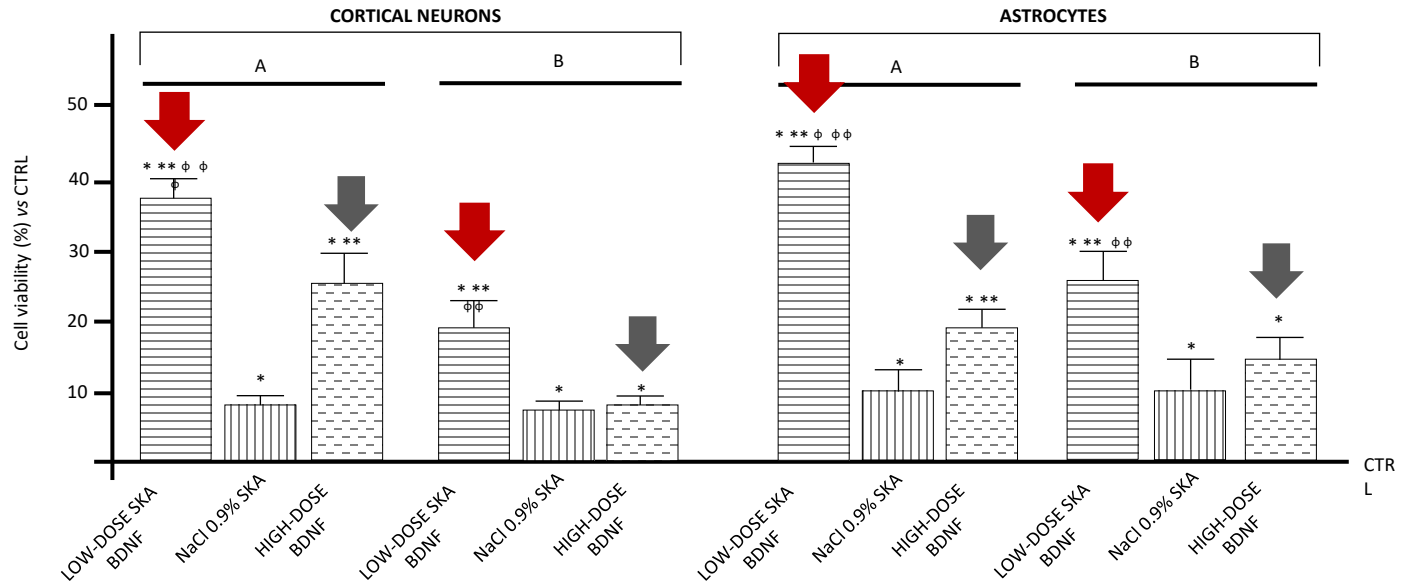


In vivo BRAIN BDNF QUANTIFICATION



12 month old mice type C57BL

CELL VIABILITY



Protocol A

a single cell treatment in 6 days

Protocol B

1 cell treatment a day for 6 days

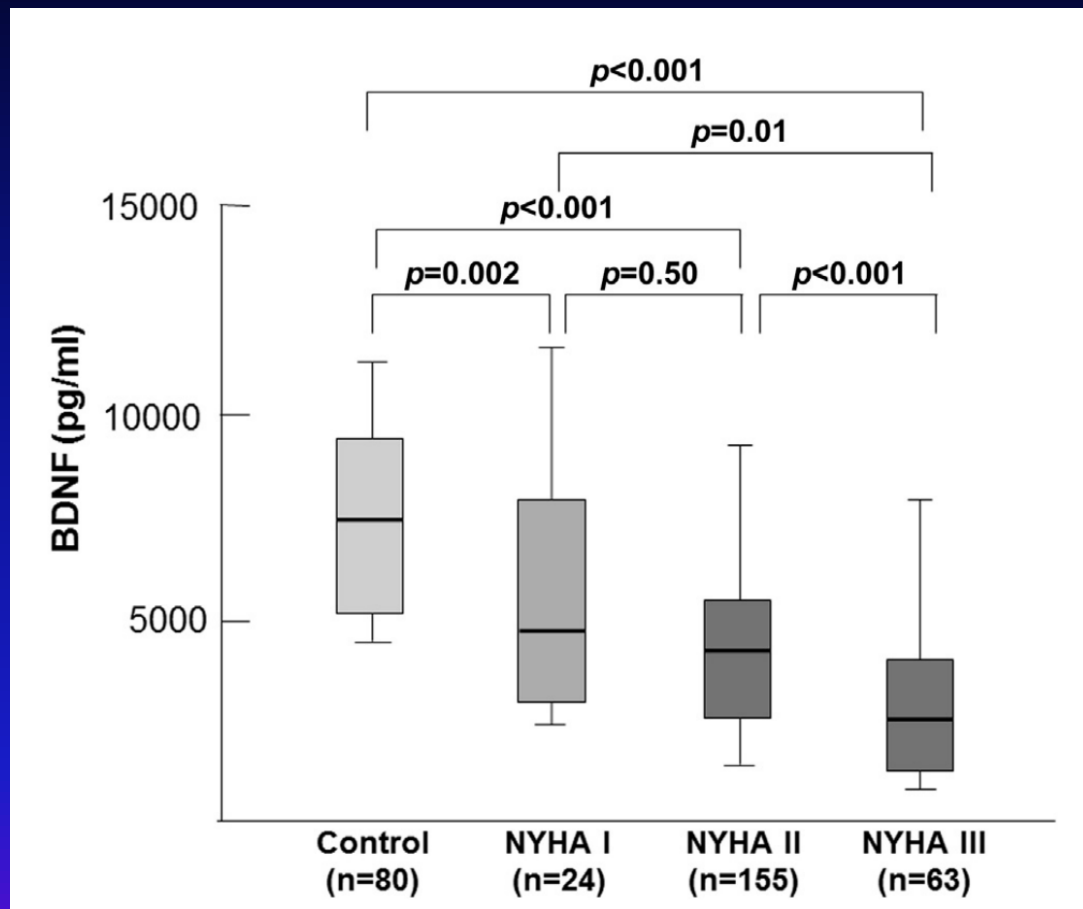
*p<0.05 vs CTRL; ** p<0.05 vs NaCl 0.9% SKA ; φ p<0.05 vs the same treatment in the two protocols;
 $\varphi\varphi$ p<0.05 vs BDNF within the same protocol

Plasma BDNF levels in Heart Failure

242 patients with HF
80 subjects without HF.
Plasma BDNF levels in patients
with HF 3,712 pg/ml
without HF 7,247 pg/ml
 $p < 0.001$.

Lower in patients with HF with
the NYHA class III
than class I $p = 0.01$ and
class II $p < 0.001$.

Log BDNF levels correlated
negatively with log B-type
natriuretic peptide



Am J Cardiol 2015;116:243e249

BDNF and Left Atrial Diameter

I.Te.S.I.



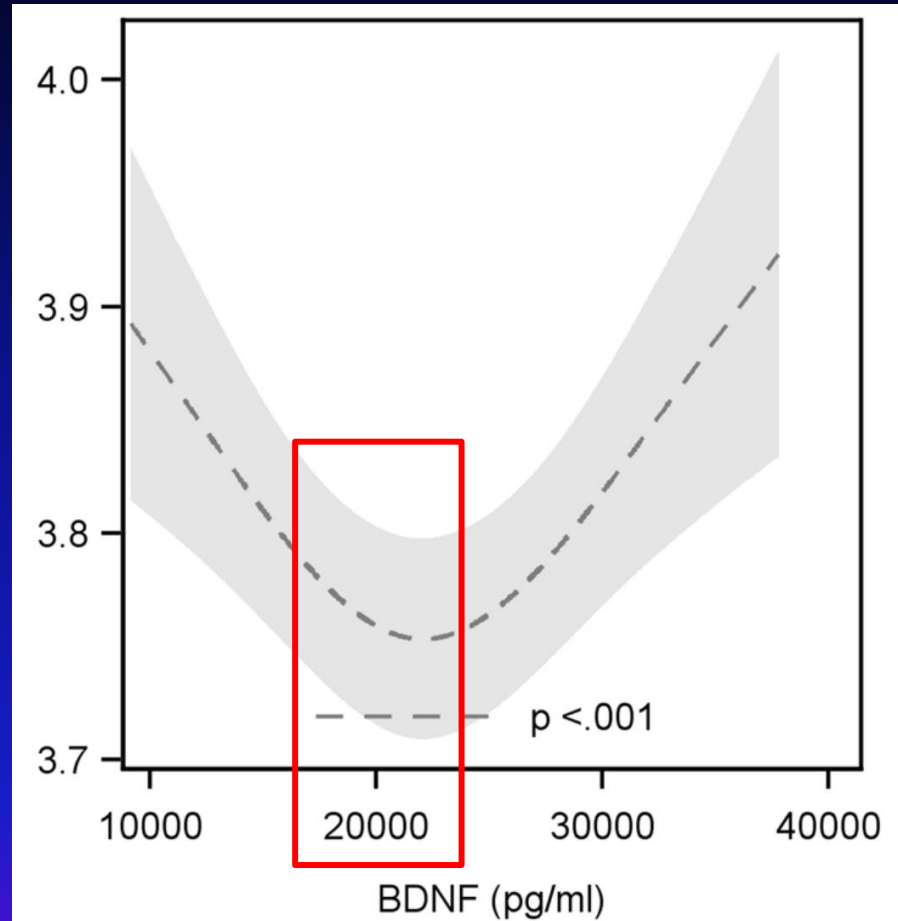
Subjects with a **BDNF** concentration around **20,000 pg/ml** had the **smallest left atrial diameter**.

An inverse association below this concentration.

Low BDNF was related with a **large left atrial diameter**.

For concentrations higher than 20,000 pg/ml a positive association was found.

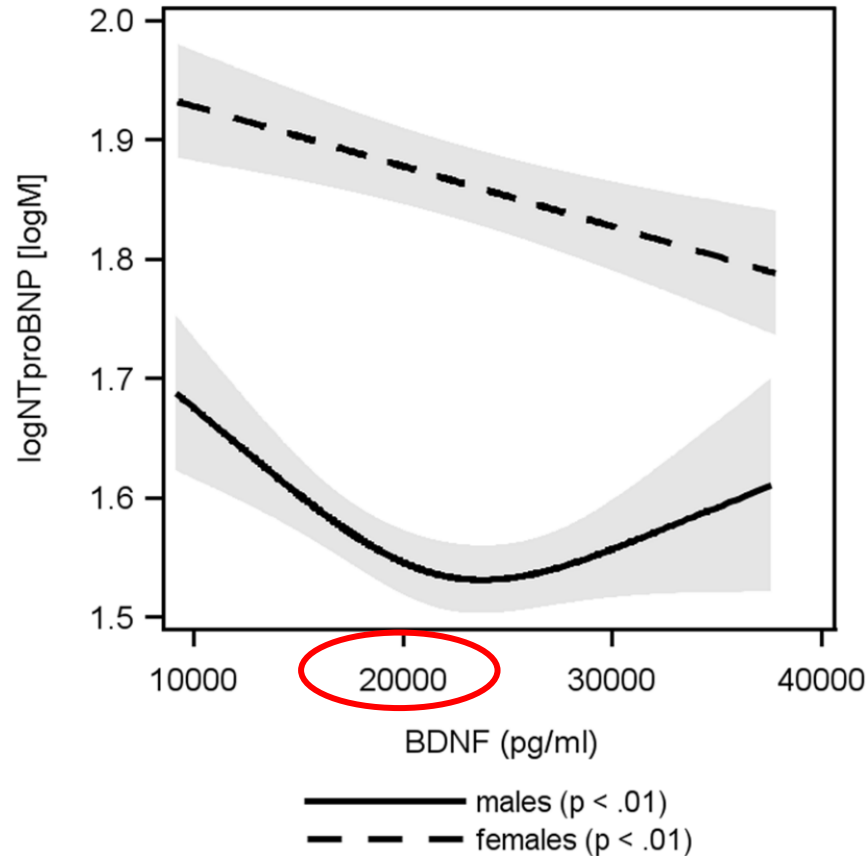
Thus, **high levels of BDNF** were also related to **larger left atrial diameters**.



Brain-derived neurotrophic factor is related with adverse cardiac remodeling and high ntproBnp
Scientific Reports | (2019) 9:15421 | <https://doi.org/10.1038/s41598-019-51776-8>

BDNF and NTproBNP

BDNF correlation with echocardiographic parameters and NTproBNP in a large population-based cohort (n= 2,976, median age 48 years; 45% male).



Brain-derived neurotrophic factor is related with adverse cardiac remodeling and high ntproBnp
Scientific Reports | (2019) 9:15421 | <https://doi.org/10.1038/s41598-019-51776-8>

ORIGINAL ARTICLE

Impact of low-dose Brain-Derived Neurotrophic Factor (BDNF) on atrial fibrillation recurrence

Massimo FIORANELLI ¹, Luigi SPADAFORA ² *, Marco BERNARDI ², Maria G. ROCCIA ¹,
Marco G. DEL BUONO ³, Giulio CACIOLI ³, Giuseppe BIONDI-ZOCCAI ^{4, 5}

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BDNF e FA

POPOLAZIONE

- 22 Ptz
- 17 M 5F
- Eta' Media 74,86 aa
- Follow Up 24 mesi

BDNF e FA

Materiali e metodi

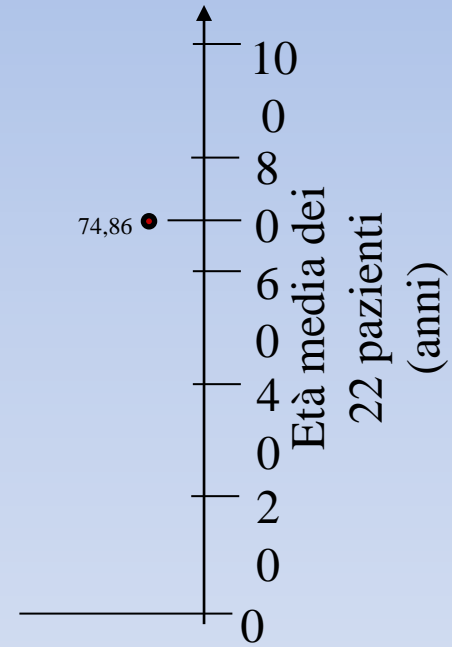
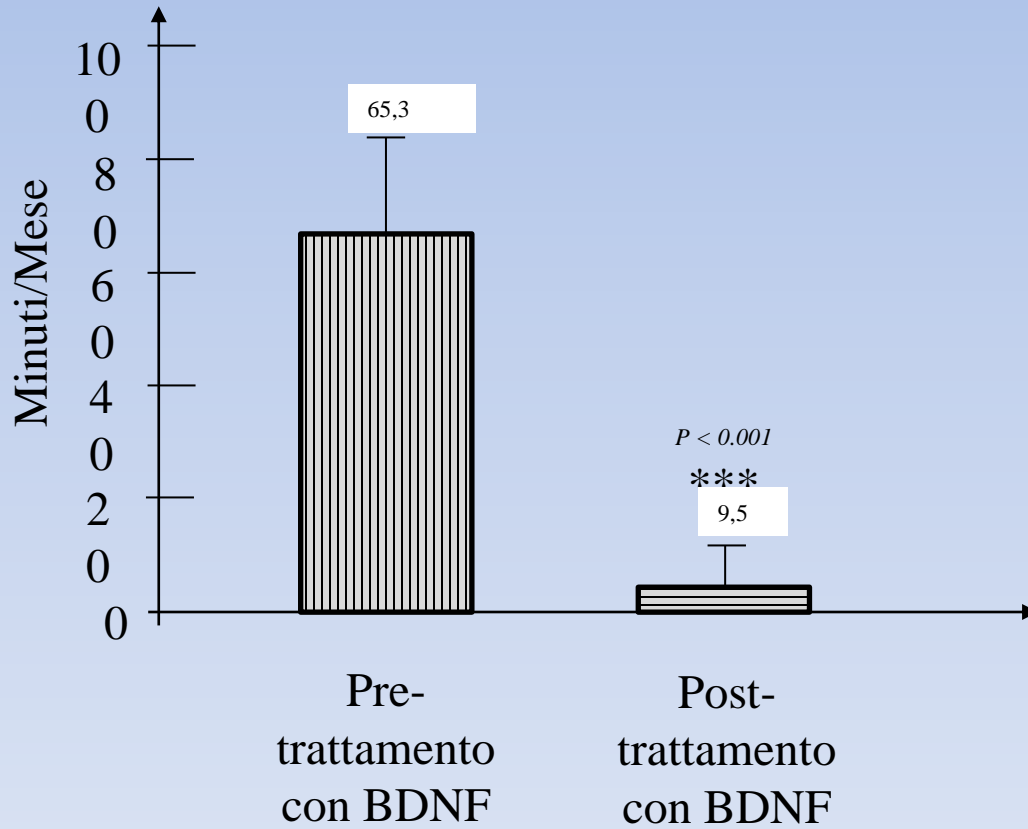
- FA parossistica
- Assenza di cardiopatia strutturale
- Trattamento farmacologico stabile da tre mesi
- Tempo in minuti mensili di FA registrati con:
 - Sintomi
 - ECG Dinamico sec. Holter
 - Loop Recorder
 - PM AICD impiantati

Baseline features of the population

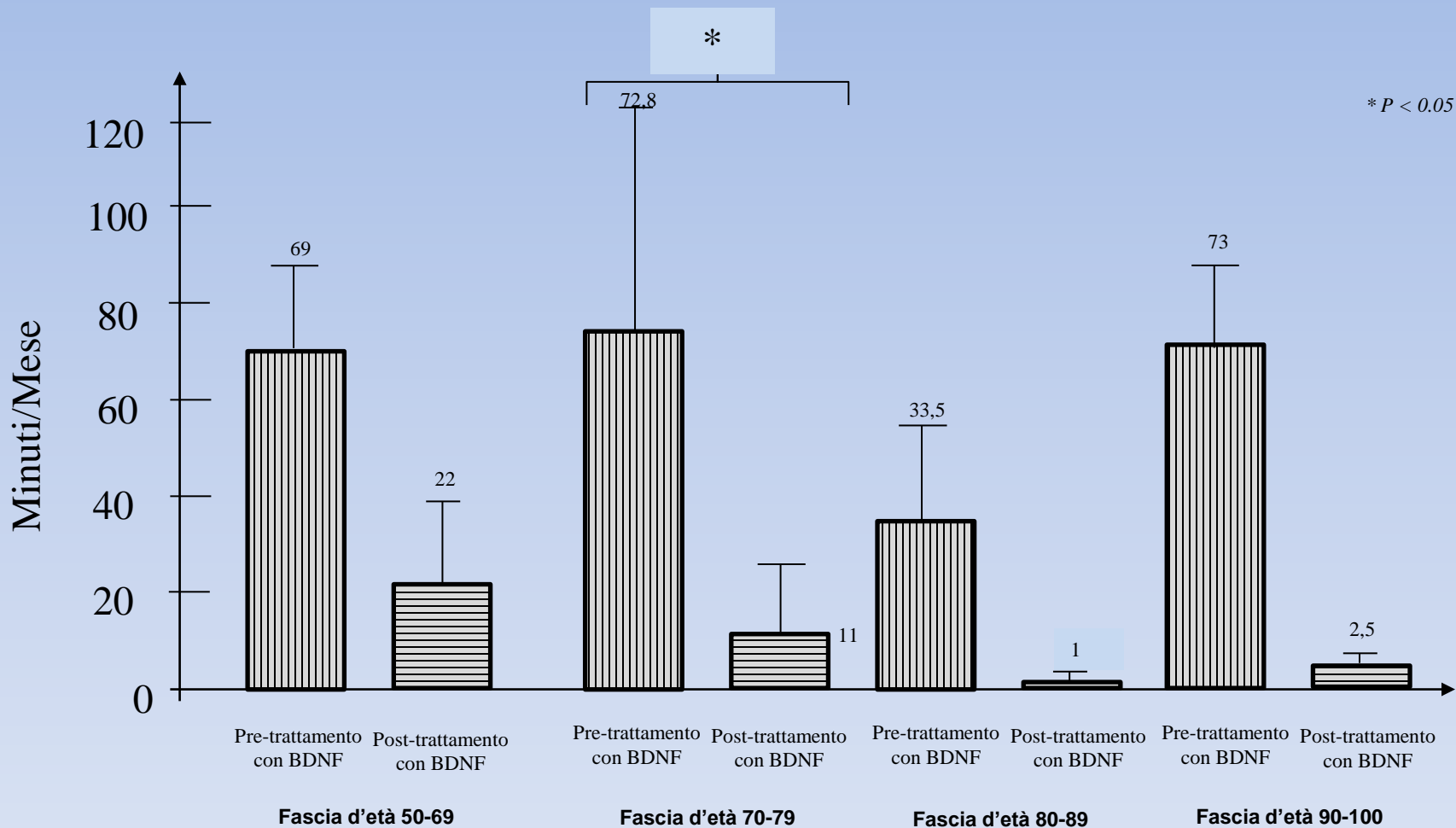
Patient	Sex	Age	Hyper-tension	Dys-lipid-emia	Type 1 dia-betes	Type 2 dia-betes	PAD	MI	PTCA	Drugs
P1	M	72	N	N	N	N	N	N	N	NOAC, amiodarone, bisoprolol
P2	M	84	N	N	N	N	N	N	Y	NOAC, amiodarone, ACE inhibitor
P3	M	90	N	N	Y	N	N	N	Y	NOAC, amiodarone, ACE inhibitor
P4	F	74	N	N	N	N	N	N	N	NOAC, bisoprolol
P5	M	87	Y	N	N	N	N	N	N	NOAC, amiodarone, amlodipine
P6	F	65	N	N	N	N	N	N	N	NOAC
P7	M	70	Y	Y	N	N	N	N	Y	NOAC, bisoprolol, amlodipine, statin
P8	M	80	Y	N	N	N	N	N	N	NOAC, ACE inhibitor, amlodipine
P9	M	83	Y	N	Y	N	N	N	N	NOAC, ACE inhibitor, amlodipine
P10	M	92	Y	Y	Y	N	N	N	N	Aspirin, bisoprolol, ACE inhibitor, insulin, statin
P11	M	71	Y	N	N	N	N	N	Y	NOAC, ACE inhibitor, bisoprolol
P12	M	60	N	N	N	N	N	N	N	NOAC
P13	M	53	N	N	N	N	N	N	N	Bisoprolol
P14	M	82	N	N	N	N	N	N	N	Dronedarone, clopidogrel
P15	M	79	N	N	N	N	N	N	N	NOAC, bisoprolol
P16	F	73	Y	N	N	N	N	N	N	Sartan, Aspirin
P17	M	71	N	N	N	N	N	N	N	NOAC, bisoprolol
P18	M	78	Y	Y	N	N	N	N	Y	NOAC, flecainide, ACE inhibitor, amlodipine, statin
P19	M	57	Y	N	N	N	N	N	N	NOAC, flecainide, Sartan
P20	F	70	Y	N	N	N	N	N	N	NOAC, Sartan, amlodipine
P21	F	70	Y	N	N	N	N	N	N	NOAC, Sartan, amlodipine
P22	M	86	Y	N	N	N	N	N	N	Aspirin, Sartan, sotalol

N: no; Y: yes; M: male; F: female; PAD: peripheral artery disease; MI: myocardial infarction; PTCA: percutaneous transluminal coronary angioplasty; NOAC: new oral anticoagulants.

Durata media mensile degli eventi di Fibrillazione Atriale



Durata media mensile degli eventi di Fibrillazione Atriale – fasce di età



Conclusion

The prevention of PAF episodes remains still a challenging issue in cardiovascular medicine. The administration of BDNF, could represent a promising and natural tool against PAF. This study shows that:

- BDNF low dose may have an impacting role in reducing or eliminating the arrhythmic burden in patients with PAF
- This holds true especially in patients aged 70 or more, without structural heart disease and under optimal medical treatment.



Systematic Review

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