UOPI Malattie Rare del Sistema Nervoso in Età Pediatrica
Scuola di Specializzazione in Pediatria
DIPARTIMENTO di MEDICINA CLINICA e SPERIMENTALE
Università degli Studi di Catania

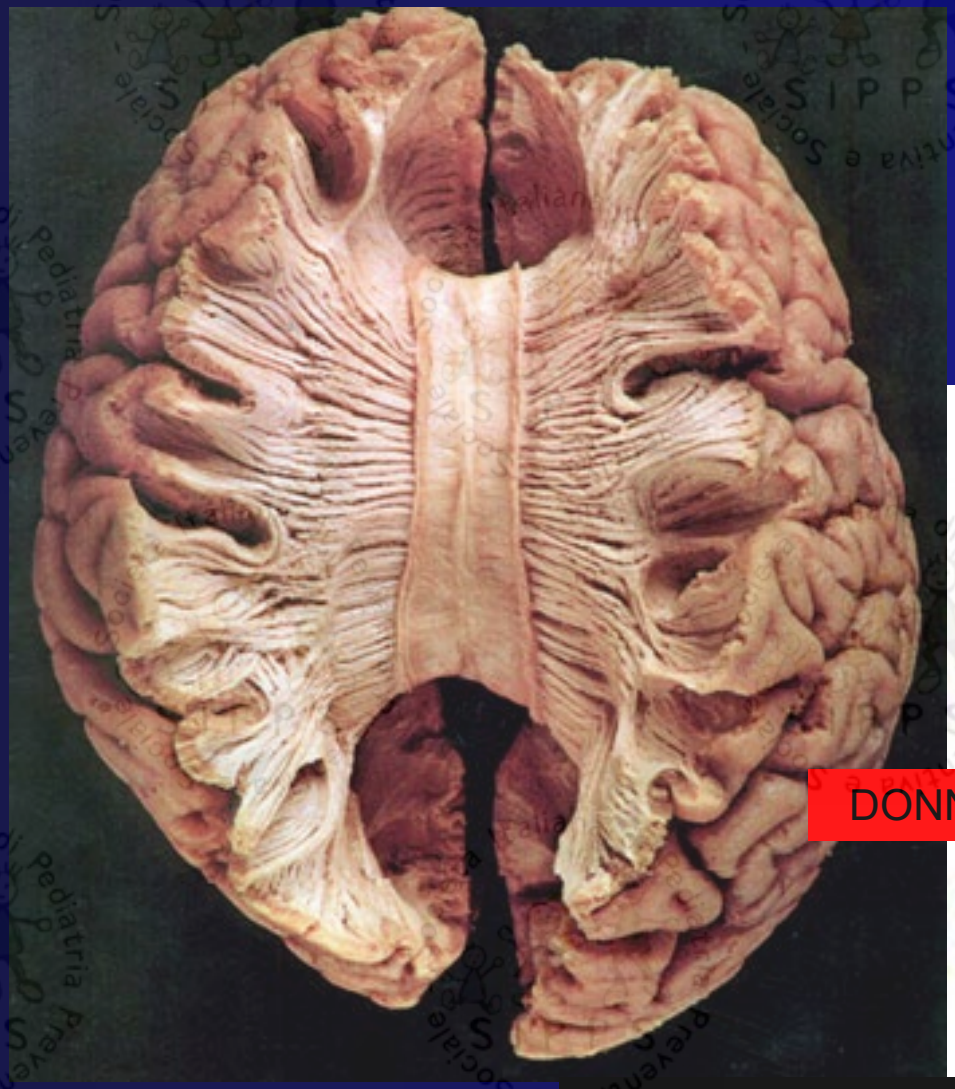
Cervello e neurologia: *differenze di "genere"*

Martino Ruggieri

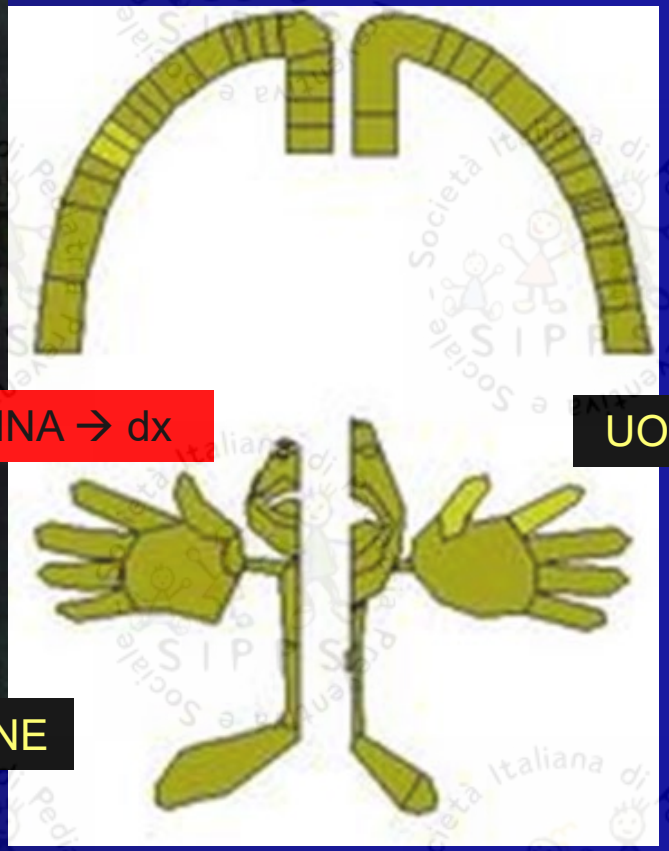
Palazzo Ingrassia

Complesso edilizio (monastero) delle Verginelle

AOU "Policlinico - Vittorio Emanuele"

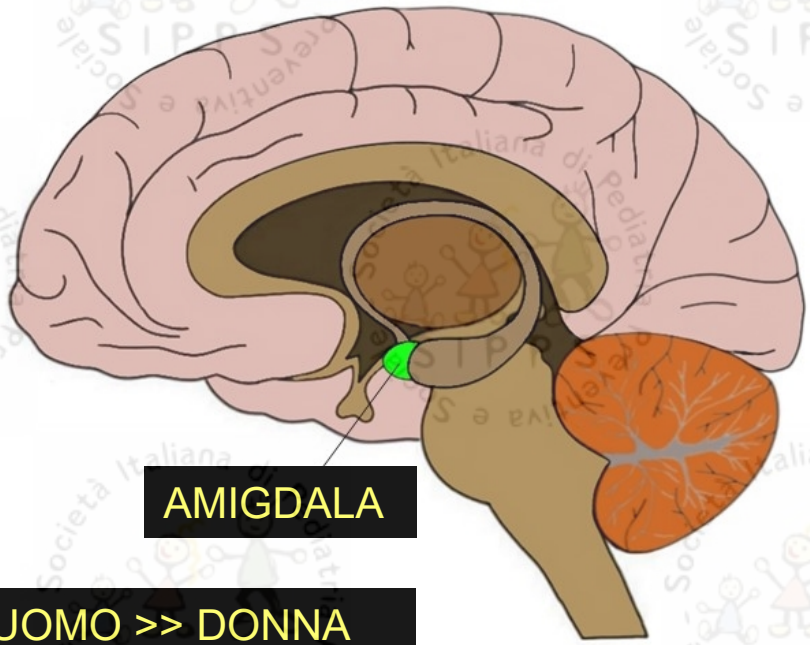


LATERALIZZAZIONE

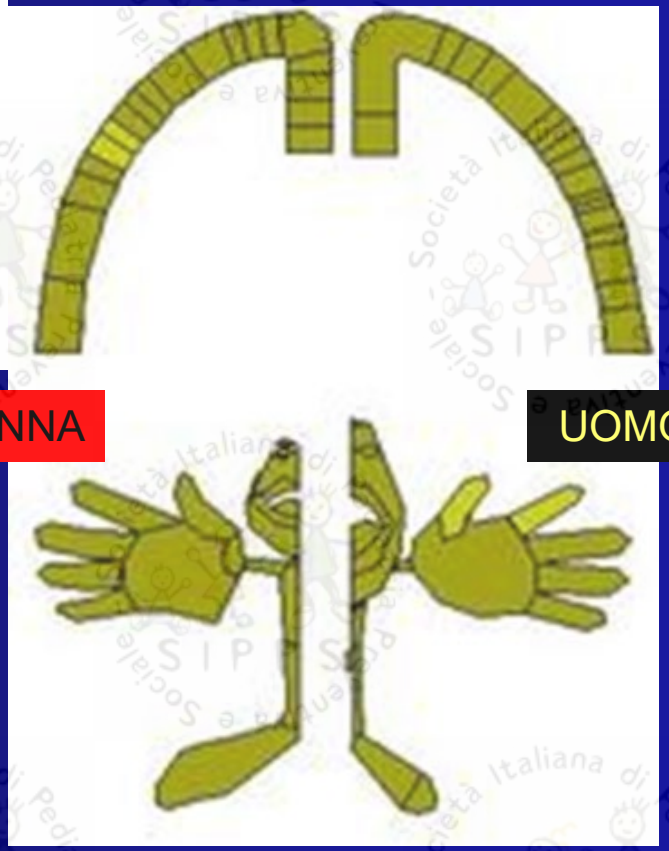


DONNA → dx

UOMO → sin

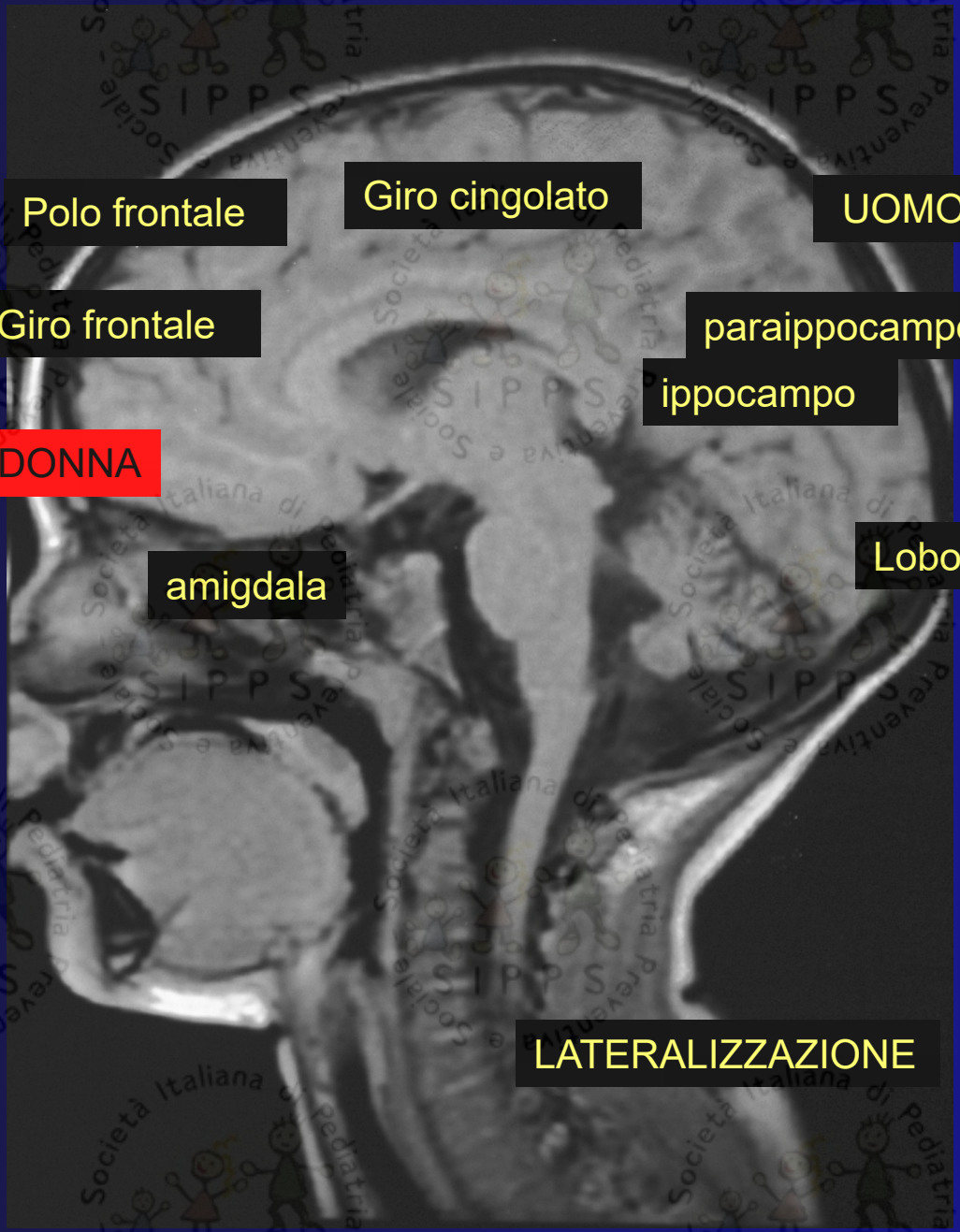


UOMO >> DONNA

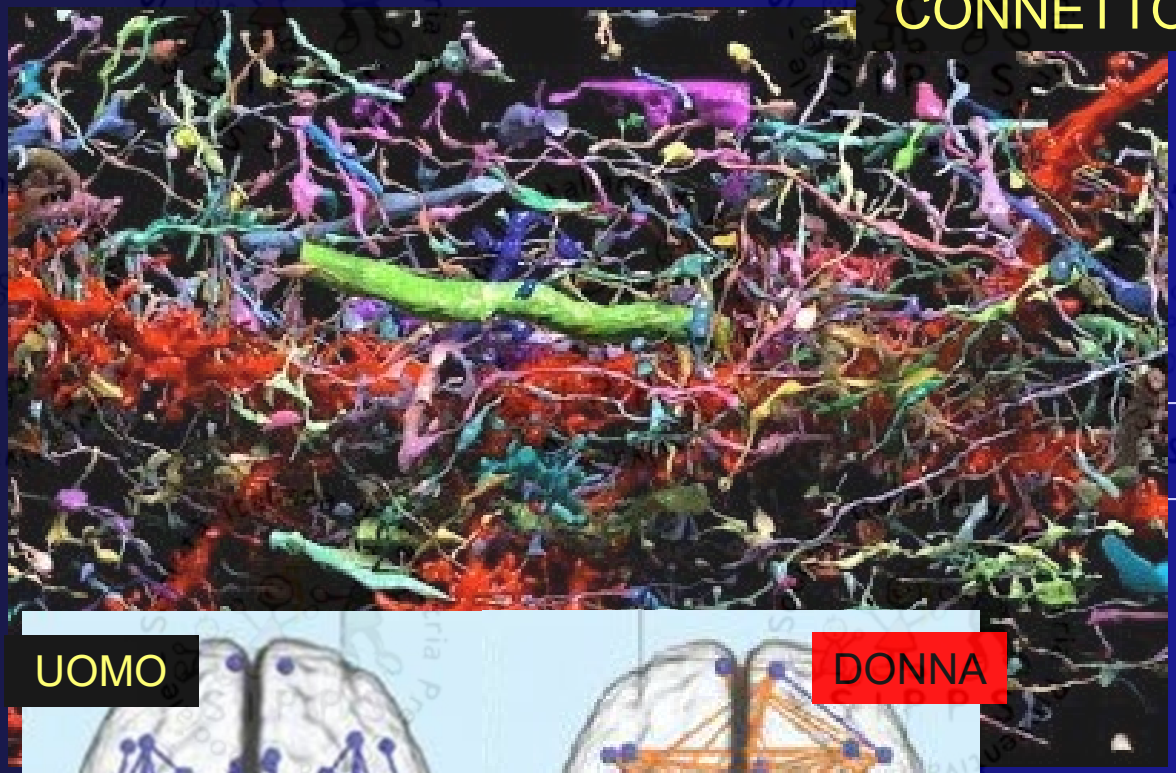


DONNA

UOMO

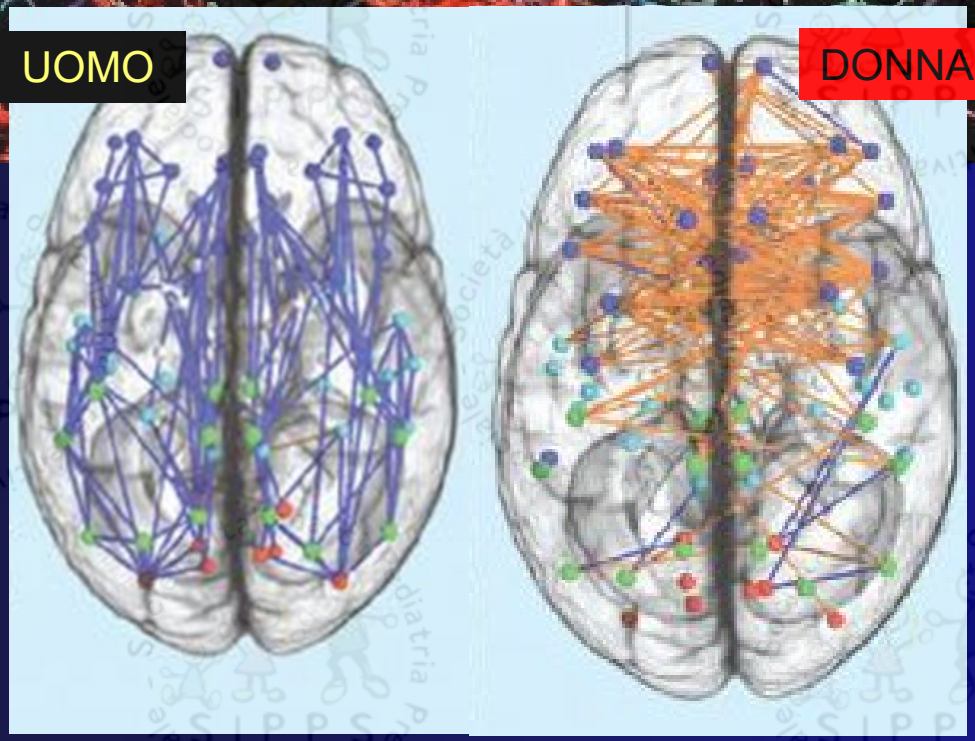

Polo frontale
Giro cingolato
UOMO
Giro frontale
paraippocampo
ippocampo
DONNA
Lobo occipitale
amigdala
LATERALIZZAZIONE

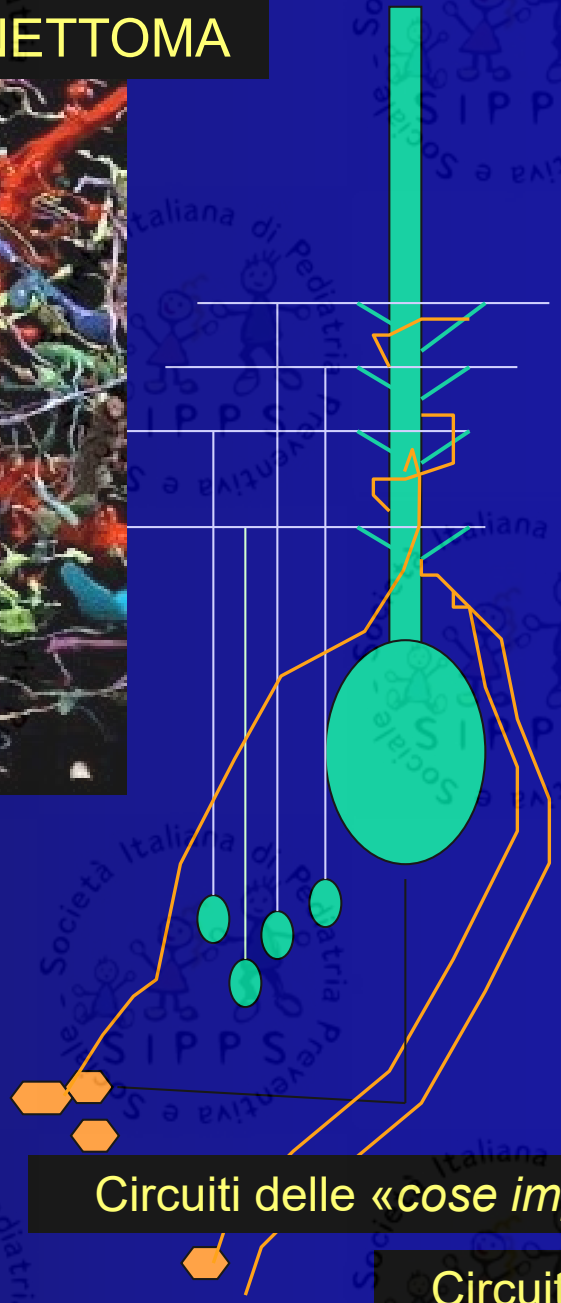
CONNETTOMA



UOMO

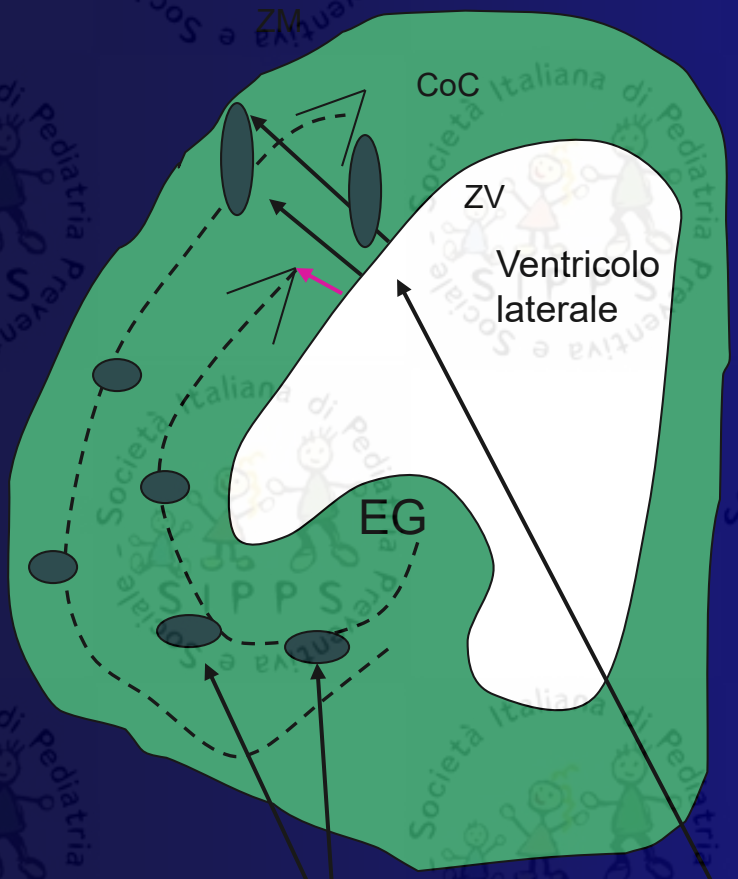
DONNA





Circuiti delle «*cose importanti*»

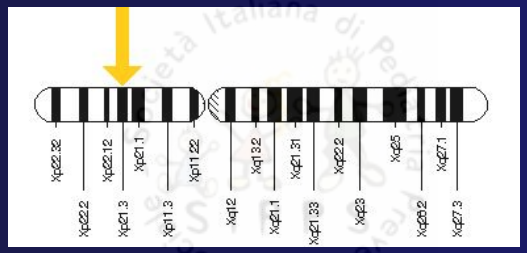
Circuiti esecutivi

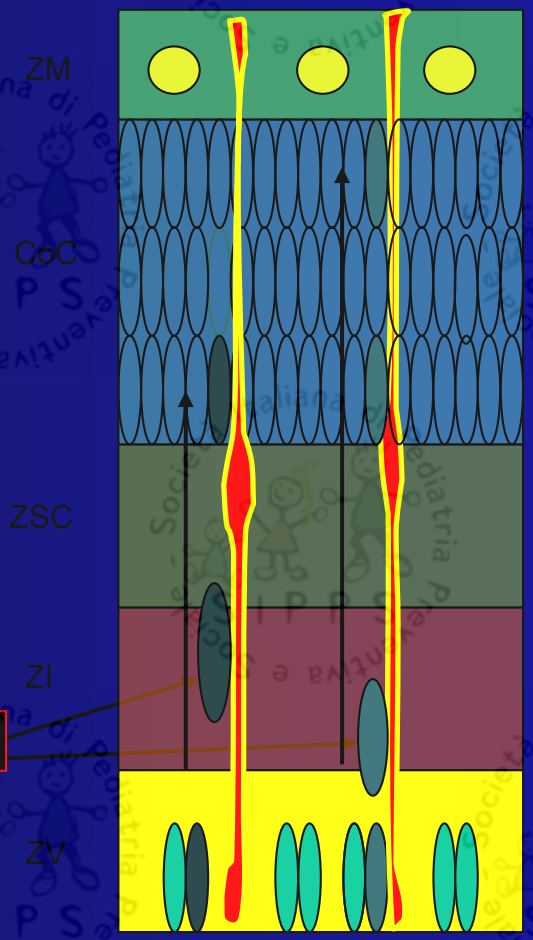


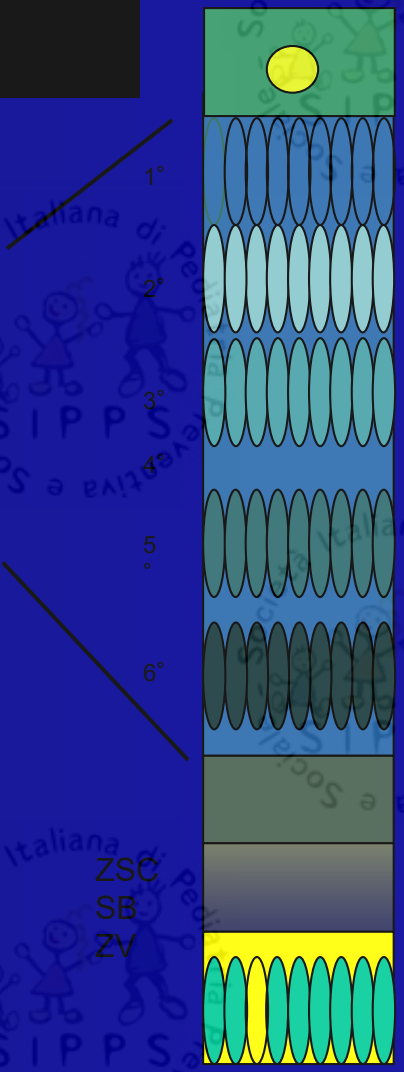
Guida assonale
Proliferazione cellulare vescicole telencefaliche
Migrazione interneuroni GABAergici corteccia
Migrazione interneuroni bublo olfattivo
Sviluppo del globo pallido
Migrazione neuronale

Migrazione (tangenziale) interneuroni GABAergici - olfattivi

Guida assonale







Beta-galactoside-alpha 2,3-sialyltranferase III

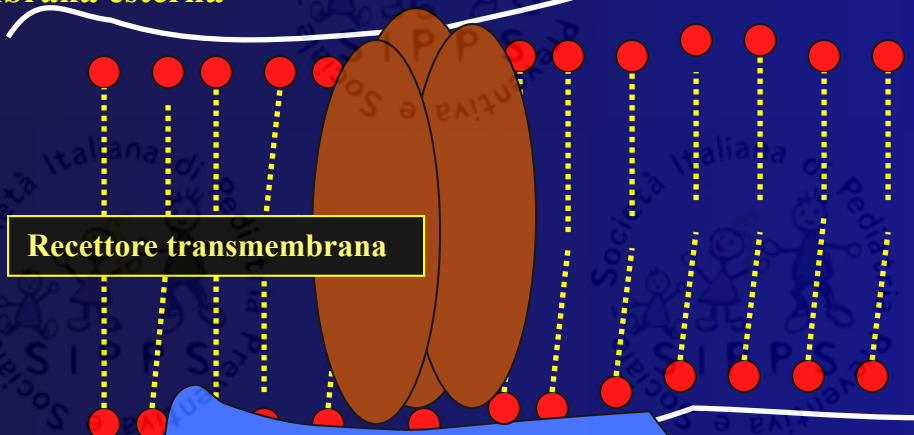
Neuroblasto

Membrana cellulare

APPARATO di GOLGI
Membrana esterna

ST3 beta-galactoside-Alpha 2,3-sialyltransferase II

E' un'enzima di membrana di tipo II (fa parte della famiglia delle glicosiltrasferasi), presente all'interno dell'apparato di Golgi o in forma solubile all'interno del citoplasma, che catalizza la formazione di sialil-Lewis X dall'acido sialico e quindi dell'epitopo di Lewis conosciuto anche come CD15 o antigene embrionale stadio-specifico 1 (SSA1), essenziale per il riconoscimento dei neuroni durante la maturazione e la migrazione



ST3GAL3

APPARATO di GOLGI
Membrana interna

CMP-acido sialico

Substrati contenenti GALATTOSIO

Acido sialico

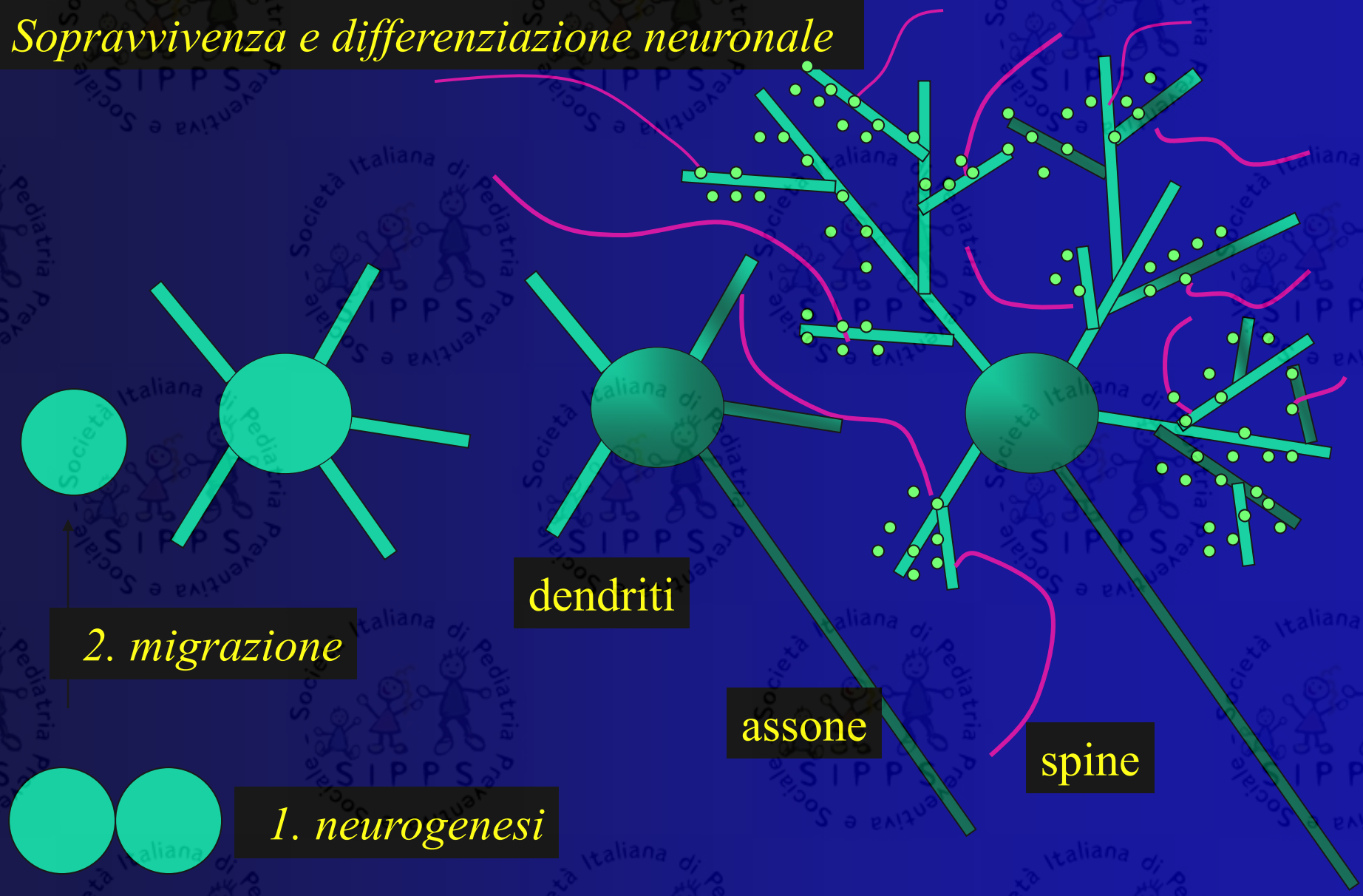
Sialil-Lewis X

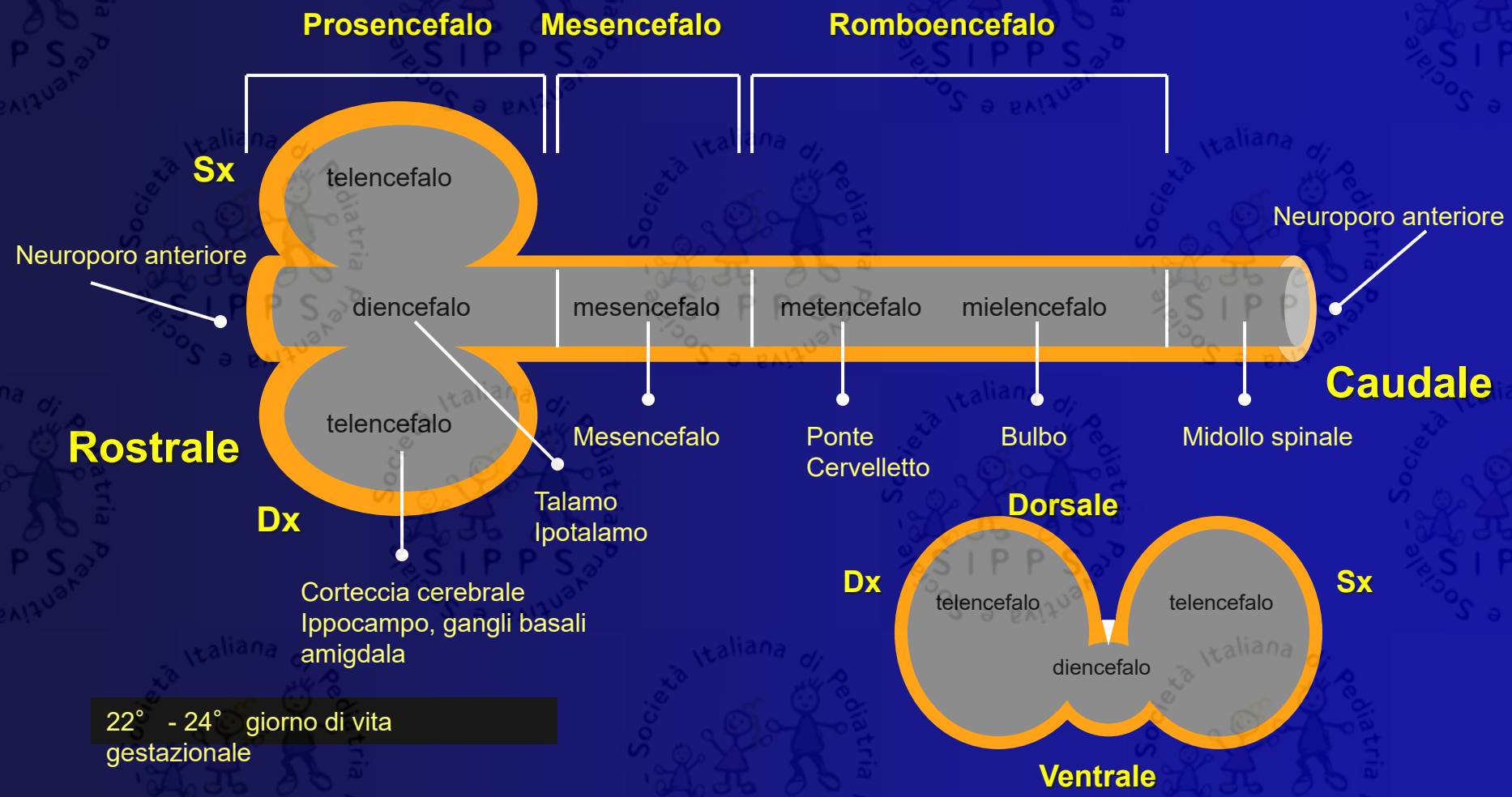
SSA1

Epitopo di Lewis → CD15

Membrana cellulare

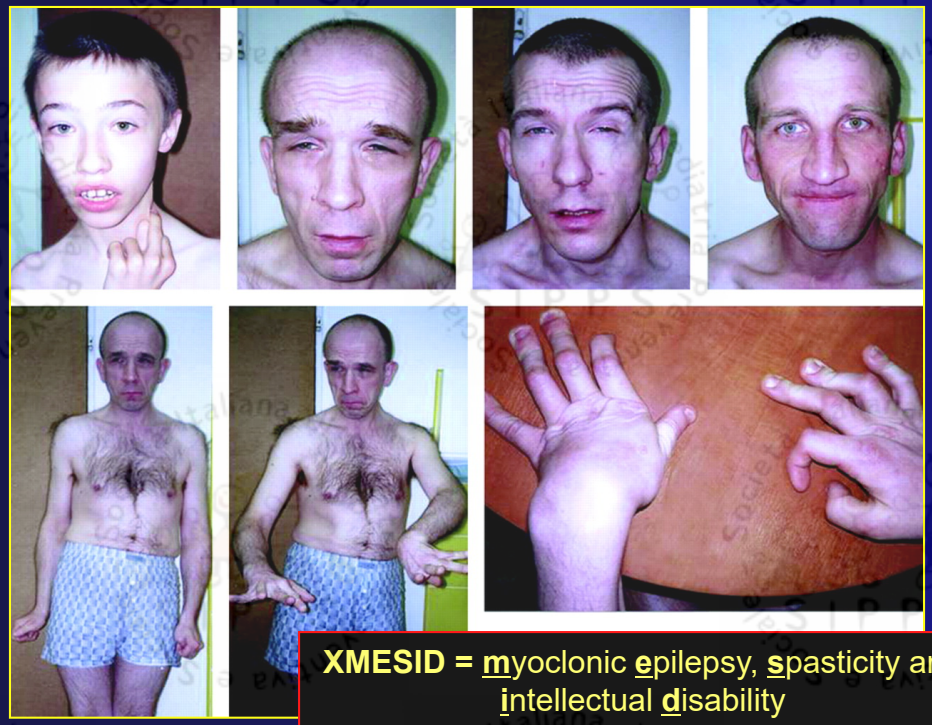
Sopravvivenza e differenziazione neuronale

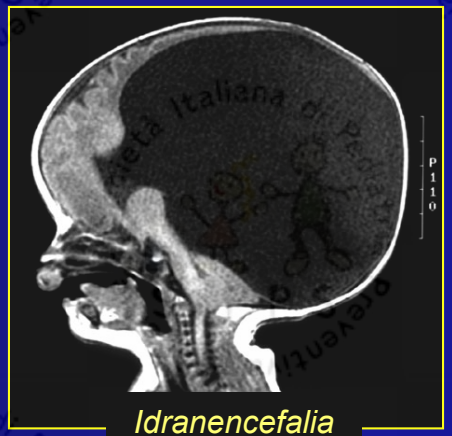




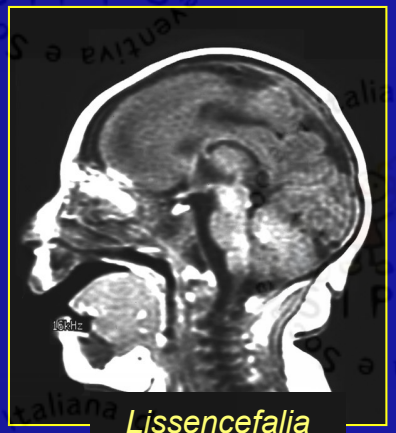
22° - 24° giorno di vita gestazionale

Sindrome degli SPASMI INFANTILI (***ISs***) - gene *Arx (Aristaless)* *Xp22.13*





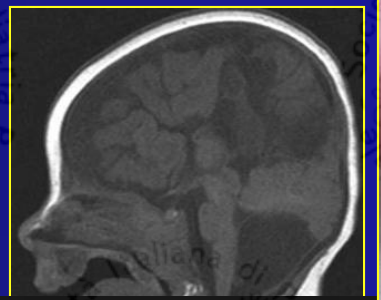
Idranencefalia



Lissencefalia

XMESID = myoclonic epilepsy, spasticity and intellectual disability

*X-linked mental retardation ARX-related with or without seizures [**MRX29,32,33,38,43,54,76,87**; MIM # 300419]*



Agenesia corpo calloso

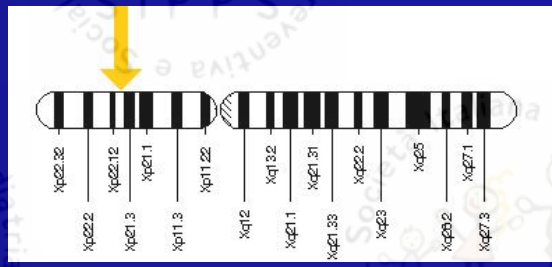
Genitali anomali

*Hydranencephaly - X-linked lissencephaly - Agenesis of corpus callosum With abnormal genitalia [MIM # 300215; **XLAG** MIM # 300215; **Proud syndrome** MIM # 300004]*

*X-linked mental retardation 36 (**Partington syndrome**) [**syndromic MR - XMR36 / MRXS1 with episodic dystonic movements, ataxia and seizures**; MIM # 309510]*

*Early-onset epileptic encephalopathy 1 / X-linked infantile spasms syndrome 1 / X-linked (subgroup) West syndrome / infantile spasms without brain malformation [**EIEE1 - ISSX1**; MIM # 308350]*

Sindrome degli SPASMI INFANTILI (***ISs***) - gene *CDKL5* *Xp22.13*



Early-onset epileptic encephalopathy 2 / X-linked infantile spasms syndrome-2 / Rett syndrome variant
Atypical infantile spasms Rett syndrome CDKL5-related
***[EIEE2 - ISSX2**; MIM # 300672]*

- *Fenotipi **simil-Rett** con spasmi infantili [spasmi clinici]*

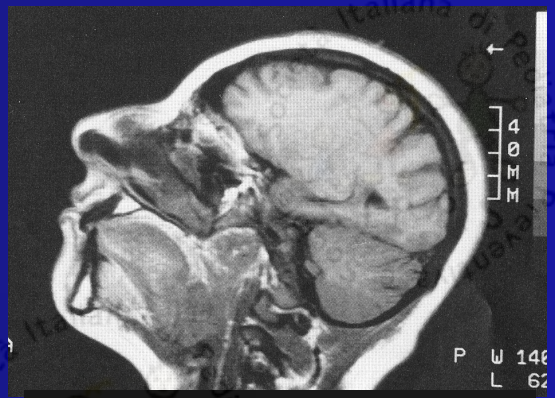
Movimenti anomali delle mani, stereotipie mani-bocca, iperventilazione, apnee, mani/piedi piccoli, disturbi linguaggio, cifoscoliosi T-L, autismo grave, microcefalia, alterazioni dello stato dell'umore, mancata interazione sociale

- *Fenotipi **Rett gravi** (sesso maschile)*

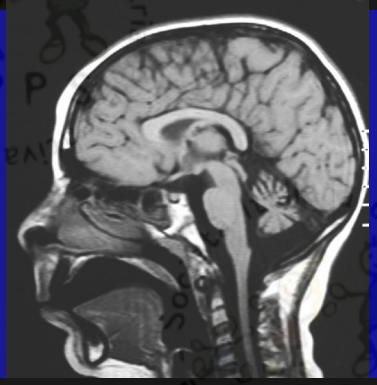
fenotipo Rett grave + segni dismorfici gravi + pubertà precoce

- *Fenotipo **simil-sindrome di Angelman***

***EEG** = sovrapposizioni con sindrome di Rett ed Angelman*
***RM encefalo** = atrofia (sostanza bianca) cerebrale*
Ritardo mielinizzazione, atrofia cerebellare



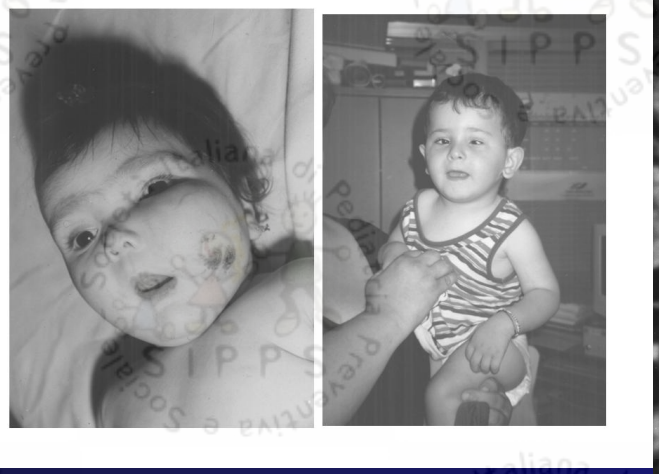
Atrofia cerebrale, microencefalia

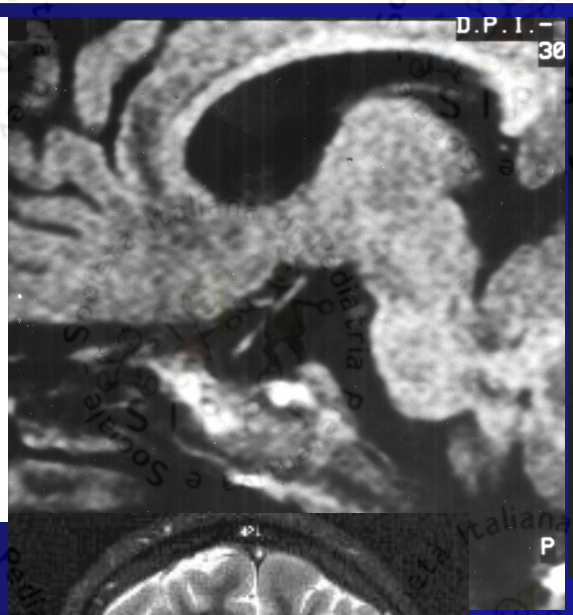


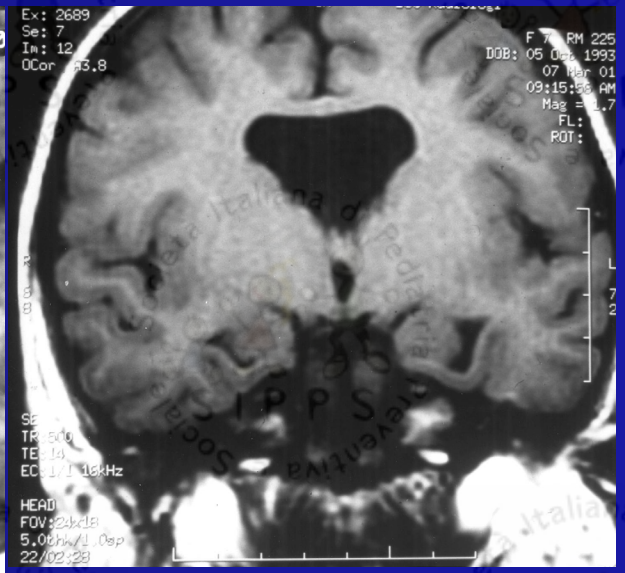
Atrofia cerebrale, atrofia cerebellare

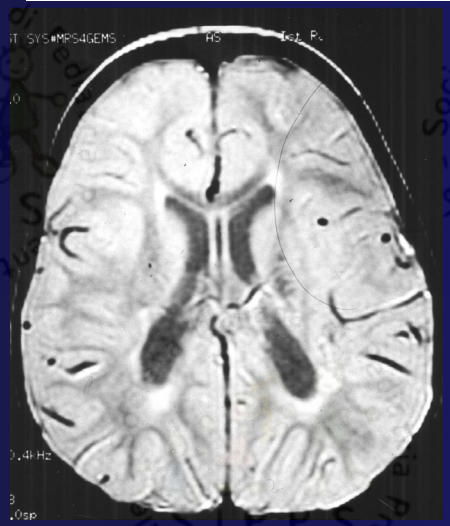
MALFORMAZIONI del PROSENCEFALO MEDIOBASALE

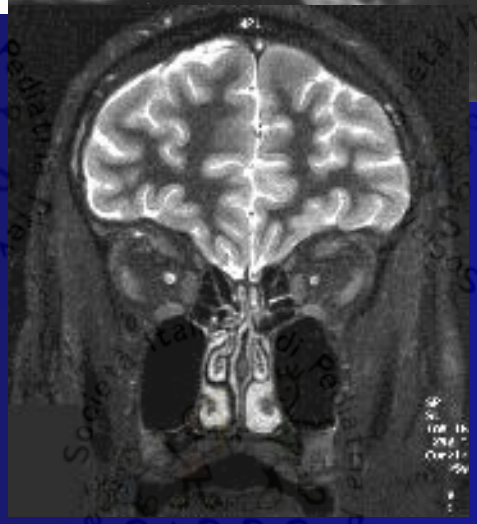
DISPLASIA SETTO-OTTICA





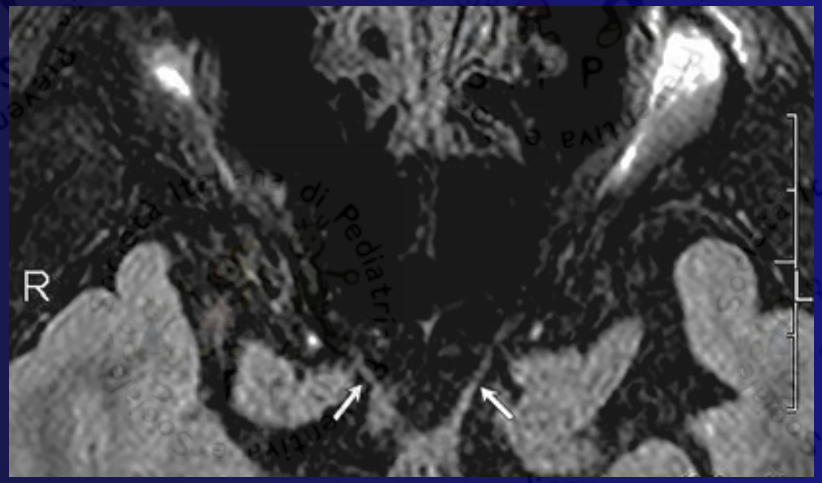


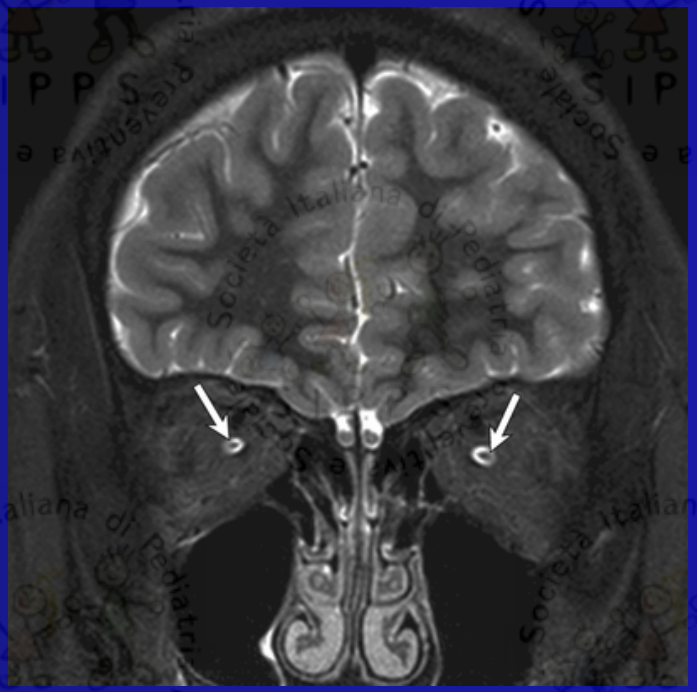


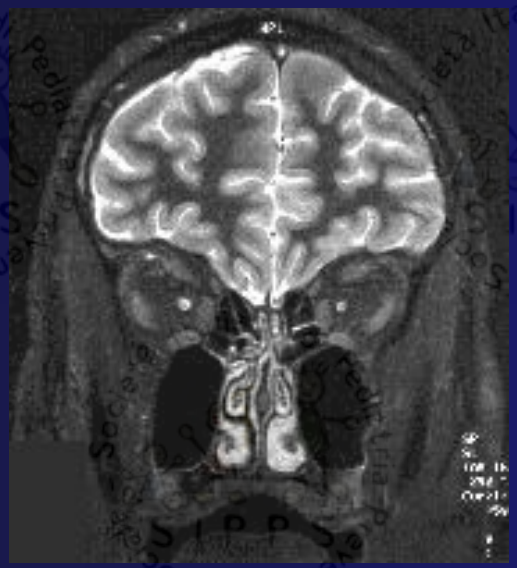


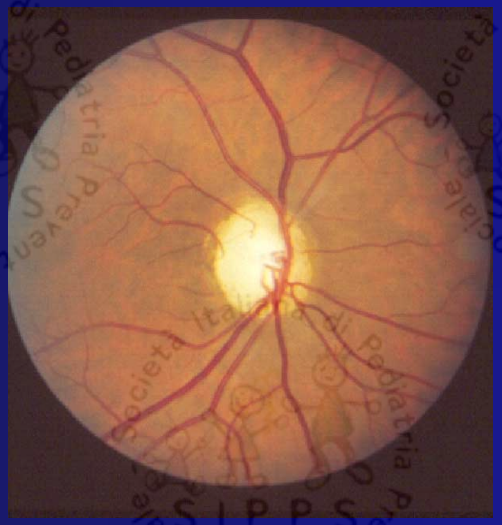
MALFORMAZIONI del PROSENCEFALO MEDIOBASALE

DISPLASIA SETTO-OTTICA







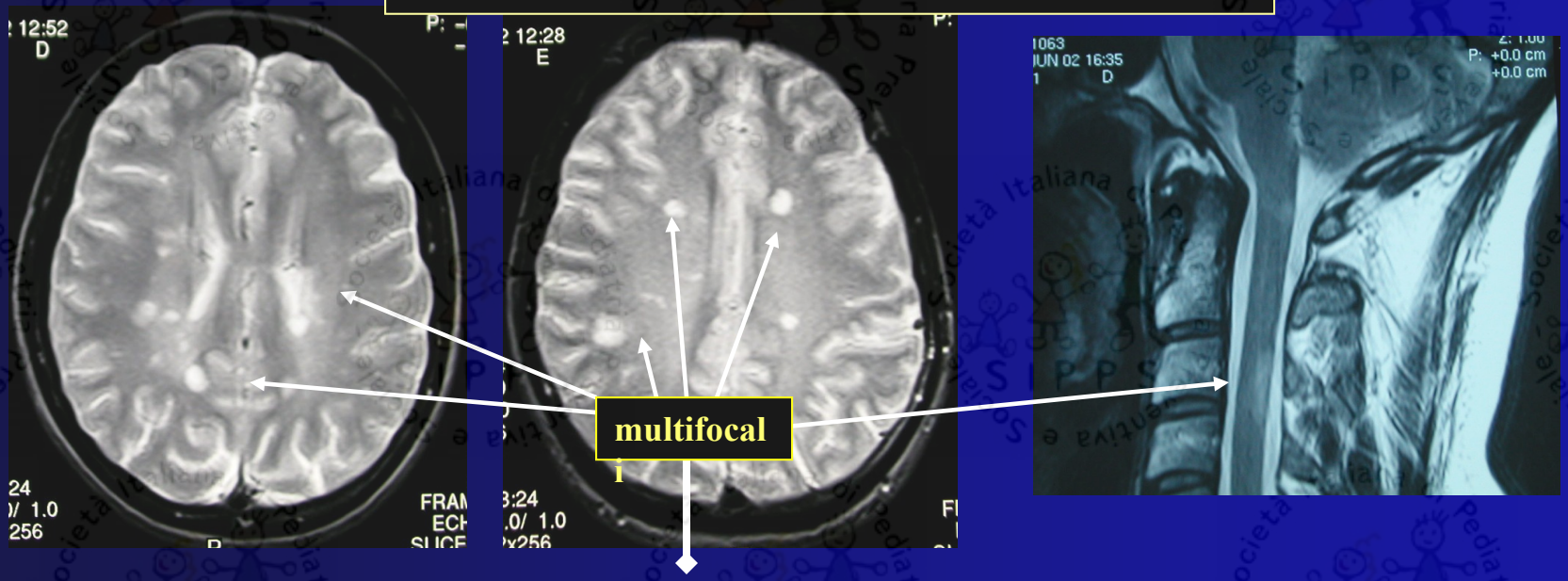


Sclerosi Multipla

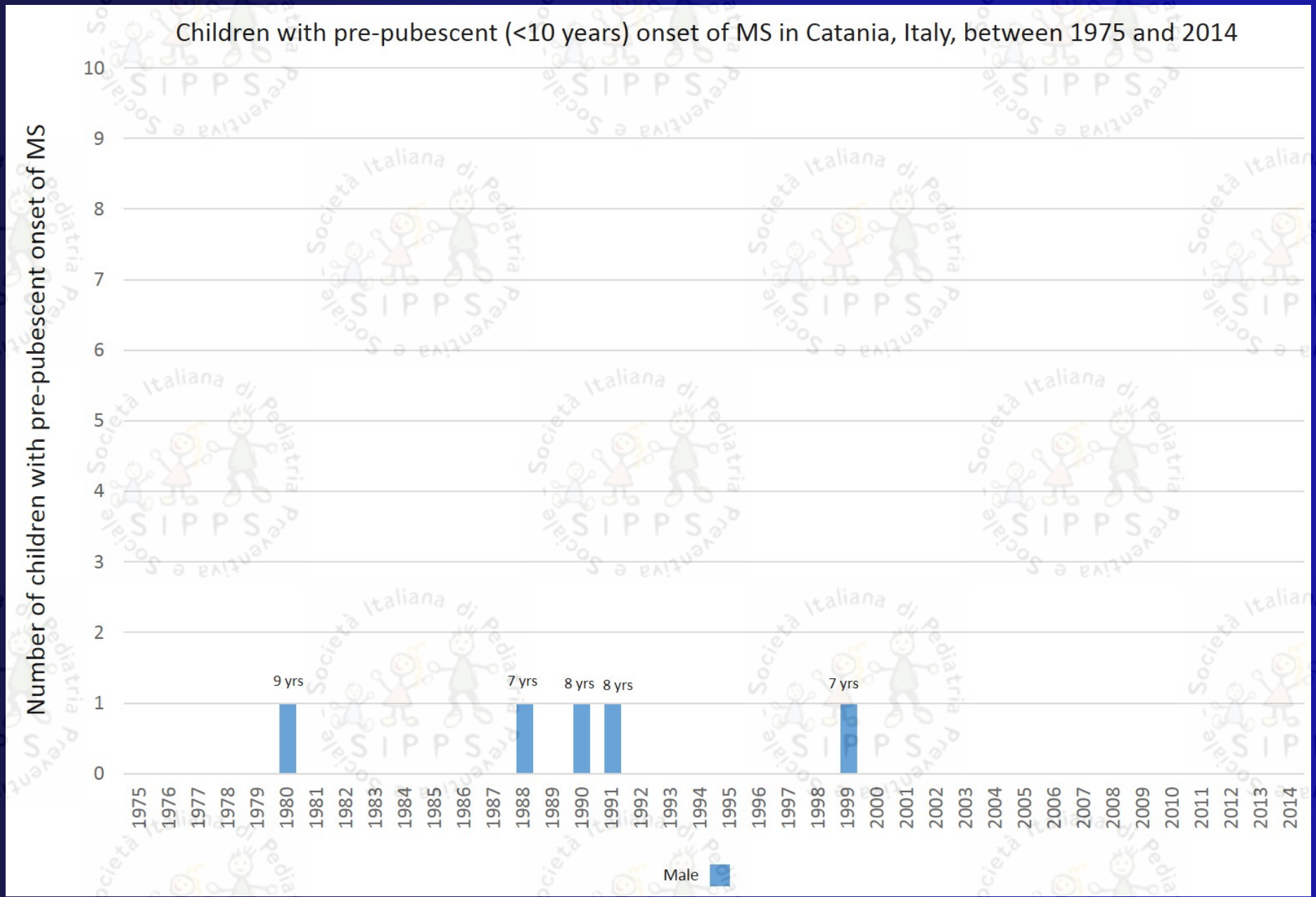
- DUE o più episodi + evidenza clinica obiettiva di due o più lesioni [o di una lesione]
- UN episodio + evidenza clinica obiettiva di due o più lesioni
- UN episodio + evidenza clinica obiettiva di una lesione [SCI]

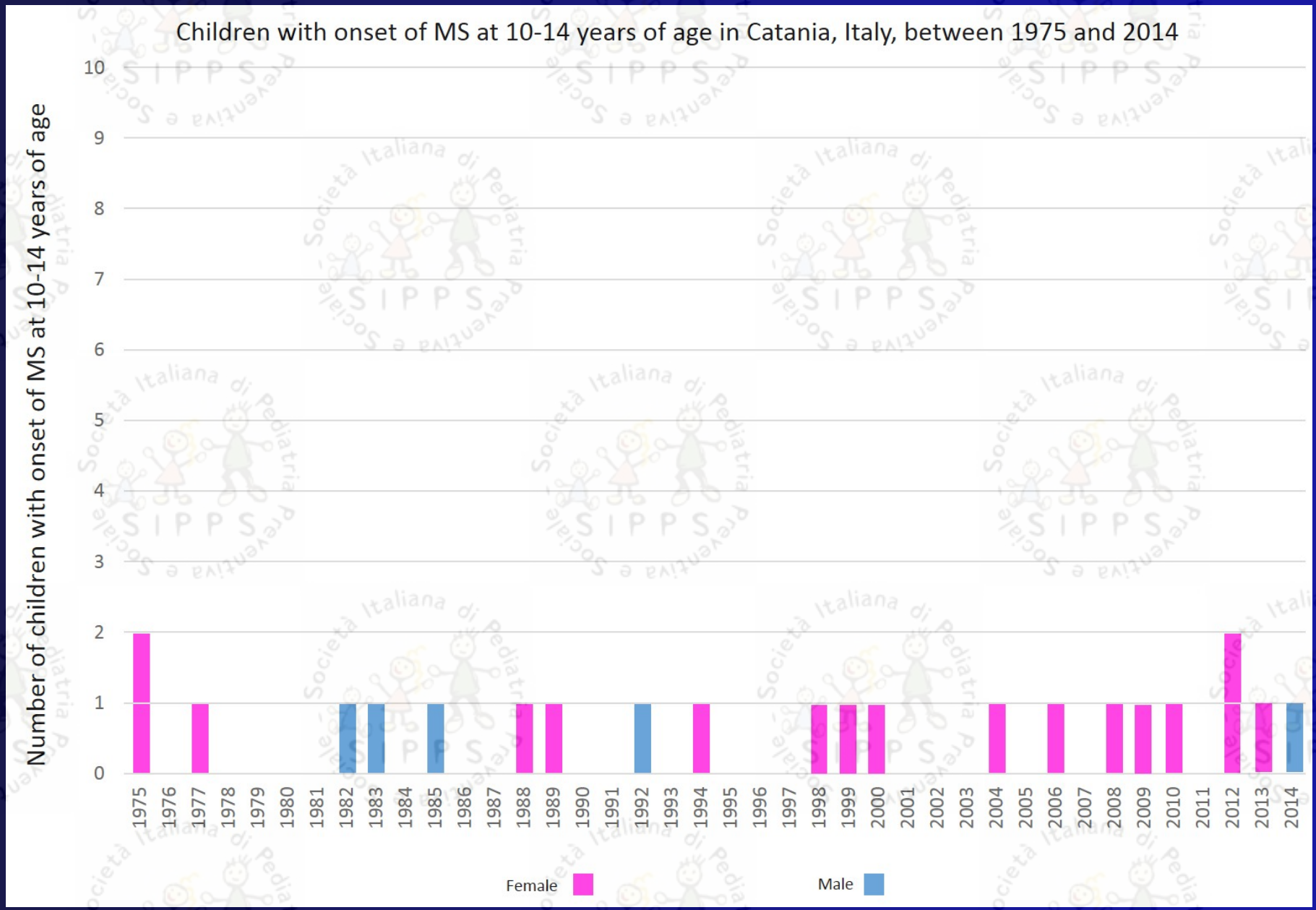
Malattia demielinizzante cronica del giovane adulto: aree disseminate di *demielinizzazione* di tipo infiammatorio, non-vasculitico, della sostanza bianca encefalo e midollo spinale e da *danno assonale*.

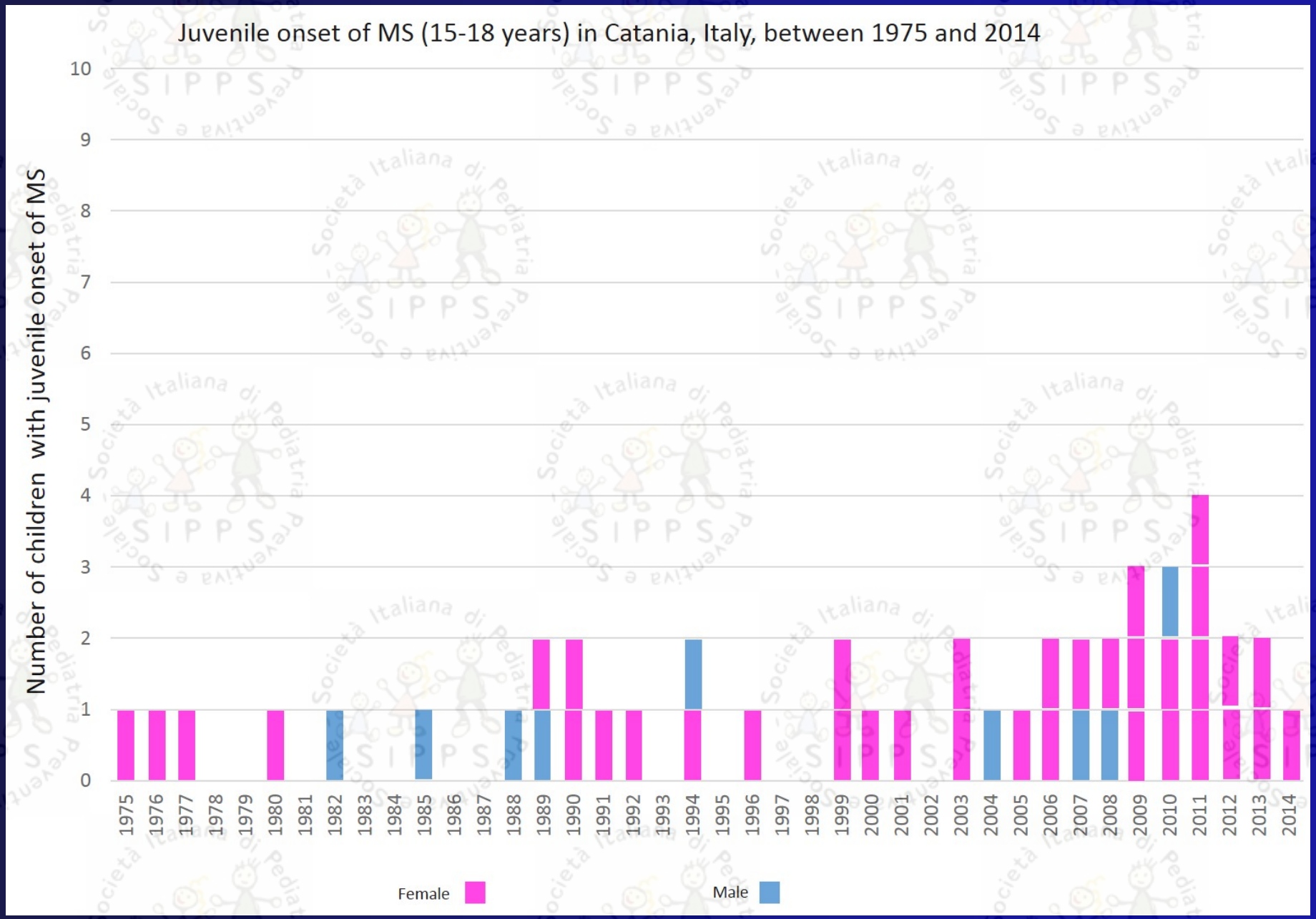
disseminazione nello SPAZIO e nel TEMPO

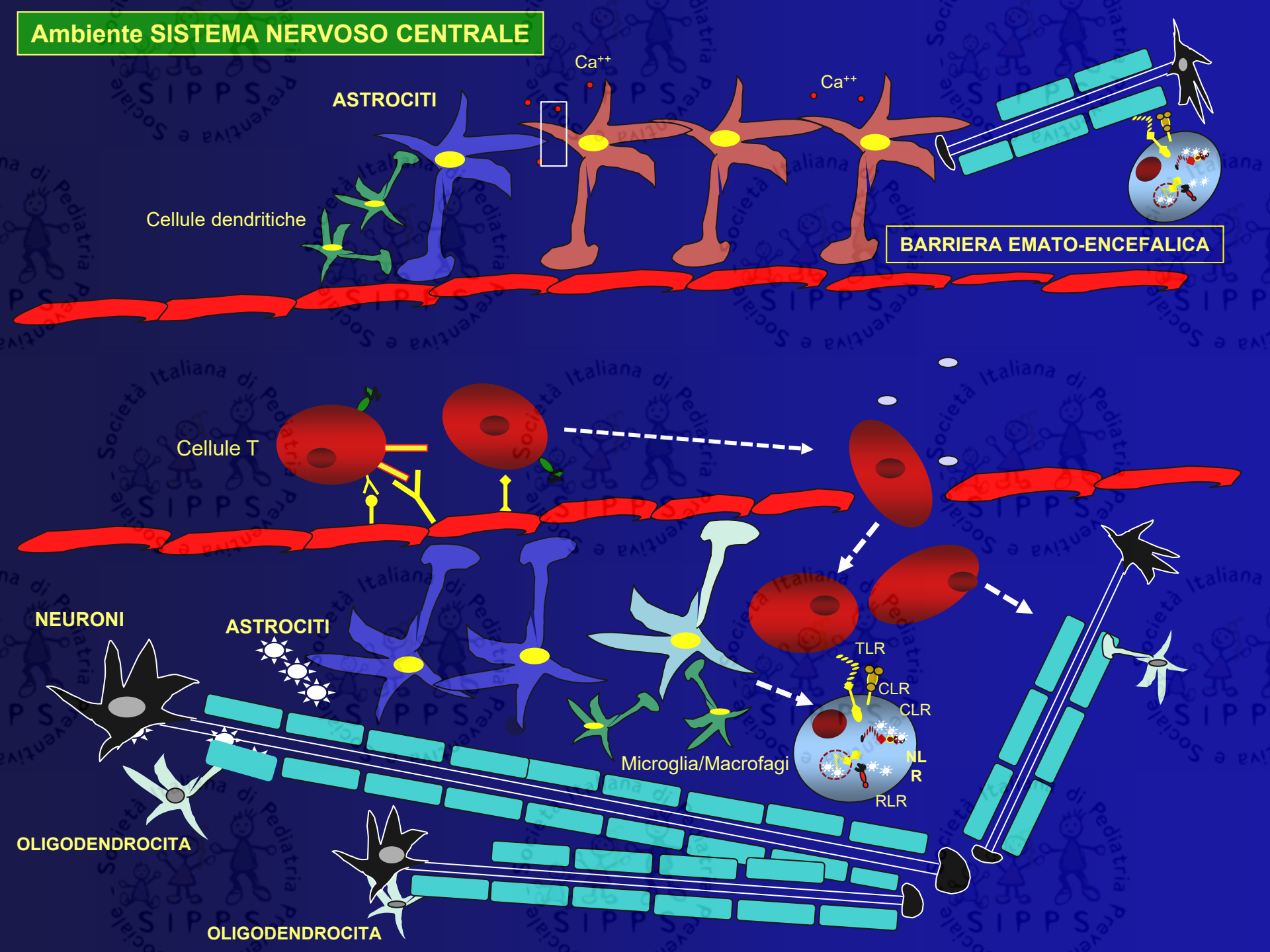


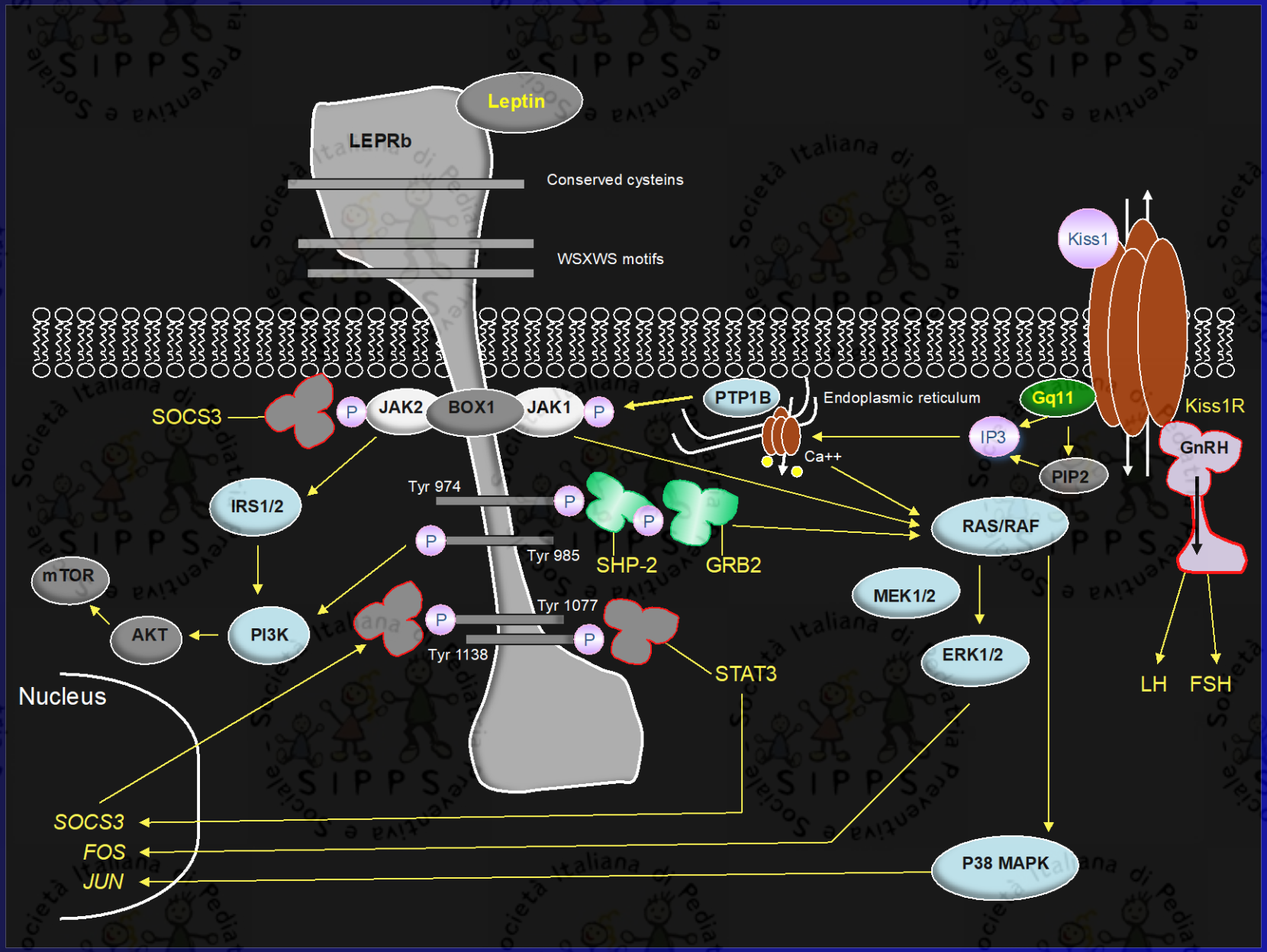
Lesioni "*anatomiche*" multifocali
"*Segni / sintomi*" neurologici multifocali

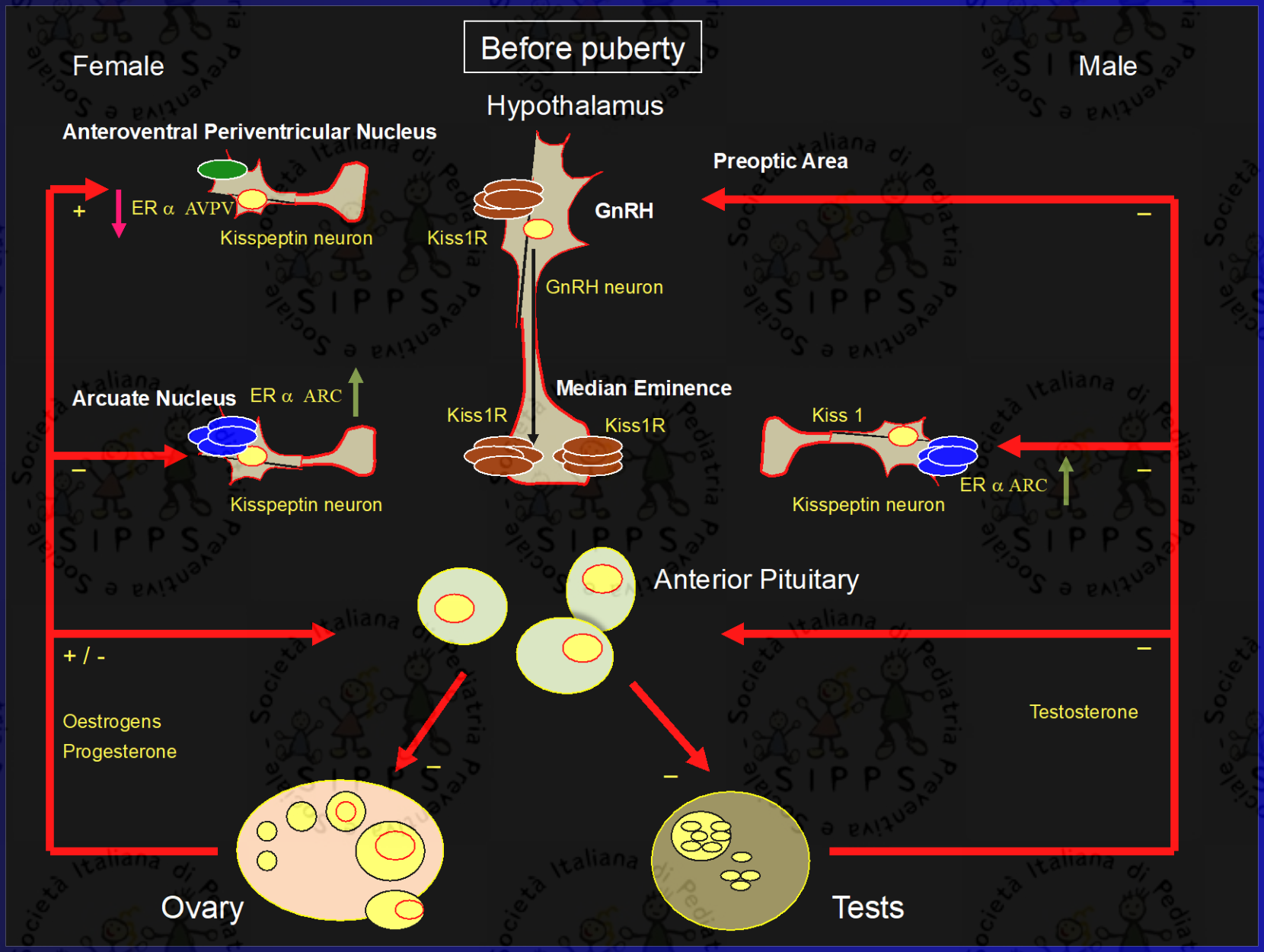

Children with pre-pubescent (<10 years) onset of MS in Catania, Italy, between 1975 and 2014
Number of children with pre-pubescent onset of MS
10
9
8
7
6
5
4
3
2
1
0
9 yrs
7 yrs
8 yrs
8 yrs
7 yrs
1975
1976
1977
1978
1979
1980
1981
1982
1983
1984
1985
1986
1987
1988
1989
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
Male

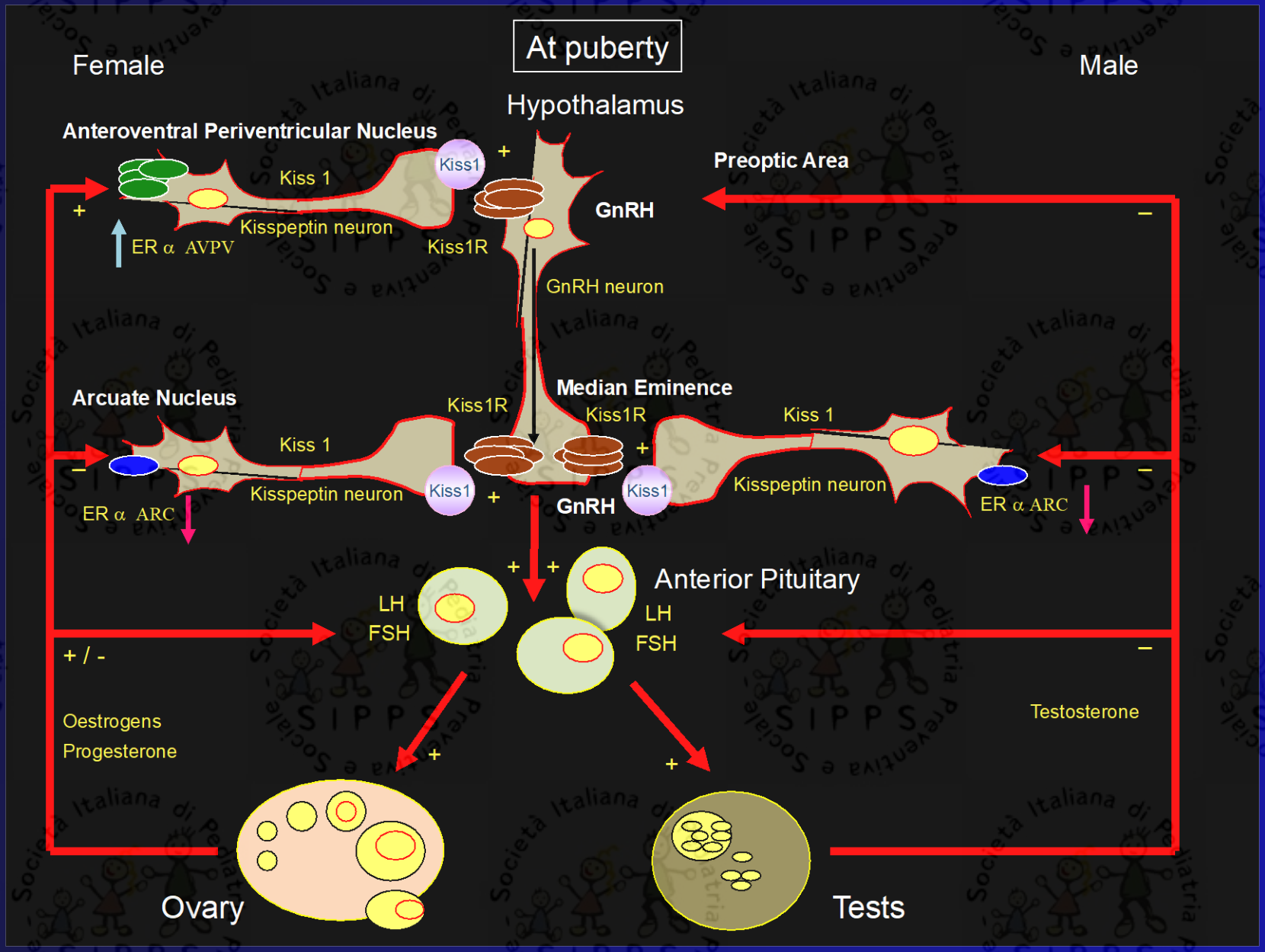

Children with onset of MS at 10-14 years of age in Catania, Italy, between 1975 and 2014
Number of children with onset of MS at 10-14 years of age
10
9
8
7
6
5
4
3
2
1
0
1975 1976 1977 1978 1979 1980 1981 1982 1983 1984 1985 1986 1987 1988 1989 1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014
Female
Male

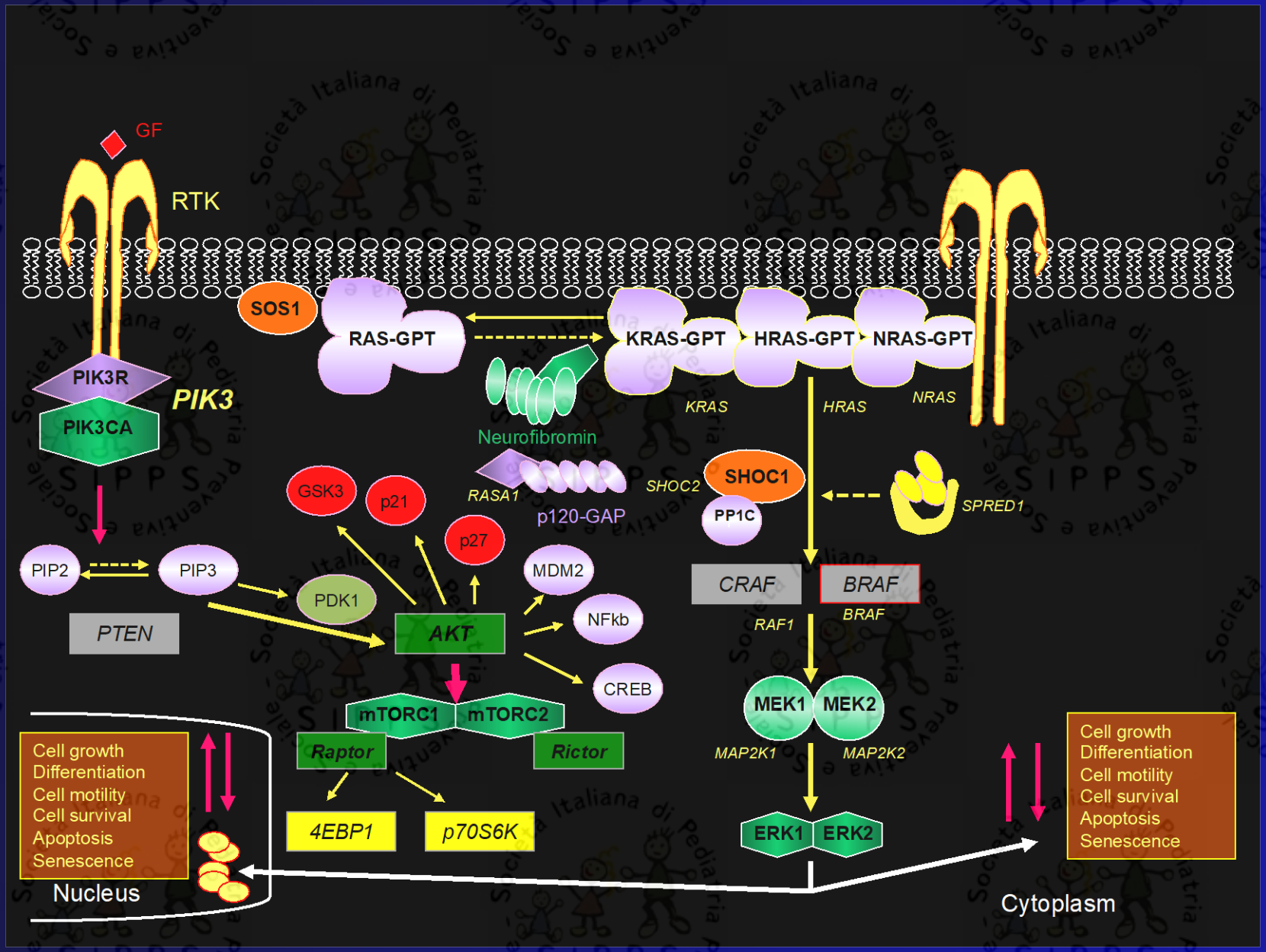

Juvenile onset of MS (15-18 years) in Catania, Italy, between 1975 and 2014
Number of children with juvenile onset of MS
10
9
8
7
6
5
4
3
2
1
0
1975
1976
1977
1978
1979
1980
1981
1982
1983
1984
1985
1986
1987
1988
1989
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
Female
Male


Ambiente SISTEMA NERVOSO CENTRALE
Ca++
Ca++
ASTROCITI
Cellule dendritiche
BARRIERA EMATO-ENCEFALICA
Cellule T
NEURONI
ASTROCITI
TLR
CLR
CLR
NL
R
RLR
Microglia/Macrofagi
OLIGODENDROCITA
OLIGODENDROCITA


Leptin
LEPRb
Conserved cysteins
WSXWS motifs
Kiss1
Kiss1R
SOCS3
P
JAK2
BOX1
JAK1
P
PTP1B
Endoplasmic reticulum
Gq11
IP3
Ca++
PIP2
GnRH
Tyr 974
P
IRS1/2
P
RAS/RAF
Tyr 985
SHP-2
GRB2
mTOR
MEK1/2
Tyr 1077
P
AKT
PI3K
P
Tyr 1138
STAT3
ERK1/2
LH
FSH
Nucleus
SOCS3
FOS
JUN
P38 MAPK


Before puberty
Female
Male
Hypothalamus
Anteroventral Periventricular Nucleus
ER α AVPV
Kisspeptin neuron
Kiss1R
GnRH
Preoptic Area
GnRH neuron
Median Eminence
Kiss1R
Kiss1R
Arcuate Nucleus
ER α ARC
Kisspeptin neuron
Kiss 1
ER α ARC
Kisspeptin neuron
Anterior Pituitary
+ / -
Oestrogens
Progesterone
Testosterone
Ovary
Tests


At puberty
Female
Male
Hypothalamus
Anteroventral Periventricular Nucleus
Kiss 1
Kiss1
Kisspeptin neuron
Kiss1R
ER α AVPV
GnRH
GnRH neuron
Preoptic Area
Arcuate Nucleus
Kiss 1
Kisspeptin neuron
ER α ARC
Kiss1R
Kiss1
Median Eminence
GnRH
Kiss1R
Kiss1
Kiss 1
Kisspeptin neuron
ER α ARC
Anterior Pituitary
LH
FSH
LH
FSH
+ / -
Oestrogens
Progesterone
Testosterone
Ovary
Tests


GF
RTK
SOS1
RAS-GPT
KRAS-GPT
HRAS-GPT
NRAS-GPT
KRAS
HRAS
NRAS
PIK3R
PIK3CA
PIK3
Neurofibromin
RASA1
p120-GAP
SHOC2
SHOC1
PP1C
SPRED1
GSK3
p21
p27
PIP2
PIP3
PDK1
PTEN
AKT
MDM2
NFkb
CREB
CRAF
BRAF
RAF1
BRAF
MEK1
MEK2
MAP2K1
MAP2K2
mTORC1
mTORC2
Raptor
Rictor
4EBP1
p70S6K
ERK1
ERK2
Cell growth
Differentiation
Cell motility
Cell survival
Apoptosis
Senescence
Nucleus
Cytoplasm
Cell growth
Differentiation
Cell motility
Cell survival
Apoptosis
Senescence