

Preterm brain development and developing executive function

8th Annual Wyeth® Nutrition Science Center Global Summit

Prof Nicholas Embleton, Consultant Neonatal Paediatrician,
Newcastle upon Tyne, UK

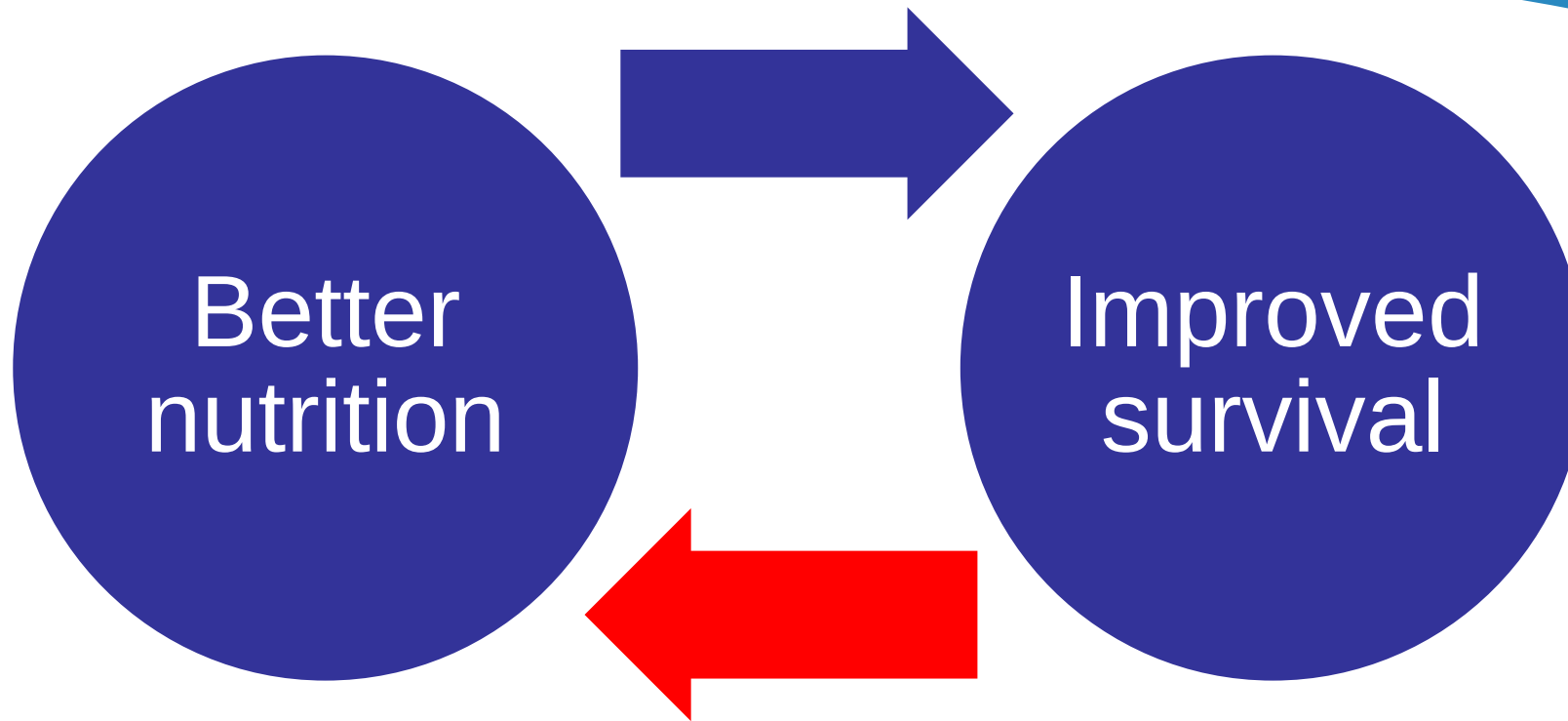


Conflicts of interest

- Research funding
 - UK NIHR & Charities
 - Prolacta Bioscience, Danone
- Speaker honoraria: Wyeth, Nestle Nutrition
- I hold no shares, financial benefits etc.
- No off-label products are discussed
- Views expressed are my own

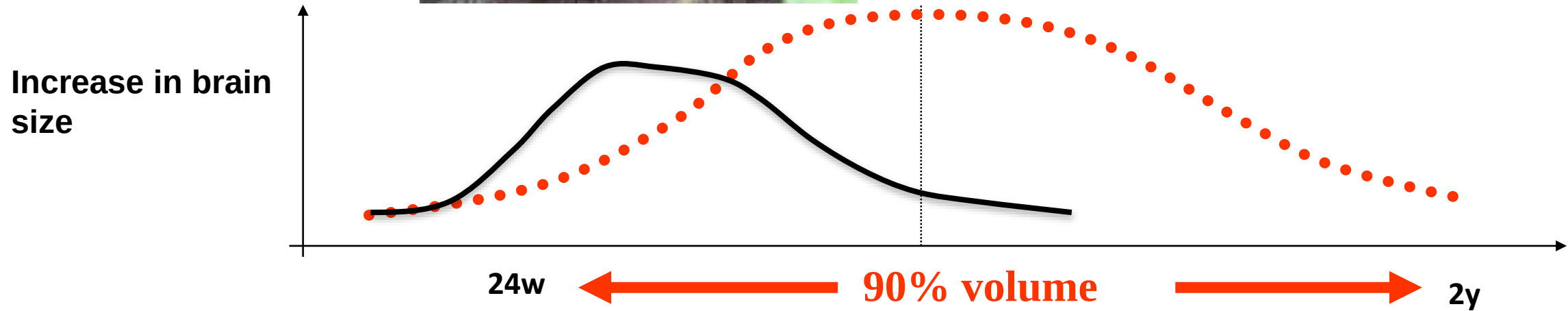


Better nutrition: improved survival & less morbidity



Improved survival: nutritional needs become more important & complex

Brain growth in early life is rapid



Nutrient requirements are very high

Risk of abnormal brain development is high

Tour de France
7000Kcal/day
100kcal/kg/day

↑ **20 - 30%**

NICU

120-130kcal/kg/day



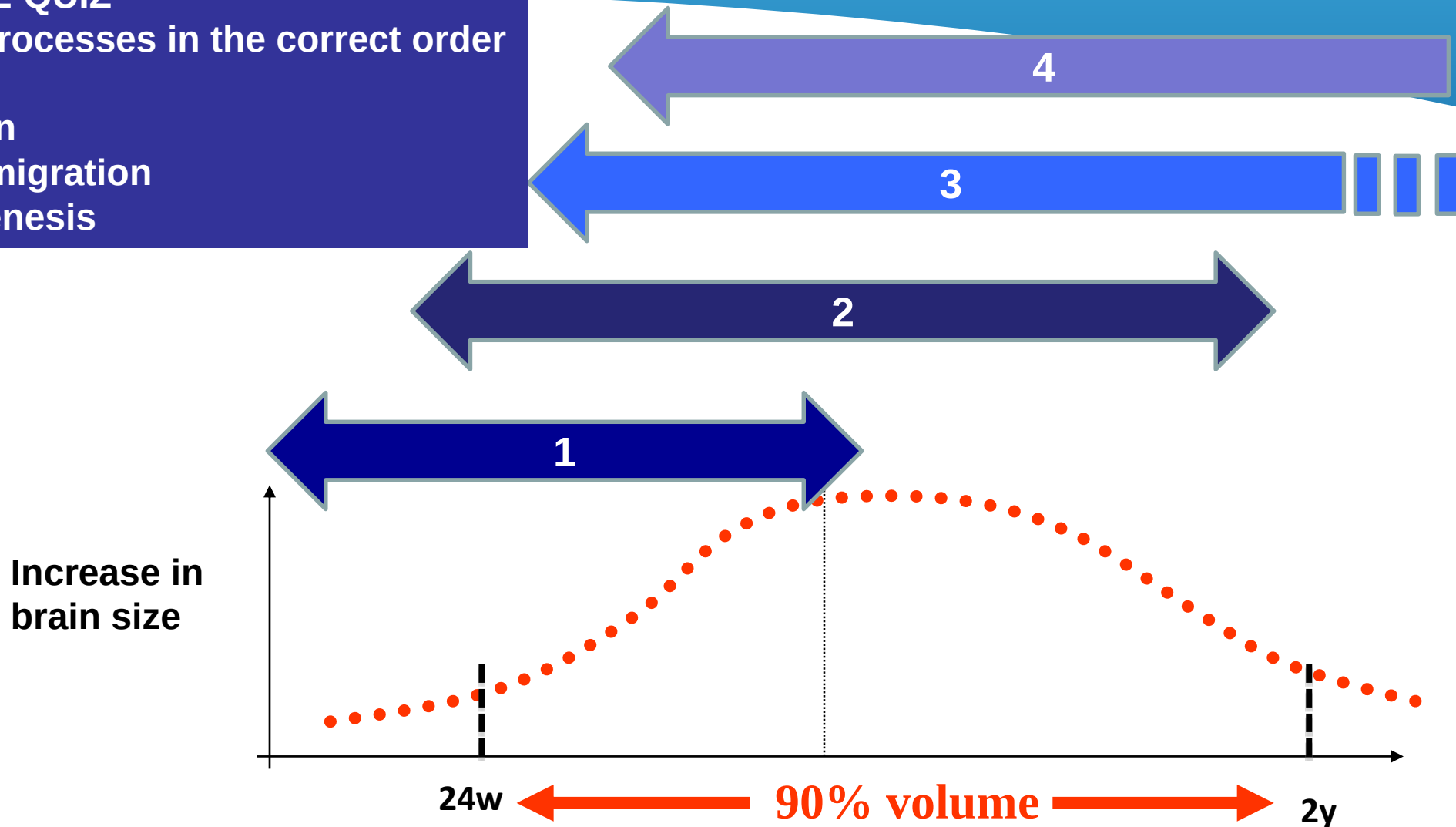
**60-70% of energy
expenditure is the
brain**

Neuronal development proceeds in sequence

INTERACTIVE QUIZ

Put these 4 processes in the correct order

- Apoptosis
- Myelination
- Neuronal migration
- Synaptogenesis

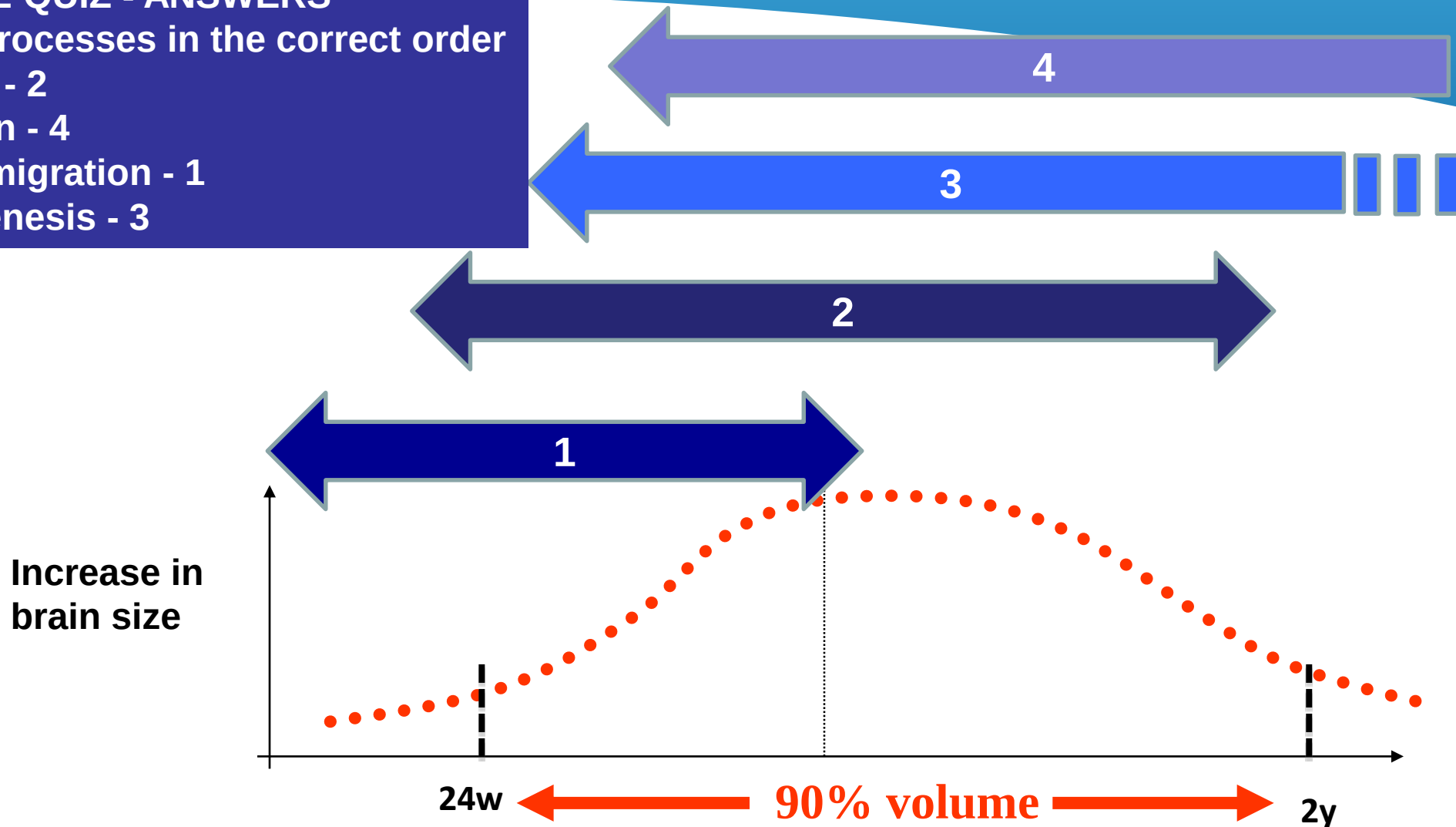


Neuronal development proceeds in sequence

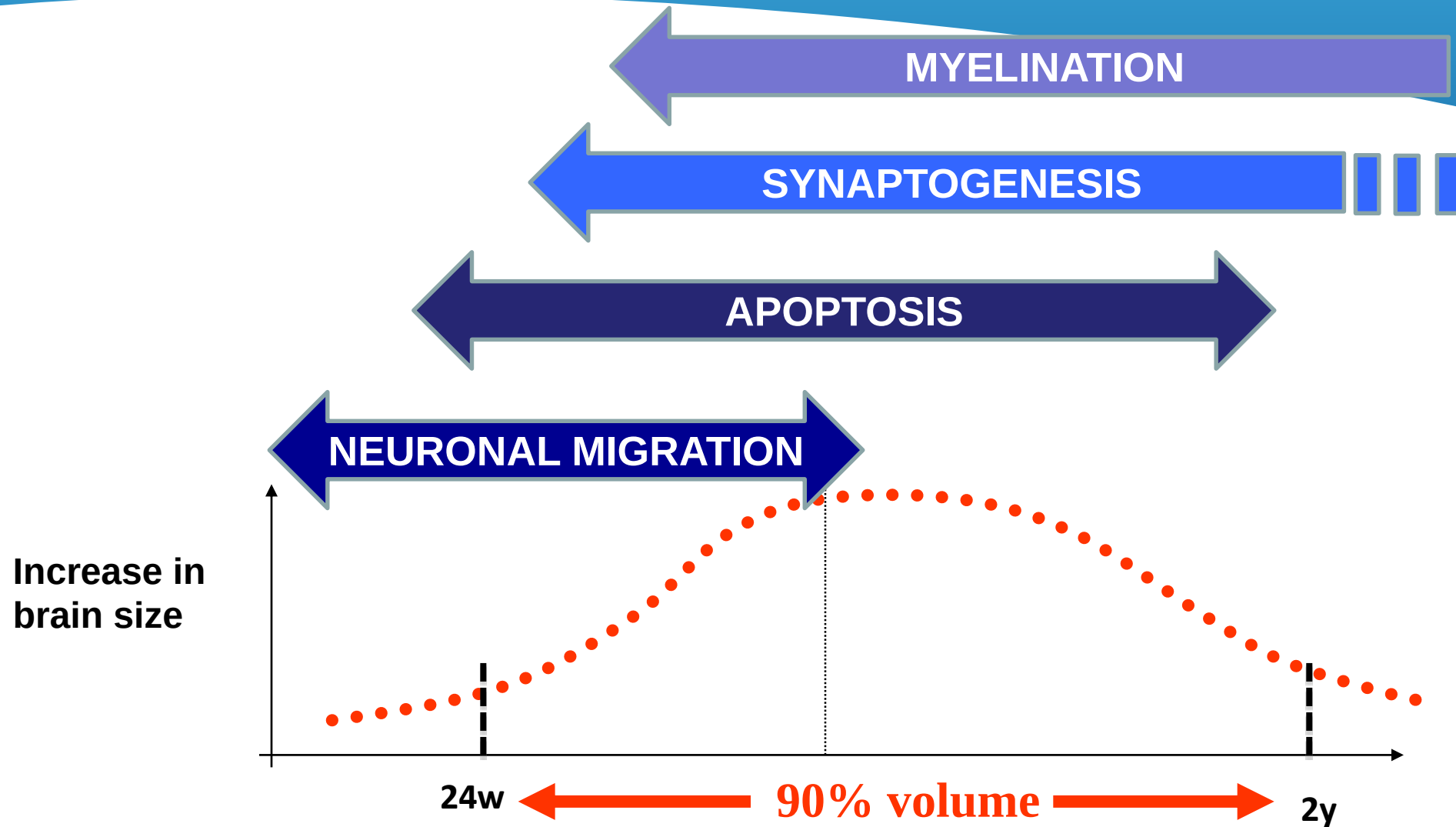
INTERACTIVE QUIZ - ANSWERS

Put these 4 processes in the correct order

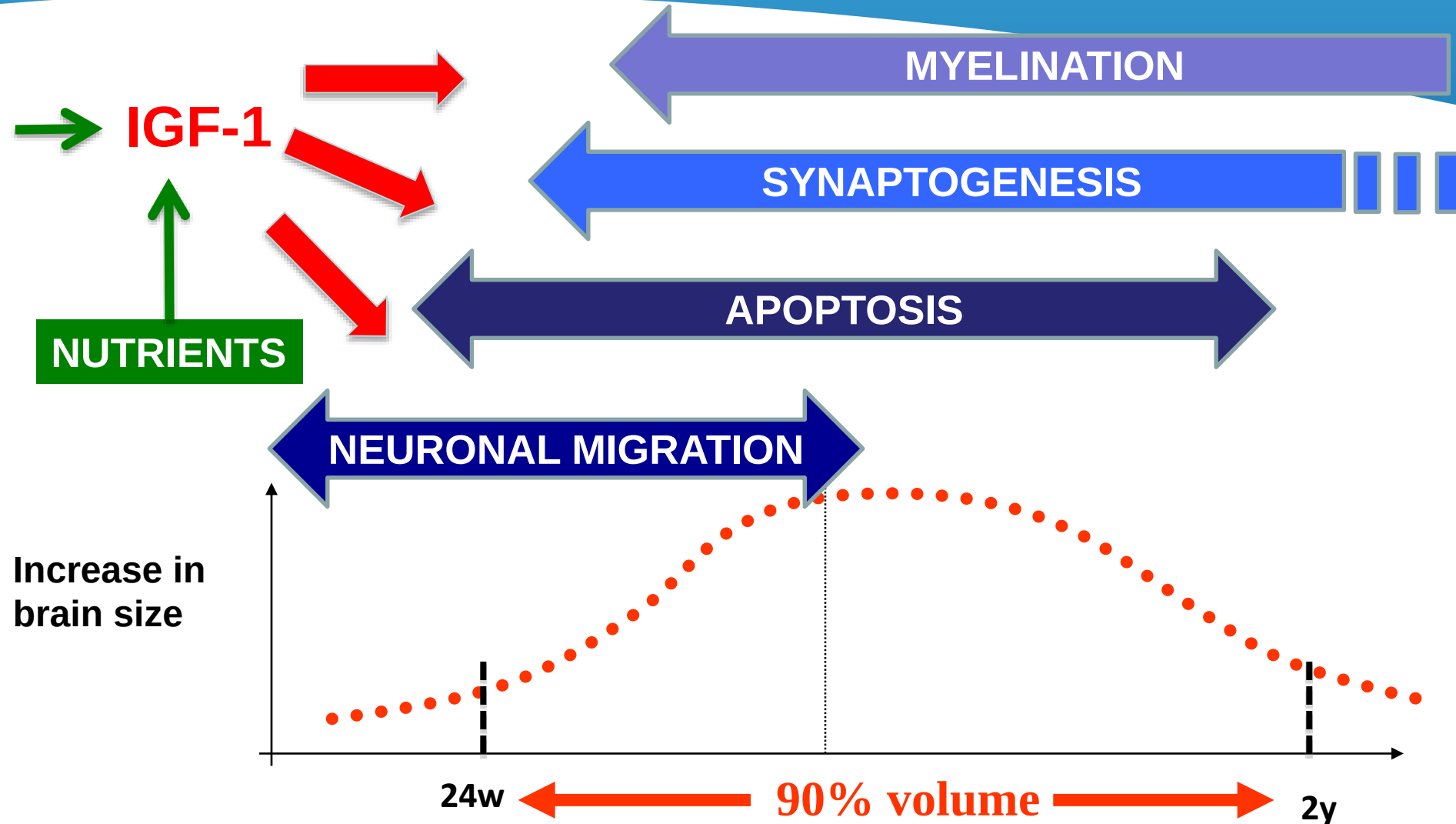
- Apoptosis - 2
- Myelination - 4
- Neuronal migration - 1
- Synaptogenesis - 3



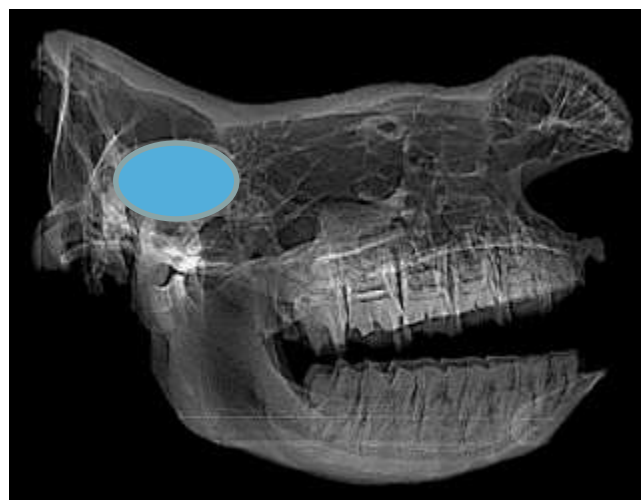
Neuronal development proceeds in sequence



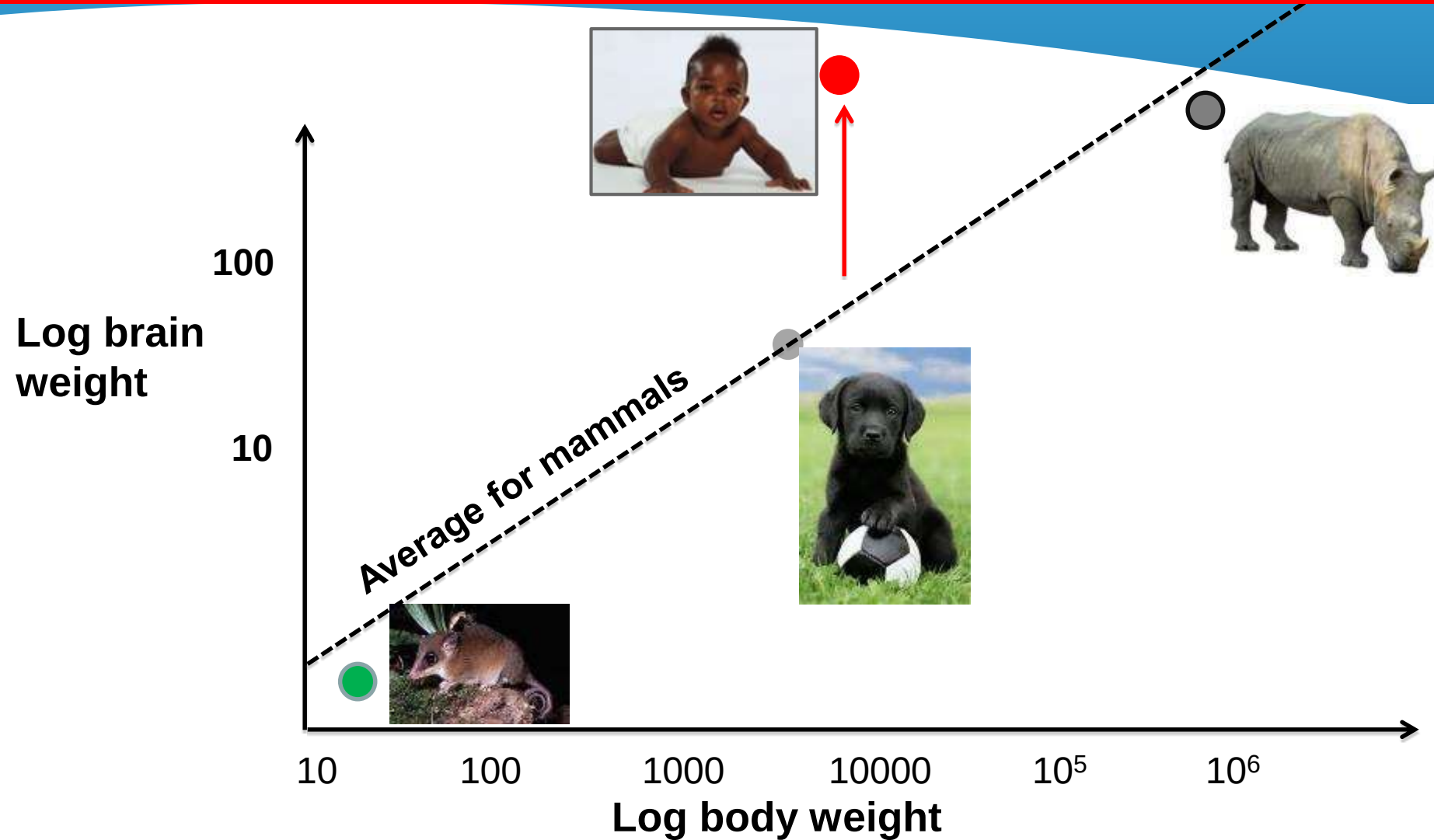
Neuronal processes influenced by growth factors, signaling & gene expression



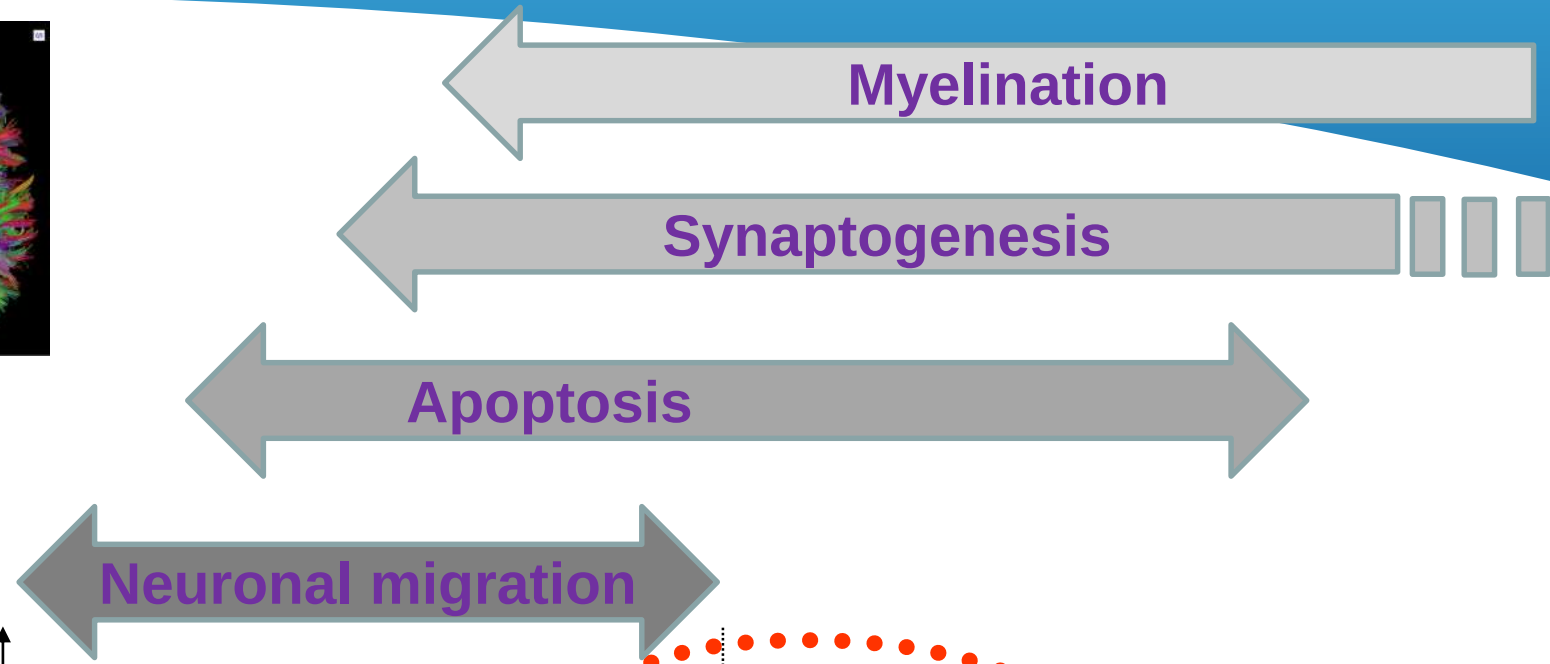
Humans: it's all about the brain!



Human brain: 10-20x as large as other mammals

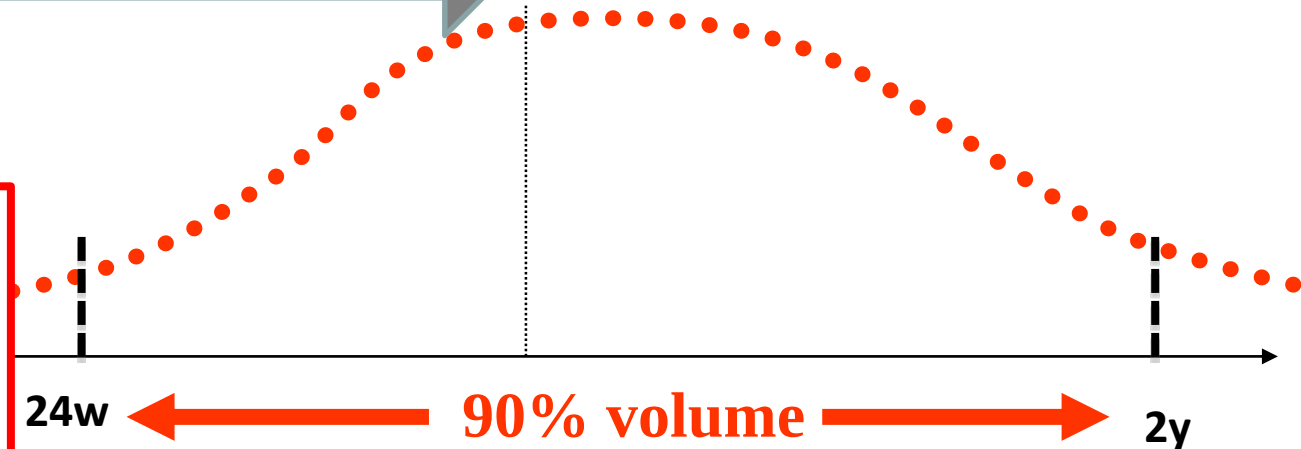


Growth & differentiation is complex



3rd trimester development

- Brain volume $\uparrow$ >3mL/day
- Cortical volume $\uparrow$ x4
- Cerebellar surface area $\uparrow$ x30



Complexity of brain development: cells & connections



Multiple anatomic
regions

Unique developmental
processes



Time-coordinated development
of key areas



Neural circuits mediate complex
behaviors

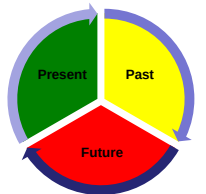
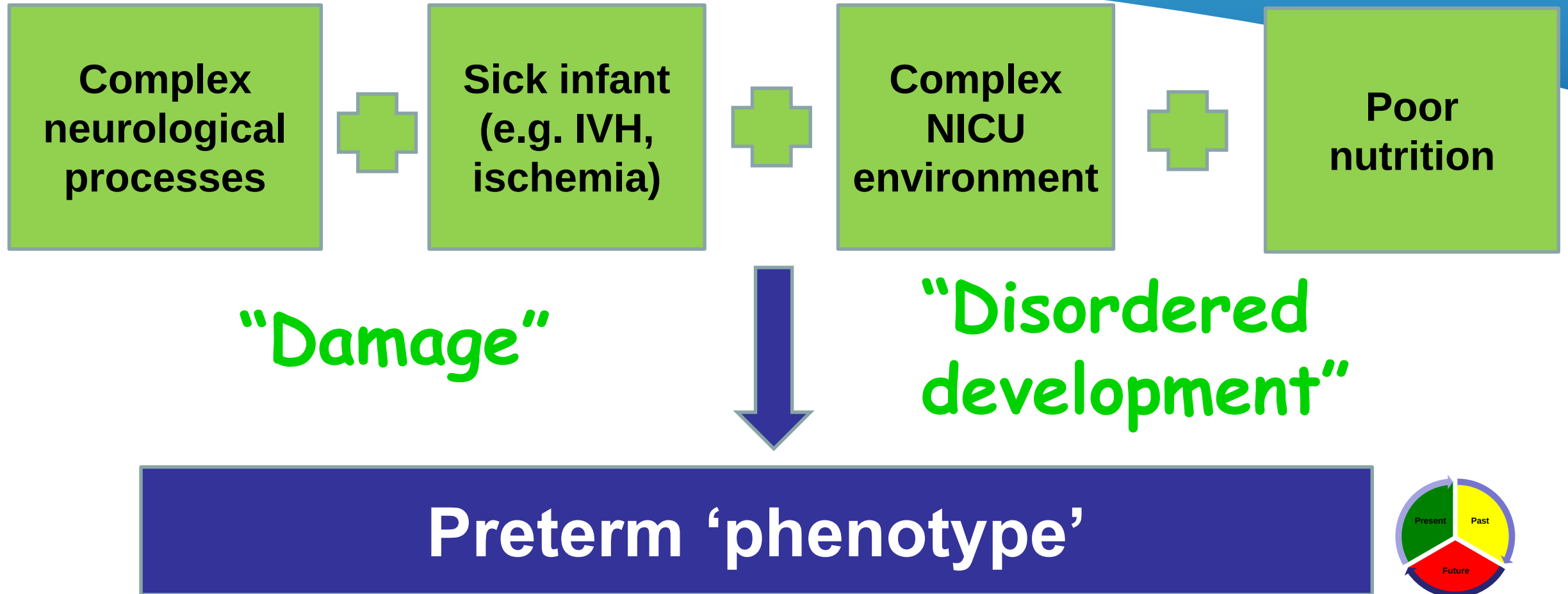


Cells



Connections

Critical window: 24 weeks – 2 years



NUTRITIONAL STATUS

Marlow, Johnson et al. 2014, 2015
Georgieff, Ramel, Cusick 2014, 2016

Complexity of the “Preterm phenotype”

Preterm ‘phenotype’

Complex – many elements – every child is different

- Deficits in overall Intelligence Quotient (IQ, DQ)
- Executive function (planning etc.)
- Visuo-spatial processing
- Visuo-motor integration

Not as simple as ‘less clever’

Executive function (EF) = cognitive processes for self-regulation of emotion & goal-directed behaviour

- Develop throughout infancy, childhood, adolescence and adulthood
- Often (but not always) compromised in ex-preterm individuals
 - *even where global development or IQ is “normal”*
- Associations: decreasing gestation, neonatal complications etc.
- Outcomes depend on home & school environments
 - suggest executive function skills are modifiable
- EF: different definitions/interpretations in the literature

Taylor et al. Sem Perinatology 2016

QUIZ - Executive function: which of the following are skills associated with executive function

Working memory

Cognitive flexibility

Inhibitory control

Executive function: 3 key elements

Working memory

Remember what time plane and how to get to hotel

Cognitive flexibility

Think about the same thing in two different ways – how can I make lecture interesting to you!

Inhibitory control

Ignore distractions & resist temptation - finish my slides rather than watch TV

Executive function – 5 key skills

1. Paying attention
2. Organise and plan
3. Initiate task and stay focused
4. Regulate emotions
5. Self-monitoring – keeping track of what you're doing

Executive function: related skills – critical for many aspects of ‘normal life’

Hot executive function

Stay on task and control impulses when something more exciting happens; resist temptation

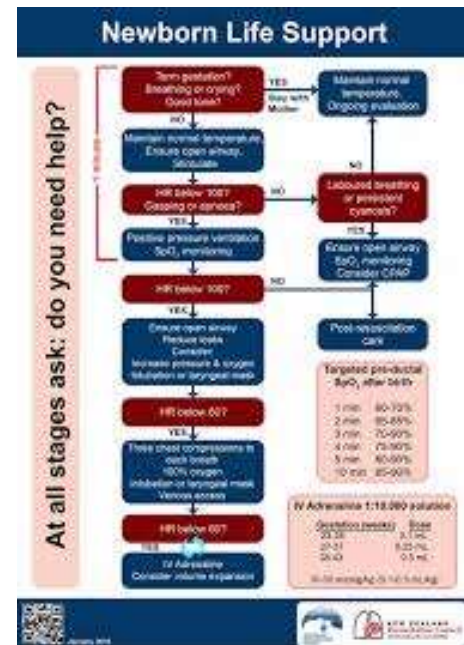
Reflection

Take time to consider, pause, think and then do

Processing speed

Do the reflection quick enough that can keep going

NLS requires lots of executive function!



Deficits in executive function (EF) - how is this manifest in ex-preterm infants & children?

Preschool

- Easily frustrated; throws things instead of asking for help
- Has trouble following directions & forgets what to do
- Frequent tantrums & aggressive behaviour instead of 'using words'
- Wants to do things a certain way, trouble making adjustments



School

- Starts one task and gets distracted, then doesn't ever finish
- Mixes up assignments; doesn't bring home books needed
- Panics when rules or routines are challenged
- Has trouble finishing in the time allotted
- Has trouble working in groups
- Tends to be impulsive





Preterm brain development & executive function

- Complex and rapid brain development in 3rd trimester & infancy
- Very high nutrient demands especially energy
- ***“Cells & connections”***
- Complex human behaviour requires complex brain connections
- Executive function (EF): set of neuro-cognitive processes
 - Goal directed behaviour
 - Emotional regulation
 - Manifests in many different ways at different stages of life
- EF - difficult to assess in infancy; long term studies essential
- EF – major issue for children and adults born preterm



Learning, intellectual disabilities are common in ex-preterm children and school outcomes are worse

- Study aim: explore 'co-morbidity' of intellectual & learning disabilities, executive function & special educational needs (EpiCure study)
- 11yr old children born <26 weeks gestation (n=161) and controls (n=153)
 - IQ
 - Mathematics skills
 - reading attainment
 - executive function
 - visuospatial processing
 - sensorimotor skills

Co-morbidity = Deficits in more than one domain

Learning disabilities in ex-preterm children without neurosensory impairment: neuropsychological profiles & school outcomes. Johnson et al. 2016

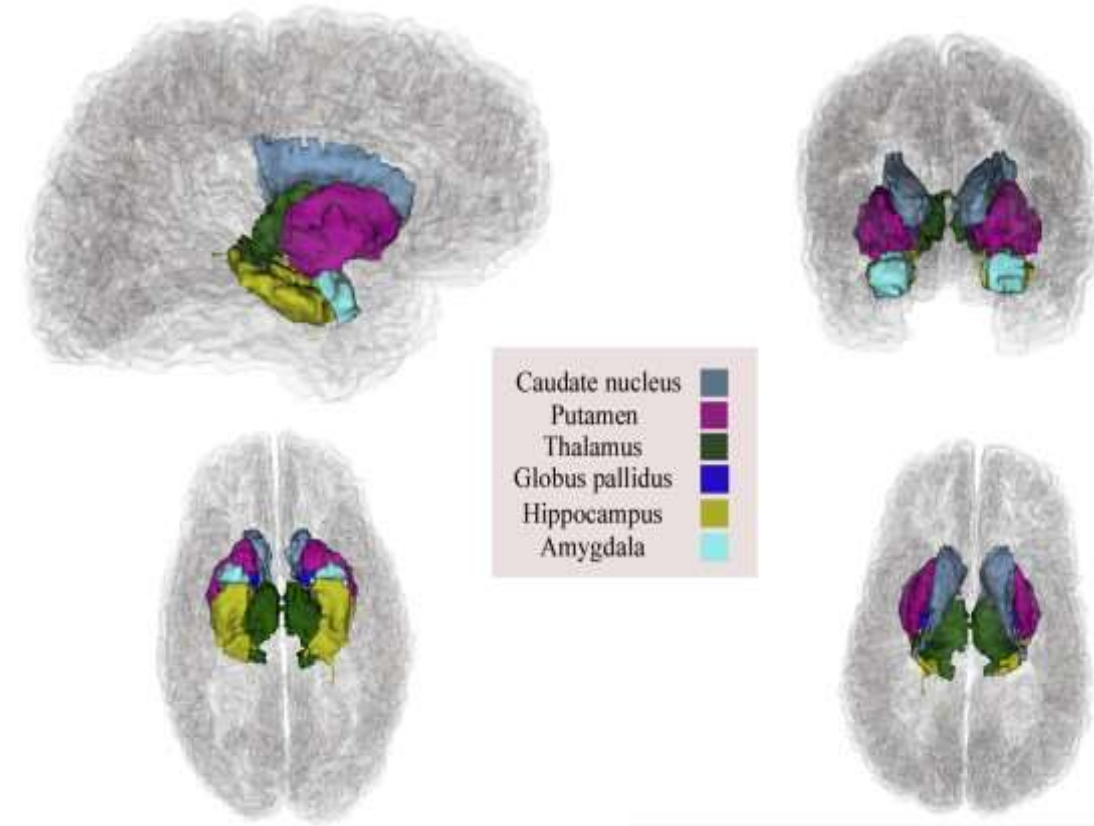
Learning, intellectual disabilities are common in ex-preterm children and school outcomes are worse

- 47% extremely preterm - intellectual or learning disability (4.6% controls)
- 24% had **comorbidity** (0% controls)
 - Comorbidity -> significantly worse abilities and attainment
- Special Educational Needs (SEN) provision often inadequate
- Mathematics much more difficult than reading
- Math problems associated with deficits in
 - working memory
 - executive function
 - visuo-spatial processing

Learning disabilities in ex-preterm children without neurosensory impairment: neuropsychological profiles & school outcomes. Johnson et al. 2016

What about adult life? Brain volumes and cognitive function in VLBW young adults

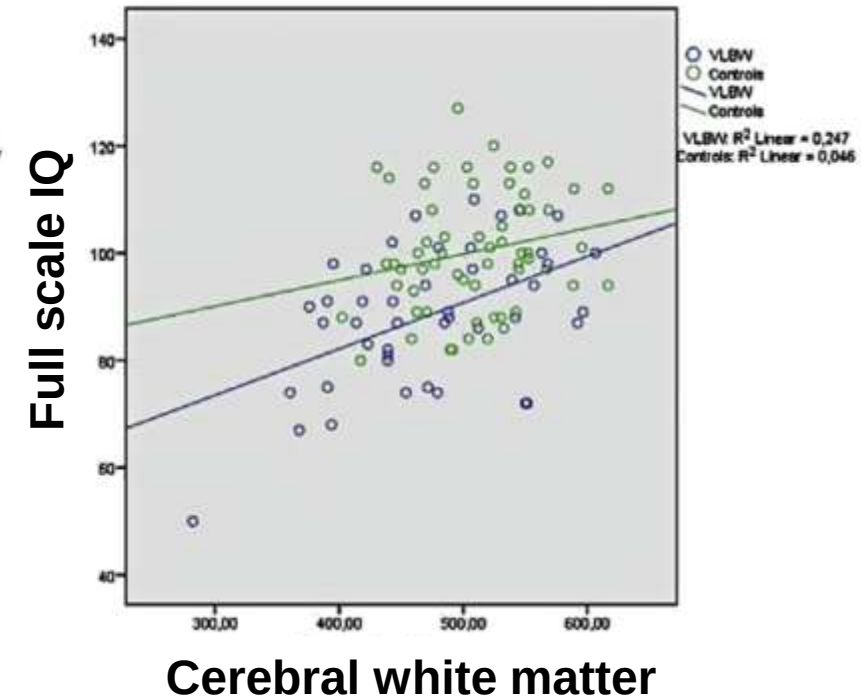
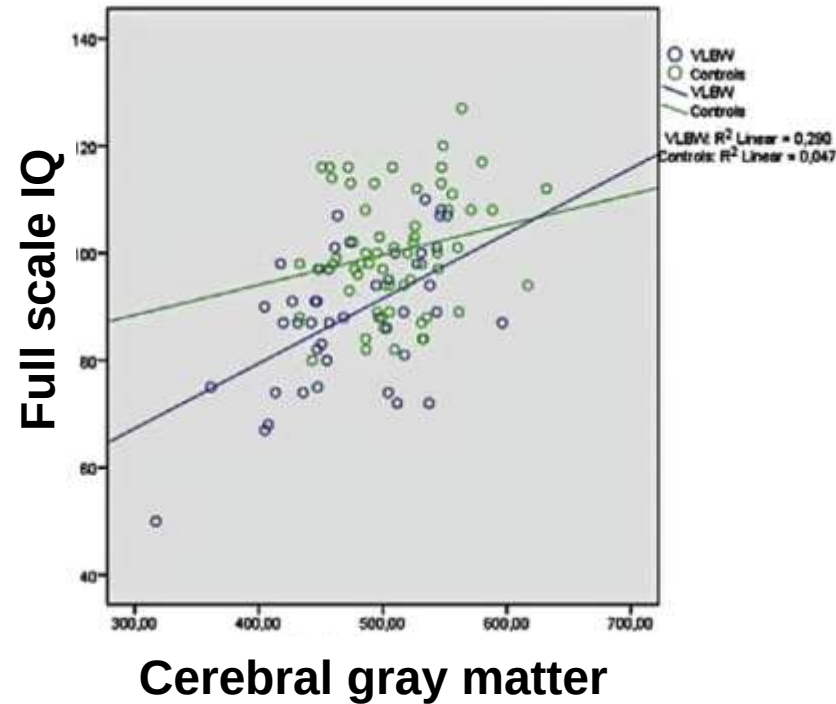
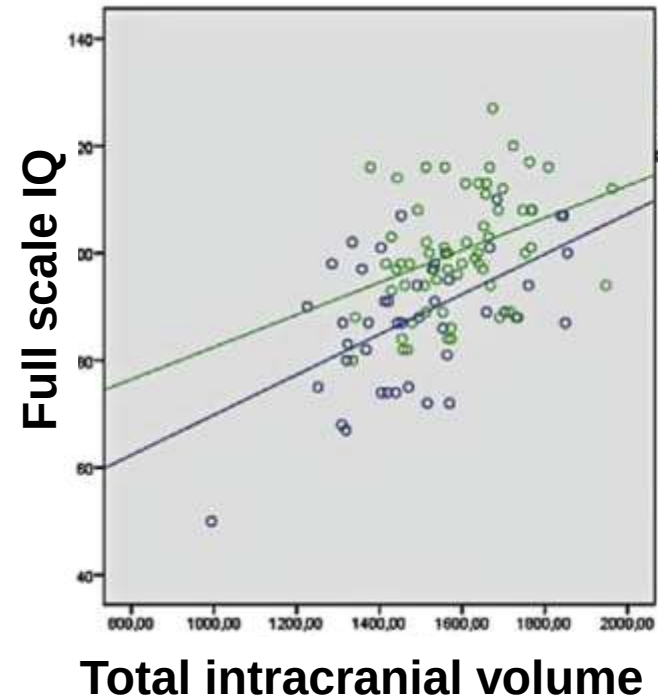
- N=44 VLBW subjects & n=60 controls
- Wechsler (WAIS-III) and MRI
- VLBW subjects - smaller brain volumes
 - thalamus, globus pallidus & corpus callosum
 - larger lateral ventricles
 - Associated: lower gestations, higher morbidity
 - Positive associations: brain volumes & full IQ
- Suggest permanent effects from perinatal brain injury with influence on later cognitive function



Adult full scale IQ associated with total brain volume, gray and white matter

○ Controls

○ VLBW



Adults born preterm: review of general health & system-specific outcomes – mental health aspects

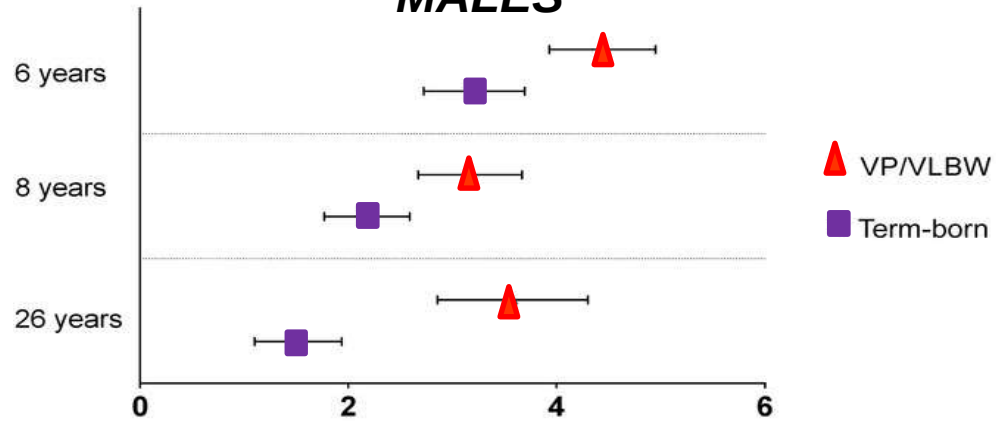
- Systematic reviews & cohort studies
- Increased risks of anxiety/depression
- Increased school problems: anxiety when transitioning to adolescence
- ‘Adults born preterm had different, not necessarily abnormal, personality types compared to term peers’
- **Less** negative emotions, more ‘dutiful’, ‘cautious’ and ‘shy’
- **Less** criminal & risk-taking behaviours, smoking, drug & alcohol abuse
- Higher prevalence of neuroticism, withdrawal & autistic behaviours
- Higher risks for being bullied
- Boys & men tended to fare worse compared to girls & women

Attention problems in very preterm children from childhood to adulthood: Bavarian Longitudinal Study

- N=260 preterm, n=229 term controls
- Data on attention: 6, 8, and 26 years of age
- Parent reports, expert behavior observations, & clinical ADHD diagnoses
- **Preterm: significantly more**
 - **attention problems**, shorter attention span
 - more frequently diagnosed with **ADHD**
 - Butattention problems decreased from childhood to adulthood
- Despite improvements, preterm born adults still had more attention problems
- Important: raise awareness for school intervention programs that reduce attention problems in very preterm children

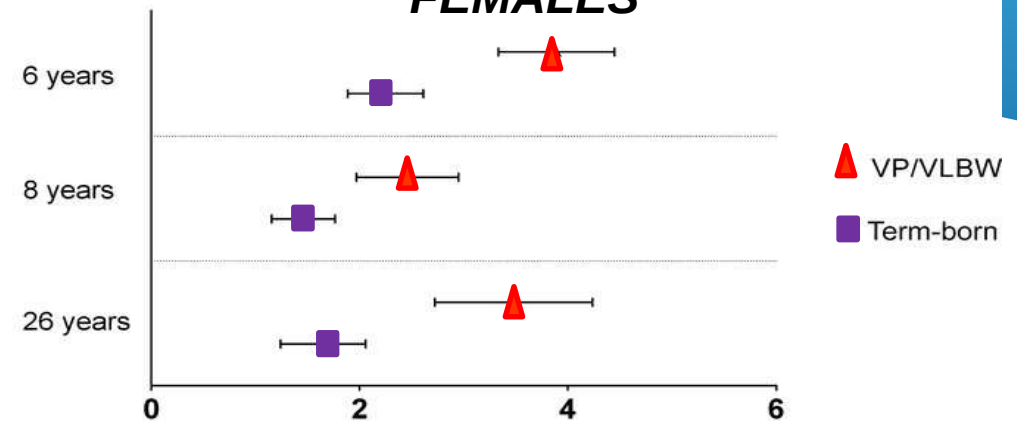
Bavarian longitudinal study

MALES



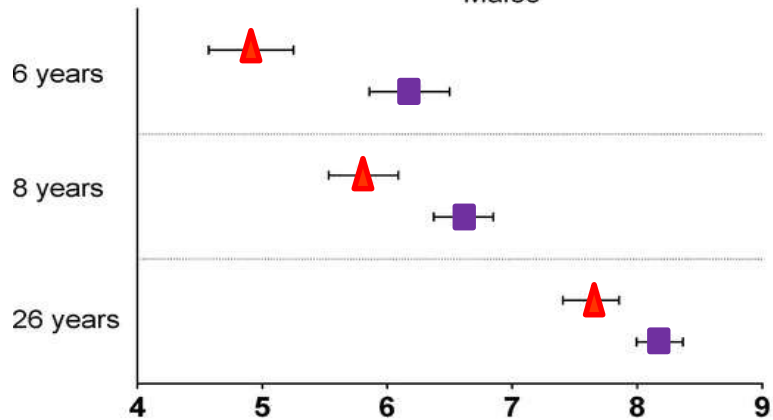
Parent-rated attention problems

FEMALES



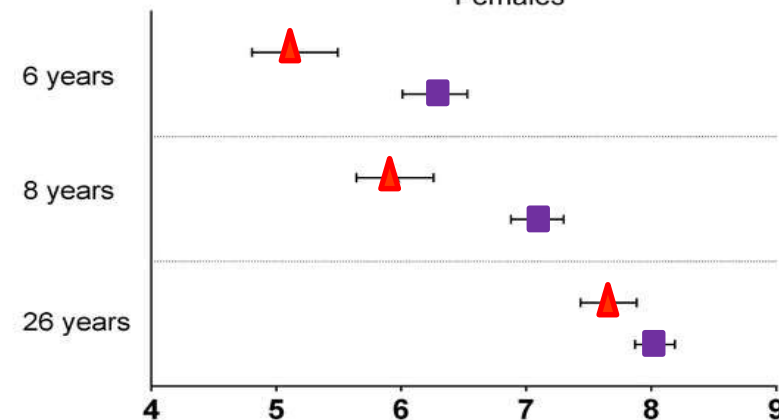
Parent-rated attention problems

Males



Observer-rated attention span

Females



Observer-rated attention span

Executive function: how do we test EF?

Working memory

Cognitive flexibility

Inhibitory control

Executive function (EF) – key skills

1. Paying attention
2. Organise and plan
3. Initiate task and stay focused
4. Regulate emotions
5. Self-monitoring – keeping track of what you're doing

Tests for executive function: need an expert!
Observation, questionnaire (parents & children)
Neuro-psychological tests

Tests of Executive Function

- **Age specific, validated** tests
 - lots of them!
- Need expert support
 - Psychology
- Questionnaires
 - BRIEF
 - CBCL
- Neuro-psychological tests
 - WISC-IV
 - NEPSY-II

IDENTIFICATION / MEMORY TEST



Listen or see



“hat”

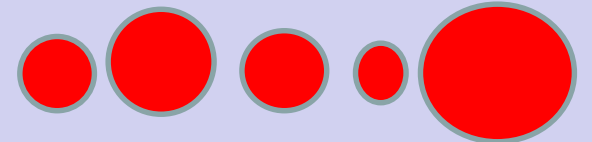
Have you
seen this
before?

SYNCHRONISATION TEST

Follow moving ball on the screen with computer arrow



SEQUENCING TEST



Put shapes of different size, or numbers in the correct order
Smallest to biggest

12 7 21 8 2 19

Tests of Executive Function

SIMULTANEITY TEST



RED

YELLOW

Follow randomly moving white ball whilst words appear

When word RED, BLUE, YELLOW appears in correct colour **RED**, **YELLOW** – click the button

RECOGNITION TEST



Three common objects – remember the order

Watch 4 series and choose which is the original order

Child Behaviour Checklist (CBCL)

Rate as

- 0 – not true
- 1 – somewhat or sometimes true
- 2 – very true or often true

Example questions

- Can't sit well, restless or hyperactive
- Demands must be met immediately
- Easily frustrated
- Doesn't want to go out of home
- Disturbed by any change in routine

CHILD BEHAVIOR CHECKLIST FOR AGES 1½-5

Please print.

CHILD'S FULL NAME: First, Middle, Last

CHILD'S GENDER: ☐ Boy ☐ Girl

CHILD'S AGE: _____

CHILD'S ETHNIC GROUP OR RACE: _____

TODAY'S DATE: Mo. Day Year

CHILD'S BIRTHDATE: Mo. Day Year

PARENTS' USUAL TYPE OF WORK, even if not working now. Please be specific— for example, auto mechanic, high school teacher, homemaker, doctor, state operator, shoe salesman, army sergeant.

FATHER'S TYPE OF WORK: _____

MOTHER'S TYPE OF WORK: _____

THIS FORM FILLED OUT BY: (print your full name) _____

Your relationship to child: ☐ Mother ☐ Father ☐ Other (specify): _____

Please fill out this form to reflect your view of the child's behavior even if other people might not agree. Feel free to write additional comments beside each item and in the space provided on page 2. **Be sure to answer all items.**

Below is a list of items that describe children. For each item that describes the child **now or within the past 2 months**, please circle the 0 if the item is **very true or often true** of the child. Circle the 1 if the item is **somewhat or sometimes true** of the child. If the item is **not true** of the child, circle the 2. Please answer all items as well as you can, even if some do not seem to apply to the child.

0 = Not True (as far as you know)	1 = Somewhat or Sometimes True	2 = Very True or Often True
0 1 2	1. Aches or pains (without medical cause; do not include stomach or headaches)	0 1 2 30. Easily jealous
0 1 2	2. Acts too young for age	0 1 2 31. Eats or drinks things that are not food—don't include weeds (describe): _____
0 1 2	3. Afraid to try new things	0 1 2 32. Feels certain animals, situations, or places (describe): _____
0 1 2	4. Avoids looking others in the eye	0 1 2 33. Feelings are easily hurt
0 1 2	5. Can't concentrate, can't pay attention for long	0 1 2 34. Gets hurt a lot, accident-prone
0 1 2	6. Can't sit still, restless, or hyperactive	0 1 2 35. Gets in many fights
0 1 2	7. Can't stand having things out of place	0 1 2 36. Gets into everything
0 1 2	8. Can't stand waiting; wants everything now	0 1 2 37. Gets too upset when separated from parents
0 1 2	9. Chews on things that aren't edible	0 1 2 38. Has trouble getting to sleep
0 1 2	10. Clings to adults or too dependent	0 1 2 39. Headaches (without medical cause)
0 1 2	11. Constantly seeks help	0 1 2 40. Hits others
0 1 2	12. Constipated, doesn't move bowels (when not sick)	0 1 2 41. Holds his/her breath
0 1 2	13. Cries a lot	0 1 2 42. Hurts animals or people without meaning to
0 1 2	14. Cruel to animals	0 1 2 43. Looks unhappy without good reason
0 1 2	15. Defiant	0 1 2 44. Angry moods
0 1 2	16. Demands must be met immediately	0 1 2 45. Nausea, feels sick (without medical cause)
0 1 2	17. Destroys his/her own things	0 1 2 46. Nervous movements or twitching (describe): _____
0 1 2	18. Destroys things belonging to his/her family or other children	0 1 2 47. Nervous, highstrung, or tense
0 1 2	19. Diarrhea or loose bowels (when not sick)	0 1 2 48. Nightmares
0 1 2	20. Disobedient	0 1 2 49. Overeating
0 1 2	21. Disturbed by any change in routine	0 1 2 50. Overfed
0 1 2	22. Doesn't want to sleep alone	0 1 2 51. Shows panic for no good reason
0 1 2	23. Doesn't answer when people talk to him/her	0 1 2 52. Painful bowel movements (without medical cause)
0 1 2	24. Doesn't eat well (describe): _____	0 1 2 53. Physically attacks people
0 1 2	25. Doesn't get along with other children	0 1 2 54. Picks nose, skin, or other parts of body (describe): _____
0 1 2	26. Doesn't know how to have fun; acts like a little adult	
0 1 2	27. Doesn't seem to feel guilty after misbehaving	
0 1 2	28. Doesn't want to go out of home	
0 1 2	29. Easily frustrated	

Be sure you answered all items. Then see other side.

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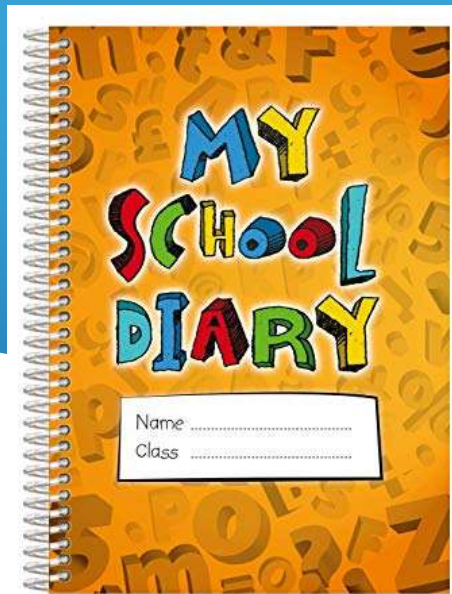
Personal case studies - anonymised

- Olivia: 23 week gestation girl, NEC
- 9 years old, physically normal
- Normal school, but slower half of class
- Very poor at maths, otherwise 'OK'
- Plays 'running around' games at break
- Cannot play 'make believe' games with girls
 - No dolls, or mummy and daddy games
- Very few close girl friends but 'happy'



Personal case studies - anonymised

- Owen: 24 week gestation boy
- Twin died at 2 weeks age
- 7 years old, physically normal
 - Very flexible/hypermobile
 - Speech not very clear / distinct
- Normal school, but 'special needs' class
- No idea what 'day of the week'
- Very poor at all academic subjects
- Great at kick-boxing
- Finds 'slap-stick' comedy hilarious
- Very likeable and sociable boy





Personal case studies - anonymised

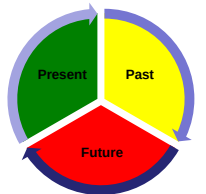
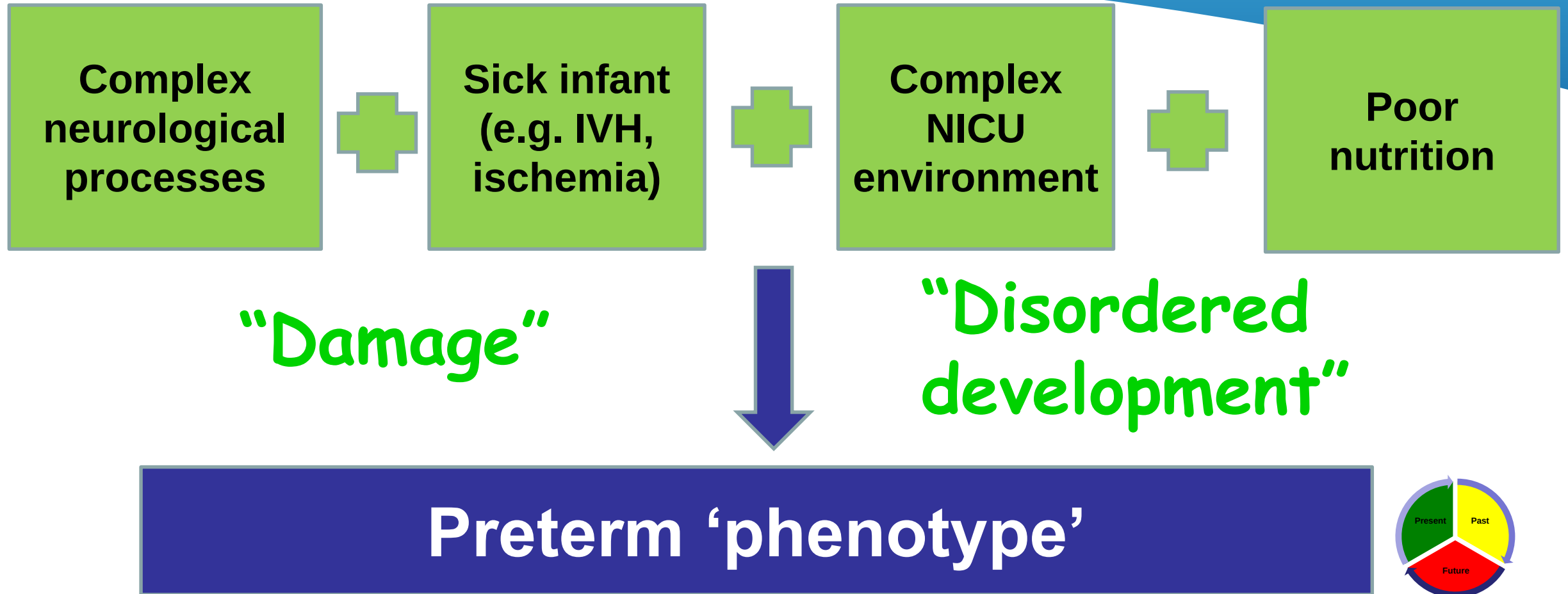
- Finn: 24 week gestation boy
- Small IVH, home in oxygen
- Now 24 years old, no medical problems
- Went to college (cookery)
- Works in school canteen
- Likes routines
- Lives at home with parents
- Tends not to 'go out'
- Struggles with big groups
- Few friends but says he is happy
- Addicted to playstation



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Aetiology of poor Executive Function?



NUTRITIONAL STATUS

Marlow, Johnson et al. 2014, 2015
Georgieff, Ramel, Cusick 2014, 2016

Aetiology of poor Executive Function?

**Complex
neurological
processes**



**Sick infant
(e.g. IVH,
ischemia)**



**Complex
NICU
environment**



**Poor
nutrition**

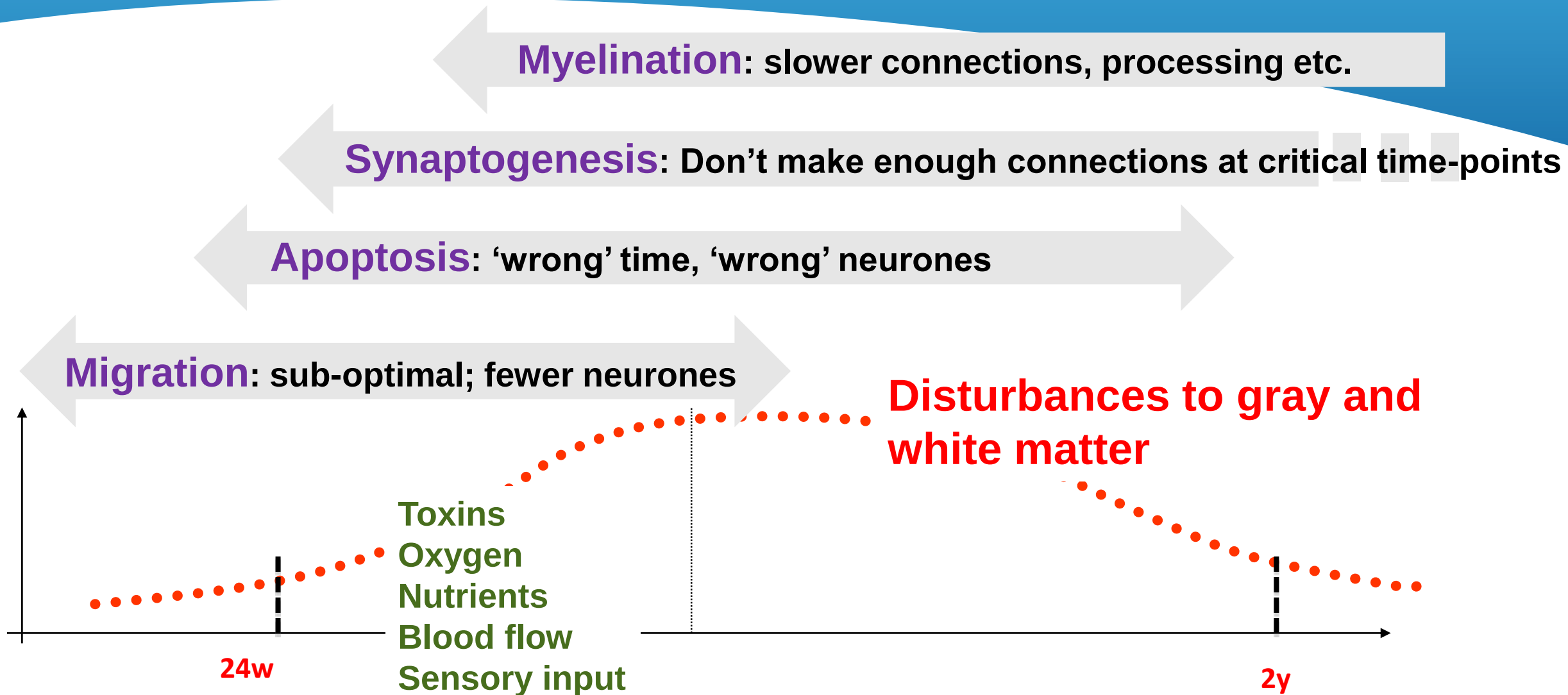
"Damage"

- Inflammation causing preterm labour
- Genetic pre-disposition
- Hypoxia or ischemia
- Toxins / drug exposures
- Environmental toxins (plastics)
- Haemorrhage or infarct (IVH, PVL etc.)

"Disordered development"

- Noise, sensory impacts on NICU
- Pain, drugs, sedatives
- Inflammation / sepsis
- Disturbed neurological processes
- Poor nutrient quantity & quality
- Disturbed gut-brain axes

Aetiology of poor EF in preterm infants





Executive function in preterm infants

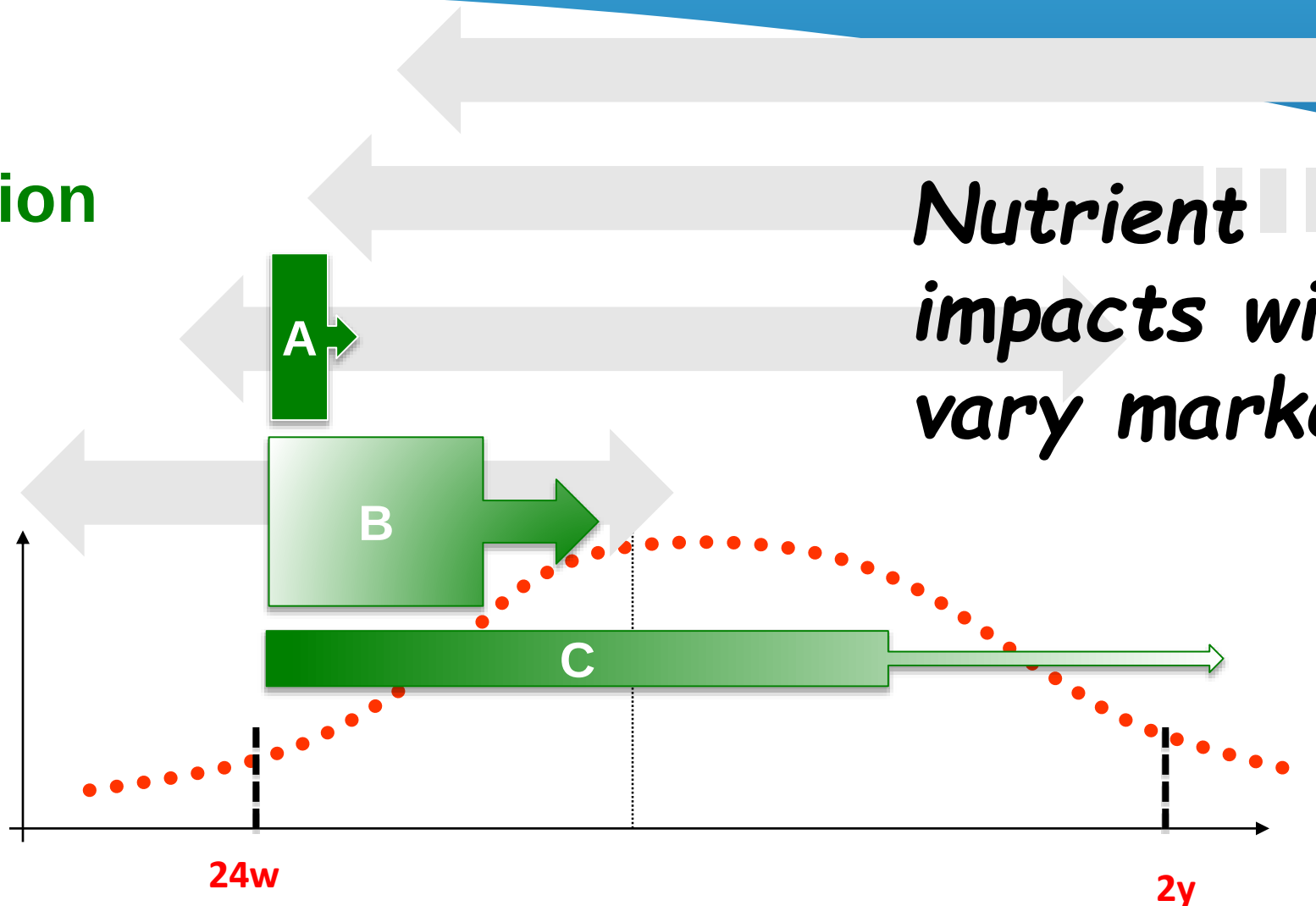
- Common but modifiable by environment
- Complex to assess: need age specific, validated tests
- Important & changing impact throughout life-course
- Neuro-imaging shows differences in brain structures
- **What can we do about it as clinicians?**
 - Recognise, refer for support, educate etc.
 - Optimise neonatal care: early stabilisation, oxygen, “neuro-NICU”, glucose
 - **NUTRITION!**



How might nutrient deficiency in preterm infants affect later function?

Amount, type,
timing & duration

*Nutrient
impacts will
vary markedly*



Nutrition for optimal brain development in high risk infants: multiple mechanisms

Nutrients for
tissue substrate

Energy to drive
the system

Signalling &
growth factors

Impacts on gene
expression

Prevention of
disease

Macro- and micronutrients

Carbohydrate, lipids & ...protein

Energy intake, BCAA → IGF-1 etc.

Folate, B12, iron, choline etc.

Breastmilk reduces NEC & sepsis

Why is poor nutrition so common on NICU?

Focus is what we can see and measure



Jaundice &
phototherapy
How high?

Central lines –
yes/no? when?

Fluids
60-90-120?

Inotropes
Which ones?

Heart rate

Oxygen
saturation
85-90-95%?

Blood pressure
How low?

CPAP, BiPAP or
Hi-flow

AC PSV VG VT VC HFOV TCPL

Malnutrition is invisible

**No machine that goes beep if nutrient
intakes are inadequate**

Temperature

Blood gases

CRP?



Malnutrition on the NICU & how to make it better

- Don't know what to give
- Don't know what we are doing
- Don't focus on nutrition
- Don't support breastfeeding
- Lack of scientific data

EDUCATION & GUIDELINES

AUDIT & LEADERSHIP

QUALITY IMPROVEMENT

EDUCATION & QI

RESEARCH

How do we make it better?

- Start good nutrition early – PN, colostrum, follow guidelines
- Audit your practice
- Educate & teach, learn, read, read, read
- Leadership: discuss it on ward rounds; inspire your team to do better

BELIEVE THAT YOU CAN MAKE A DIFFERENCE





Specific nutritional interventions & exposures

- Overwhelming data to **support mothers own breastmilk**
 - Higher IQ, bigger brains, more white matter
 - Microbiome & Gut-Brain interactions
- Meeting macronutrient targets
 - Protein & energy
 - Fats especially essential fatty acids e.g. DHA (in breastmilk)
- Iron
- Novel nutrients - Choline



Choline – fish, meat, eggs, sprouts, milk



- Infants need ~125mg/day
- Adults 500mg: toxicity may occur at very high (3000mg) intakes
- Need
 - Higher intakes during pregnancy & lactation
 - Similar effects to folate (spina bifida)
 - Adults: may protect against liver or CVS disease

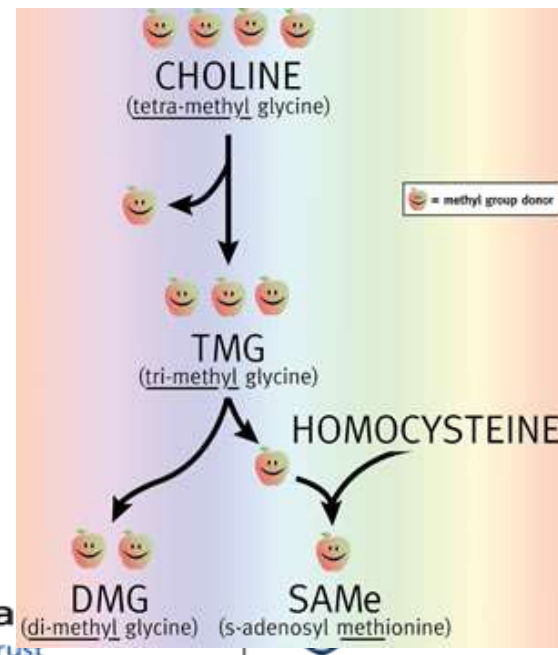
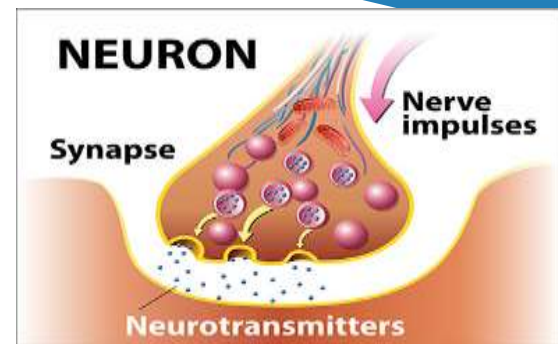
Choline - high demand during 3rd trimester

- Fetal & placental growth & **DNA methylation**
- Precursor of acetylcholine - regulates
 - neuronal proliferation & differentiation
 - migration, maturation, plasticity, and survival
 - synapse formation
 - substrate for phosphatidylcholine & sphingomyelin
- Preterm infant intakes are often low



Choline - high demand during 3rd trimester

- Maternal choline supplementation in **rats** improves
 - spatial memory & attention
 - reduces age-related cognitive decline
 - neuroprotective against prenatal neural insults
- Mechanisms unclear but will be complex
 - Neuroanatomical
 - Neuro-transmitter
 - Gene expression (methyl donor)



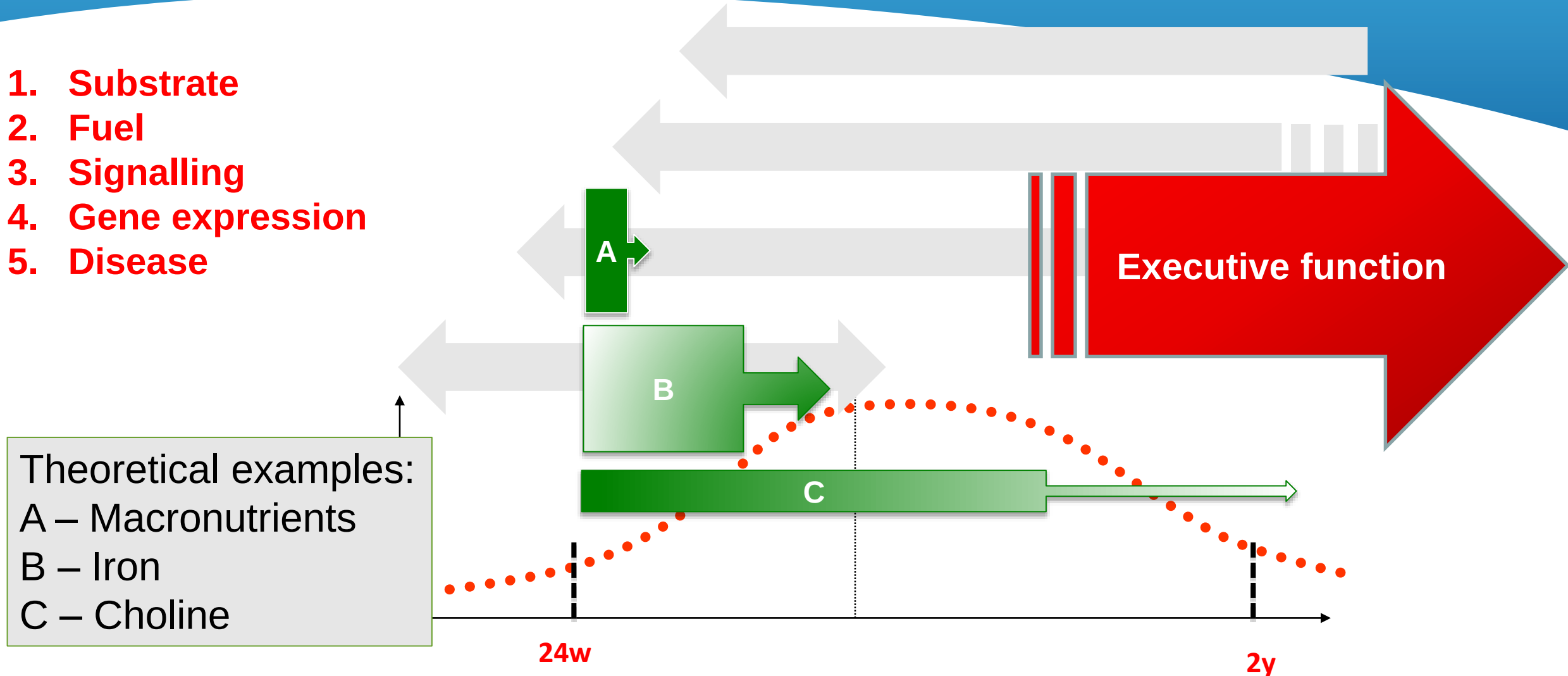
Maternal choline supplementation in 3rd trimester improves infant processing speed

- Healthy 'normal' pregnant women who deliver at term
- Maternal supplementation study: 480mg v 930mg choline/day
- Complex 'meal' intervention n=24 completed
- Infant processing speed & visuospatial memory
- **Significantly faster processing in higher choline**
- In 480mg group: **significant linear effect of exposure duration i.e. infants exposed longer showed faster reaction times**

Caudill et al. 2018 Maternal choline supplementation during the third trimester of pregnancy improves infant information processing speed: a randomized, double-blind, controlled feeding study. FASEB journal

Impact of nutrition on complex brain outcomes: amount, type, timing & duration

1. Substrate
2. Fuel
3. Signalling
4. Gene expression
5. Disease





Take home messages: executive function

1. EF is complex: major & changing impact throughout life course
2. Increasingly recognised in preterm adults: better designed long-term studies
3. Complex multi-factorial aetiology: cells & connections
4. Deficient nutrient intakes remain common – focus more on nutrition
 - Audit, QI, Education & Leadership
5. Support & promote maternal breast milk on NICU and after discharge
6. Urgent need for well-designed trials – support research!
 - Multiple areas of future promise

www.neonatalresearch.net

