

Bridging cognition, the brain and molecular genetics: evidence from Williams syndrome

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Overview

- This article describes the cognitive, neuanatomical, neurophysiological and molecular genetic probes used to improve understanding of the neurobiological bases of Williams syndrome (WMS)

What is Williams Syndrome?

- Occurs in 1 in 20,000-30,000 live births
- 95% have a deletion of one copy of perhaps 20 contiguous genes, which include the gene for elastin on chromosome 7.
- The deletion of elastin has provided a new genetic marker for WMS.

Diagnostic Characteristics



<http://www.williams-syndrome.org/what-is-williams-syndrome>

- Specific facial and physical features
- Cardiovascular difficulties including supraaortic stenosis (SVAS)
- Failure to thrive in infancy
- Transient neonatal hypercalcemia
- Delayed language and motor milestones
- Cognitive challenges
- Hyperacusis
- Overly friendly (excessively social) personality

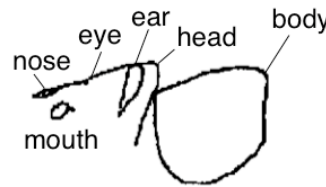
Cognitive Profile of WMS

- Cognitive deficits
- Expressive language abilities
- Abnormally high linguistic affect
- Strengths and deficits in visually based cognition in WMS
- Different trajectories in cognitive domains

Cognitive Deficits

- Dissociation between language and spatial cognition
 - Very strong language abilities
 - Severely impaired in spatial cognition

Elephant drawing

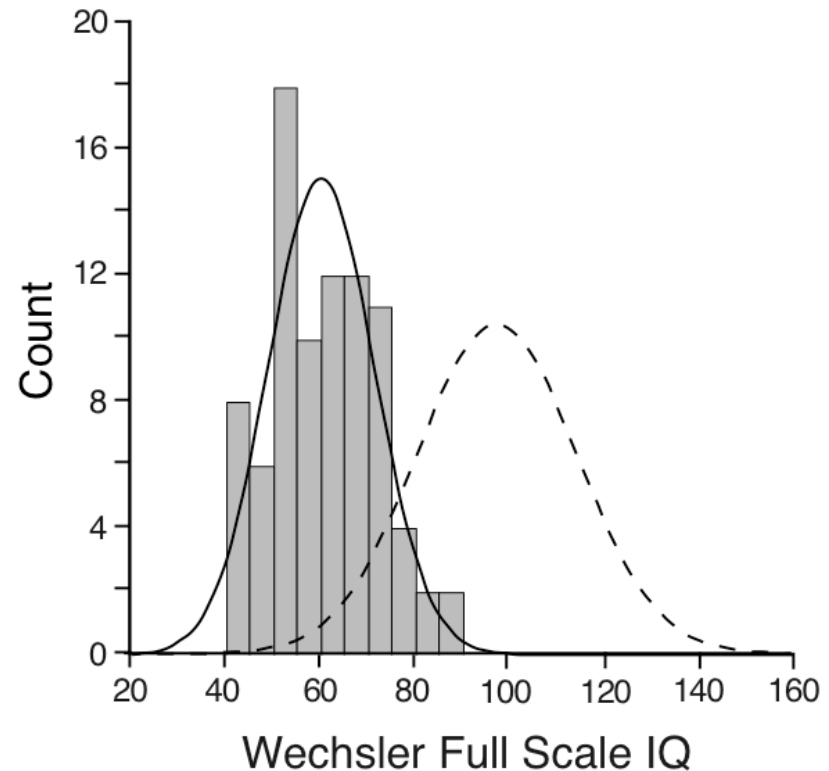


Elephant description

And what an elephant is it is one of the animals. And what the elephant does, it lives in the jungle. It can also live in the zoo. And what it has, it has long gray ears, fan ears, ears that can blow in the wind. It has a long trunk that can pick up grass, or pick up hay... If they're in a bad mood it can be terrible... If the elephant gets mad it could stomp; it could charge. Sometimes elephants can charge. They have long tusks. You don't want an elephant as a pet. You want a cat or a dog or a bird...

Cognitive Deficits

- Consistent cognitive deficits
 - Full Scale IQ scores range from 40-100
 - Mean around 60



Cognitive Deficits

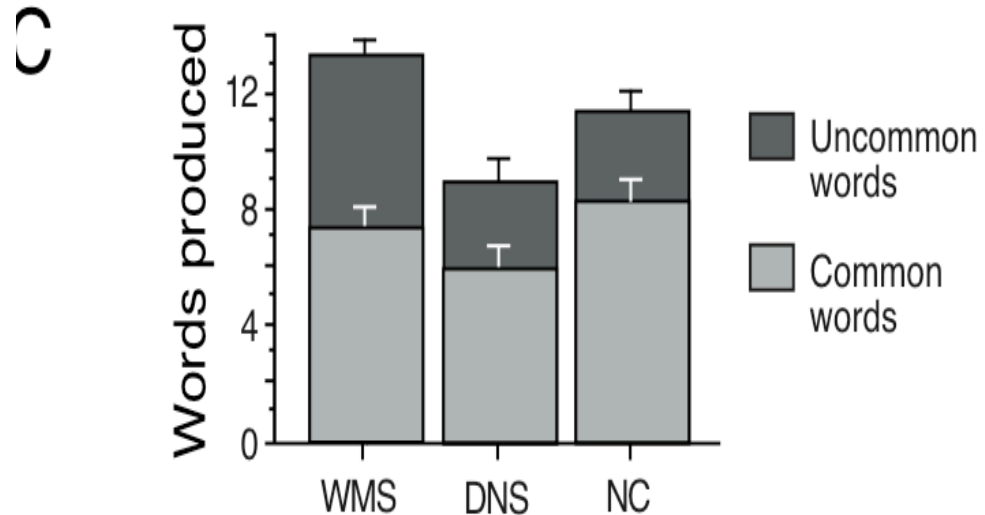
- Aspects of general problem solving are difficult
 - Handling money
 - With such a high variability with ability between people, it is possible that someone with WMS can live alone, with a roommate, or in a supervised apartment living complex.
- Display characteristic ‘peaks’ and ‘valleys’ in specific cognitive abilities.
 - Peaks: language and expressive abilities
 - Valleys: spatial cognition particularly at the level of global organization.

Expressive Language Abilities

- Significant delay in language development
- Strong language abilities in contrast to the overall impairment in cognitive abilities.
- When matched in age and Full Scale IQ to adolescents and adults with DNS the differences in language skills are evident at all levels
 - WMS subjects score significantly higher on measures of receptive word knowledge than on measures of general cognitive functioning, and perform dramatically better than their counterparts with DNS.

Expressive Language Abilities

- Word-fluency test
- WMS subjects scored similarly to normal subjects at the same mental age.
- WMS subjects gave significantly more uncommon responses than either matched subjects with DNS or normal subjects matched for mental age.



Word fluency (60s test): 'Name all the animals you can'

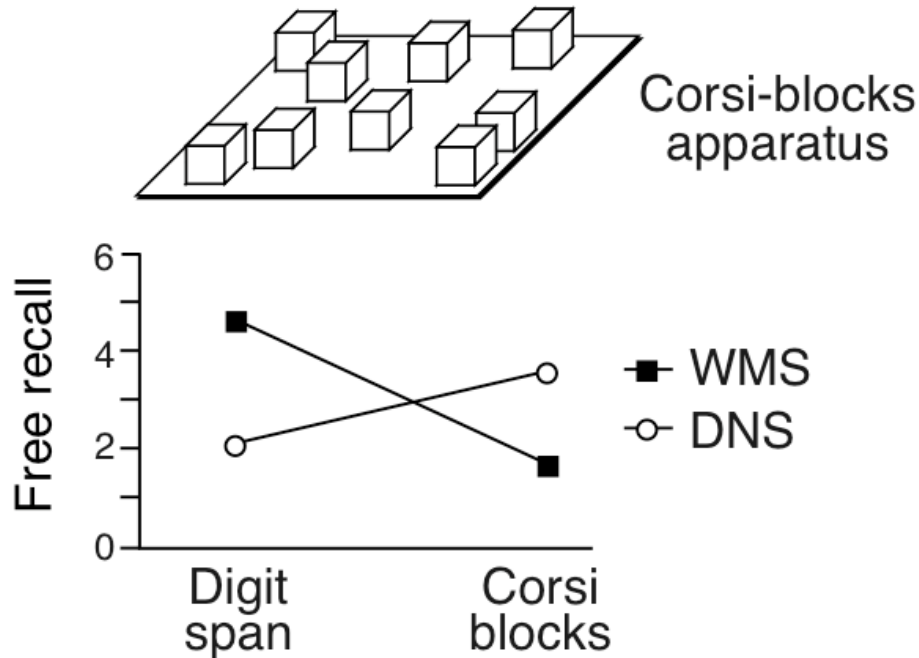
WMS: brontosaurus, 'tryrandon', dinosaurs, ibex, brontosaurus rex, elephant, dog, cat, lion, baby hippopotamus, whale, bull, yak, zebra, puppy, kitten, tiger, koala, dragon

DNS: dogs, cats, fish, bird, fish

Expressive Language Abilities

- Short-term memory for speech sounds or phonological working memory is relatively preserved in the WMS population
 - Basis for their strength in language

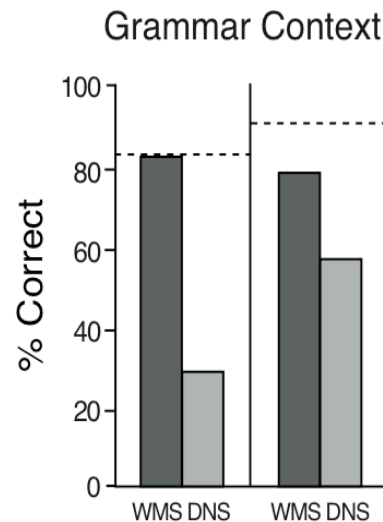
Expressive Language Abilities



- Individuals with WMS and DNS demonstrate a differential ability to remember a list of numbers in order (digit span) versus remembering location and order of blocks (corsi blocks)

Expressive Language Abilities

- Individuals with WMS perform significantly better than individuals with DNS in syntactic processing tasks on both grammar and content
- Individuals with WMS might be perceived to be more capable than they really are



Experimenter question:
'What if you were a bird?'

DNS 1: Bird seeds.
DNS 2: You'd be strong.
DNS 3: I don't fly.
DNS 4: I not a bird, you have wing.
DNS 5: Fly in the air.

WMS 1: You could fly, you could have babies, fly north or south, east or west.
WMS 2: Good question. I'd fly through the air being free.
WMS 3: I would fly through the air and soar like an airplane and dive through trees like a bird and land like a bird.
WMS 4: I would fly through the air where my parents would never find me. Birds want to be independent.
WMS 5: I would fly and if I liked a boy, I would land on his head and start chirping.

Expressive Language Abilities

- Language might develop in somewhat different ways than in normal children
- Morphological errors abate more slowly
 - But far more rapidly than in DNS
 - Errors show some differences from those of normal children.
- Far more errors in the use of spatial prepositions and in the use of language about space

Expressive Language Abilities

- The relationship between language and cognition is still being debated by researchers:
 1. An example of the modularity of language as a system that is separate from general cognitive abilities.
 2. There is a sufficient substrate of cognitive abilities for the development of complex syntax, and thus, WMS does not represent a dissociate between language and general cognitive functions.
- Generally, researchers agree that language is a strength in WMS, which is apparently different from other syndromes such as DNS

Abnormally High Linguistic Affect

- Ability to use their heightened linguistic skills to engage others socially
- Strong impulse towards social contact and affective expression
- The intersection of language behavior and social engagement in individuals with WMS has been investigated through a series of narrative tasks

Abnormally High Linguistic Affect

- Examples of expressive language in subjects with WMS compared to subjects with DNS.
- Subjects are asked to tell a story from a wordless picture book
- Individuals with WMS use more:
 - Affective prosody
 - Audience 'hookers'
 - Linguistic affective devices
 - The WMS subjects tend to be dramatic story tellers.

WMS age 17, Full Scale IQ = 50

Once upon a time when it was dark at night...the boy had a frog. The boy was looking at the frog...sitting on the chair, on the table, and the dog was looking through...looking up to the frog in a jar. That night he slept and slept for a long time, the dog did. But, the frog was not gonna go to sleep. And when the frog went out...the boy and the dog were still sleeping. The next morning it was beautiful in the morning. It was bright and the sun was nice and warm. Then suddenly when he opened his eyes...he looked at the jar and then suddenly the frog was not there. The jar was empty. There was no frog to found (whispered).



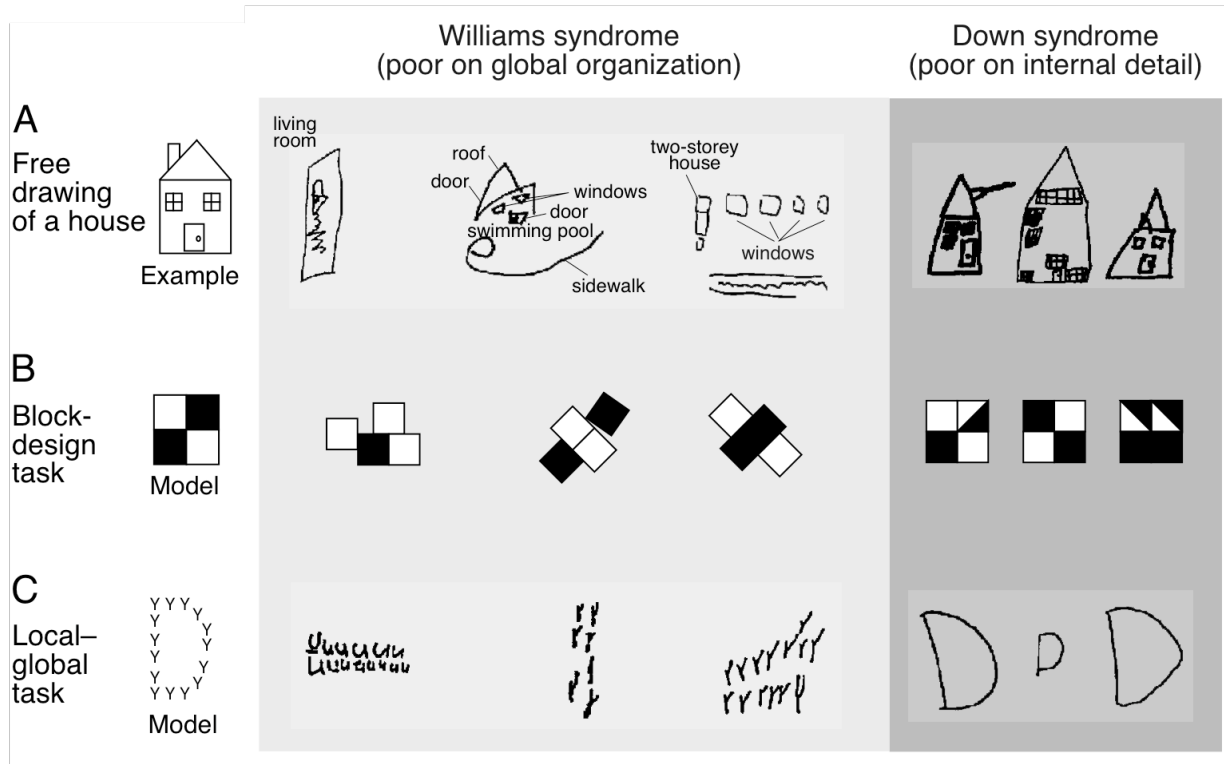
DNS age 18, Full Scale IQ = 55

The frog is in the jar. The jar is on the floor. The jar on the floor. That's it. The stool is broke. The clothes is laying there.

Strengths and Deficits in Visually Based Cognition in WMS

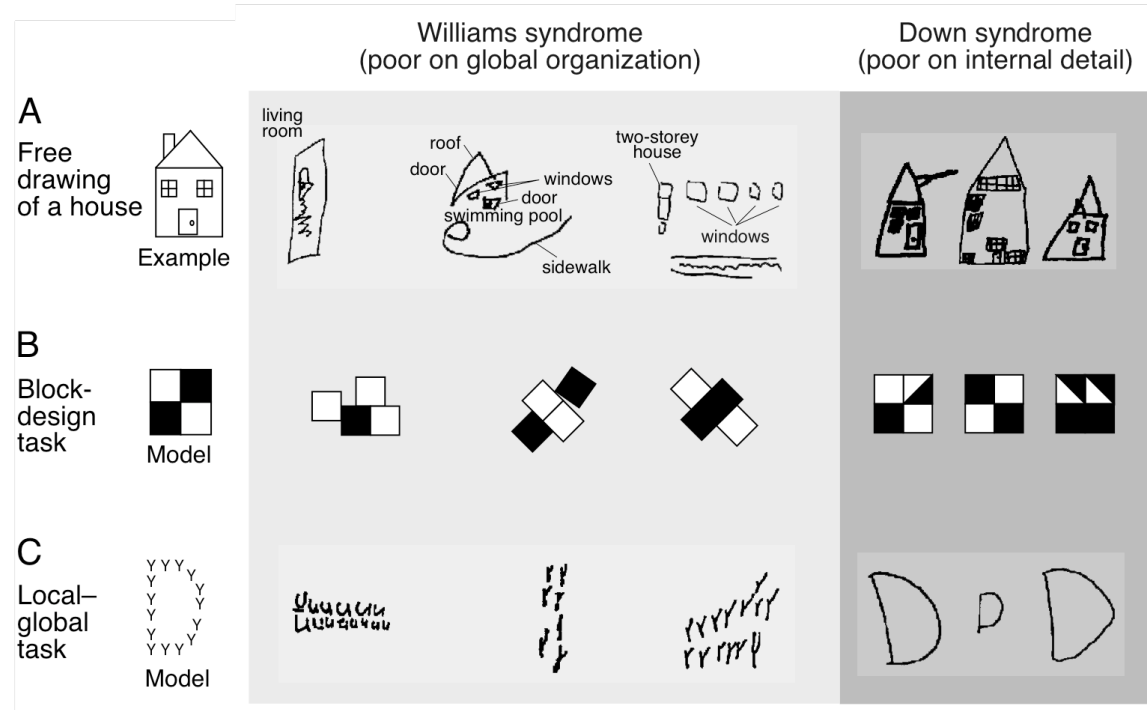
- In studies that examine spatial cognition subjects with WMS are significantly more impaired than subjects with DNS across all age ranges examined.
- Difficulties with spatial cognition
 - Especially with respect to the global, rather than the local, levels of spatial organization

Strengths and Deficits in Visually Based Cognition in WMS



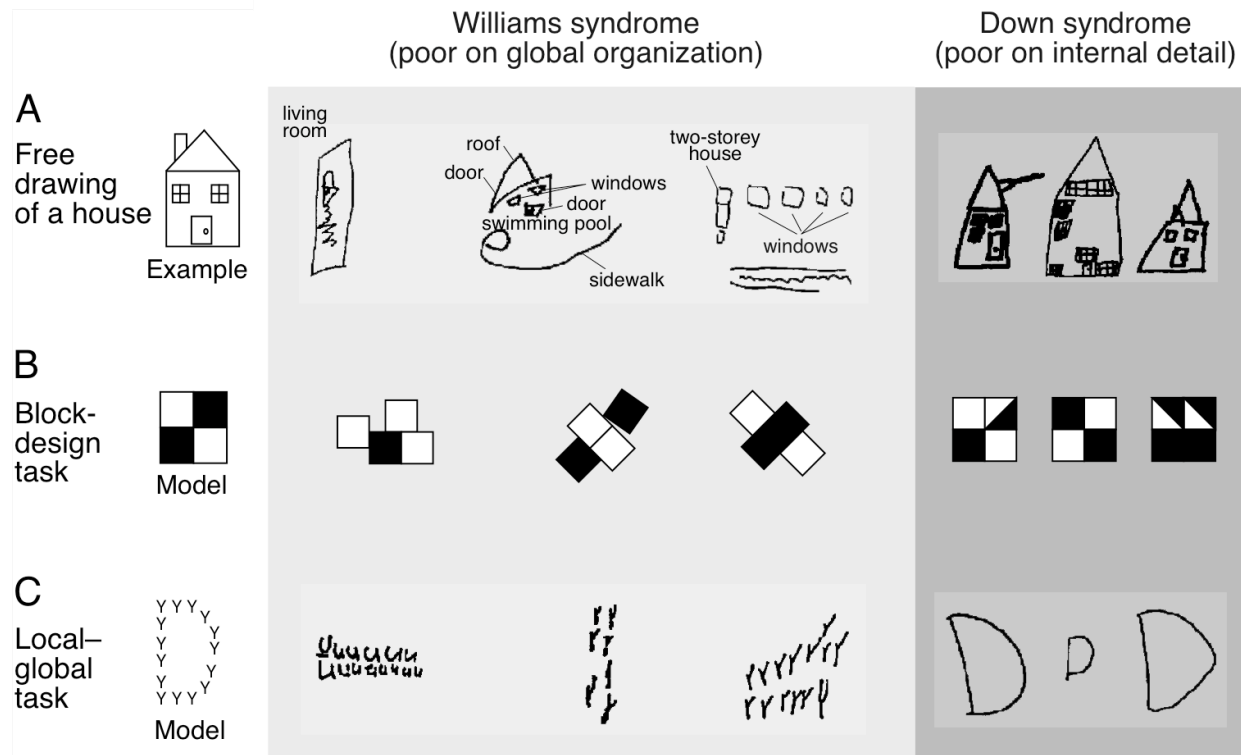
- Lack of cohesion or global organization is typical in drawing by subjects with WMS, while subjects with DNS tend to show a different effect.

Strengths and Deficits in Visually Based Cognition in WMS



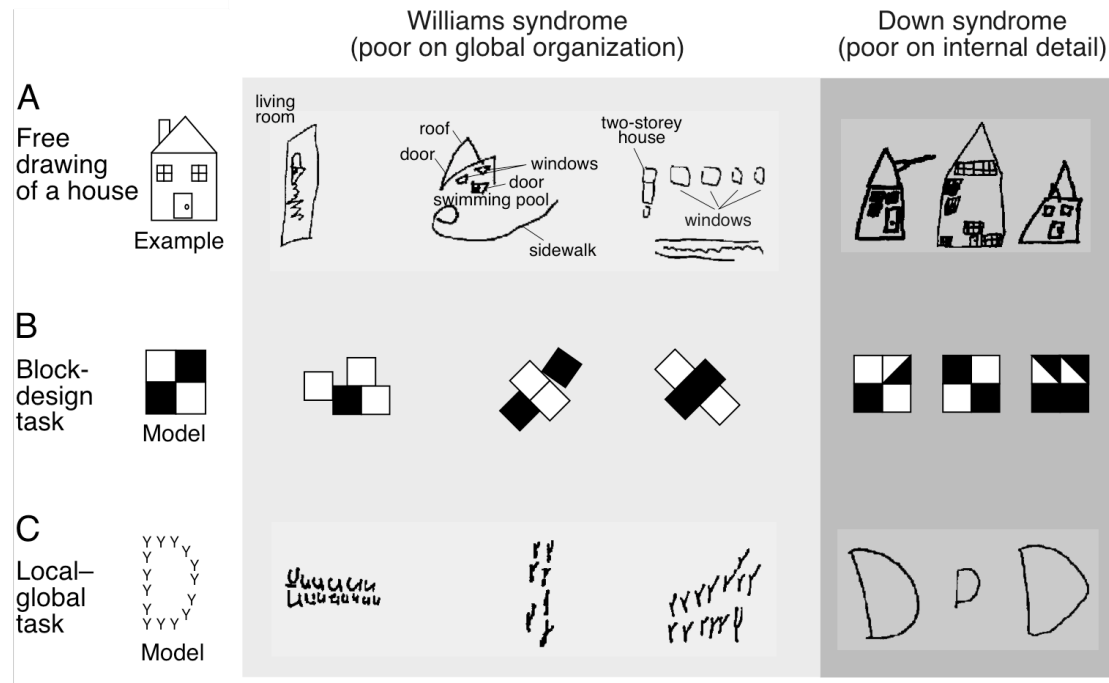
- Free drawing of a house: the windows and doors are separate entities from the house
- The house drawn by the subject with DNS is simplified, but exhibits proper gestalt relationship among elements

Strengths and Deficits in Visually Based Cognition in WMS



- Block design task: both WMS and DNS performed poorly, but in different ways.
 - The WMS subjects couldn't organize the blocks into the overall pattern while the DNS made the error in the internal detail

Strengths and Deficits in Visually Based Cognition in WMS

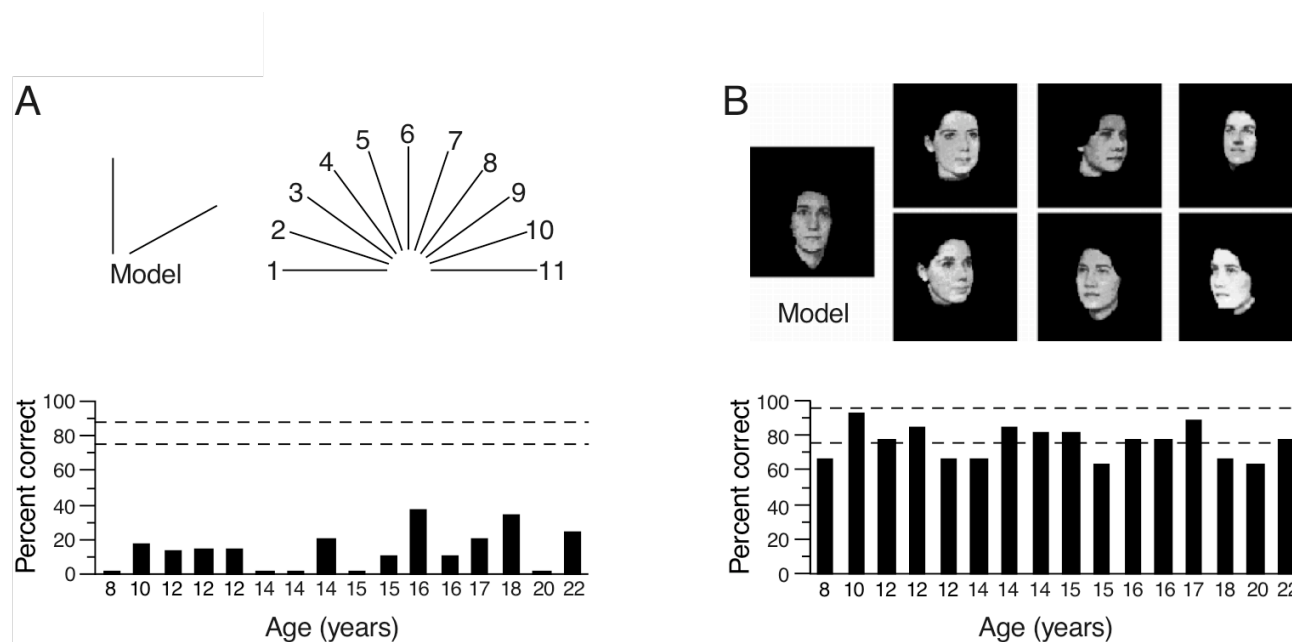


- Local-Global task: WMS subjects fail to produce the global form, the D, but instead draw the local form, a bunch of Y's.
 - DNS subjects do the opposite

Strengths and Deficits in Visually Based Cognition in WMS

- Face processing is a remarkable strength in individuals with WMS, in great contrast to their other visual-spatial cognitive deficits

Strengths and Deficits in Visually Based Cognition in WMS



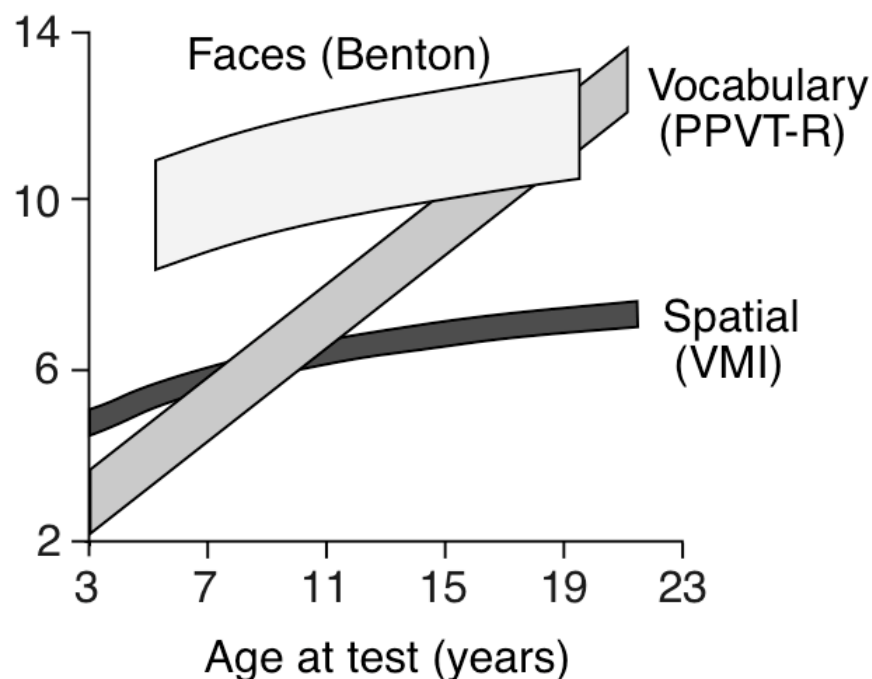
- Individuals with WMS show extreme difficulty with the spatial task
- The same WMS individuals show remarkable strength in the ability to recognize

Different Trajectories in Cognitive Domains

- There are areas of serious deficits:
 - general intelligence
 - visuo-spatial abilities
- But also areas of relative strengths
 - face processing
 - expressive language

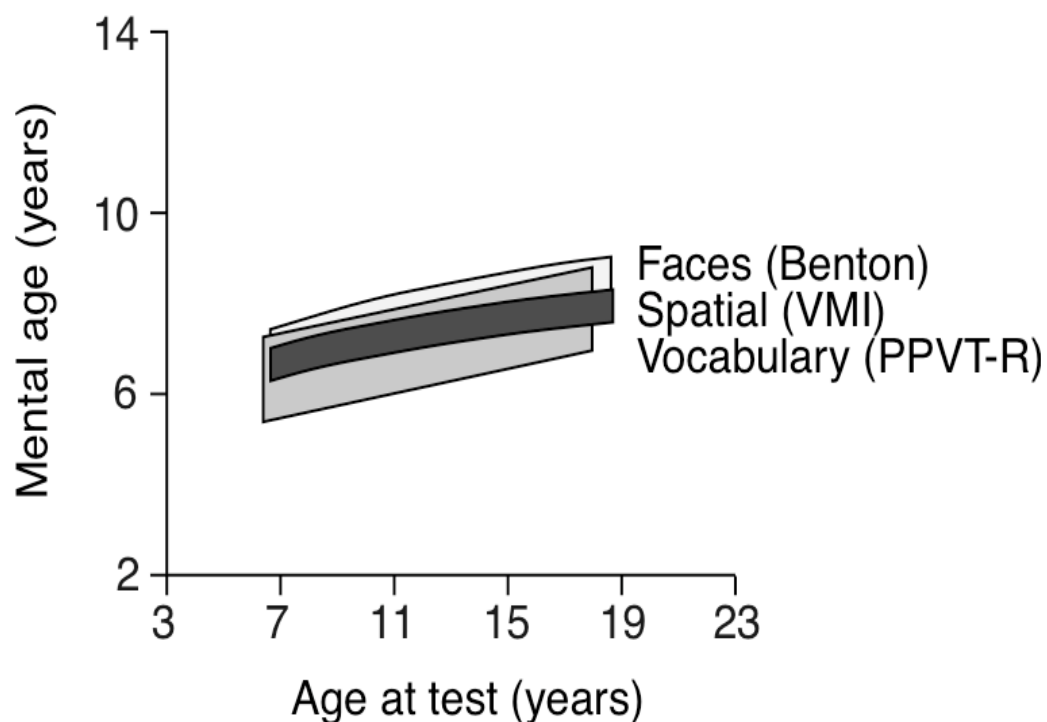
Different Trajectories in Cognitive Domains

- Different trajectories across the three domains reported
 - Lexical knowledge
 - Spatial cognition
 - Face-processing
- Vocab: subjects start with low scores and then show a sharp increase in scores with age
- Spatial cognition: consistently below those of subjects with DNS and plateau at an early age.
- Face processing: subjects perform extremely well even at very young ages.

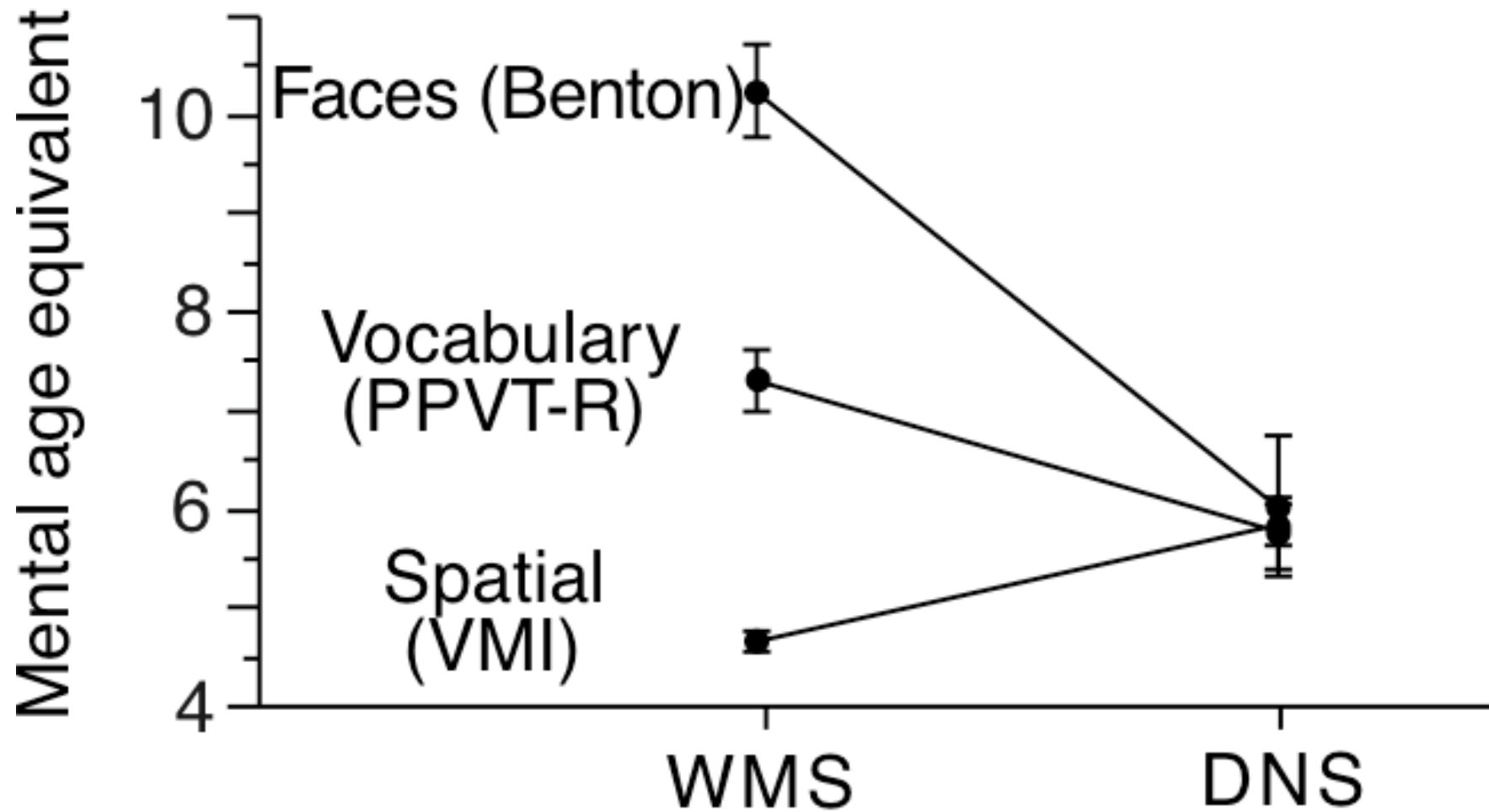


Different Trajectories in Cognitive Domains

- DNS show essentially uniformly depressed development
- Essentially the same developmental trajectories across the three domains



Different Trajectories in Cognitive Domains



This raises some questions:

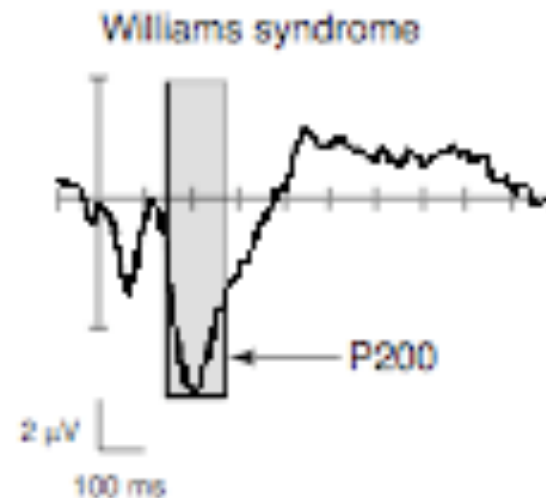
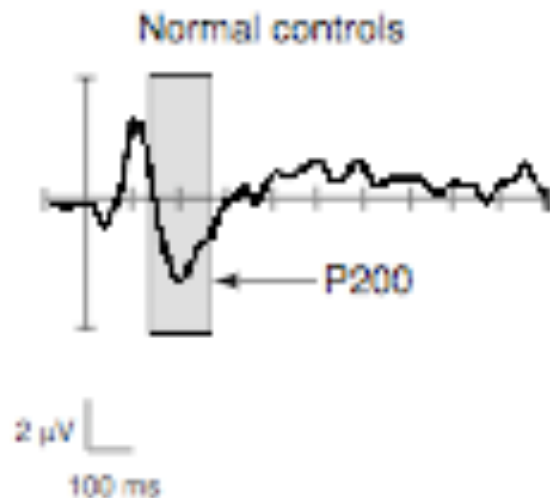
- Do the different cognitive abilities depend on one another or can they be dissociated from one another?
- Do they change throughout development?
- What are the underlying brain systems for these strengths and deficits in abilities in cognitive domains?

Neurophysiological Profile of WMS

- Specific patterns or “markers” are being found through studies of brain function using event-related potentials (ERPs)
- Examples:
 - Auditory Language Processing
 - Face Processing

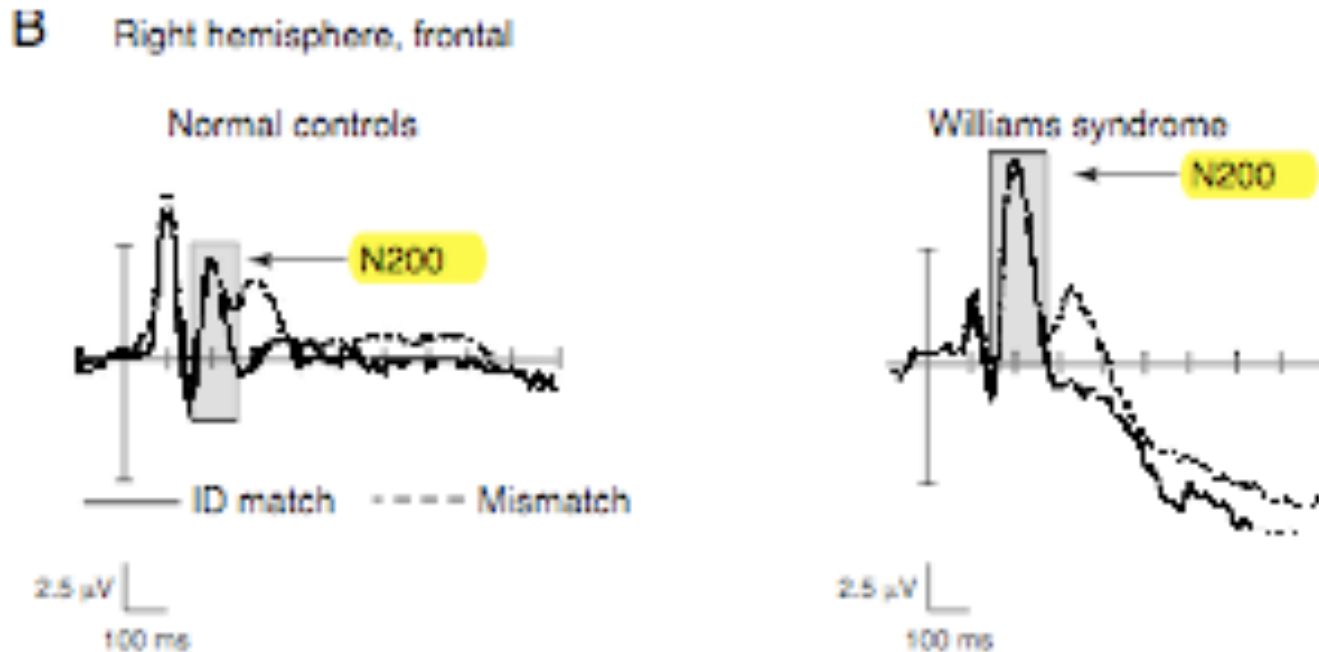
Auditory Language Processing

- To test, they read a sentence where the last word provided good closure or was semantically anomalous
- “ I have five fingers on my moon”
- WMS subjects do not show any difference between open and closed classed words (data not shown). Instead they have a hallmark pattern
- Although WMS has language sparing, the neural organization is different



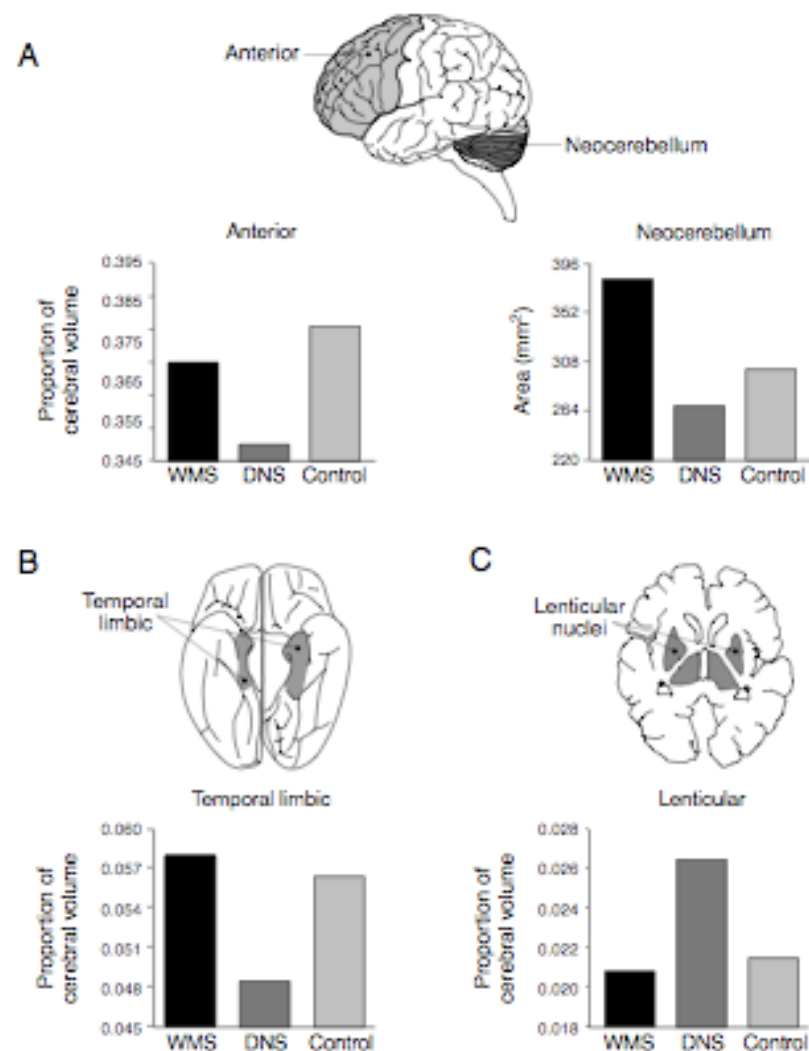
Face Processing

- Saw two sequential faces, subjects had to identify if it was the same face or different
- WMS show large peak at N200 in response to upright faces but not to pictures of objects



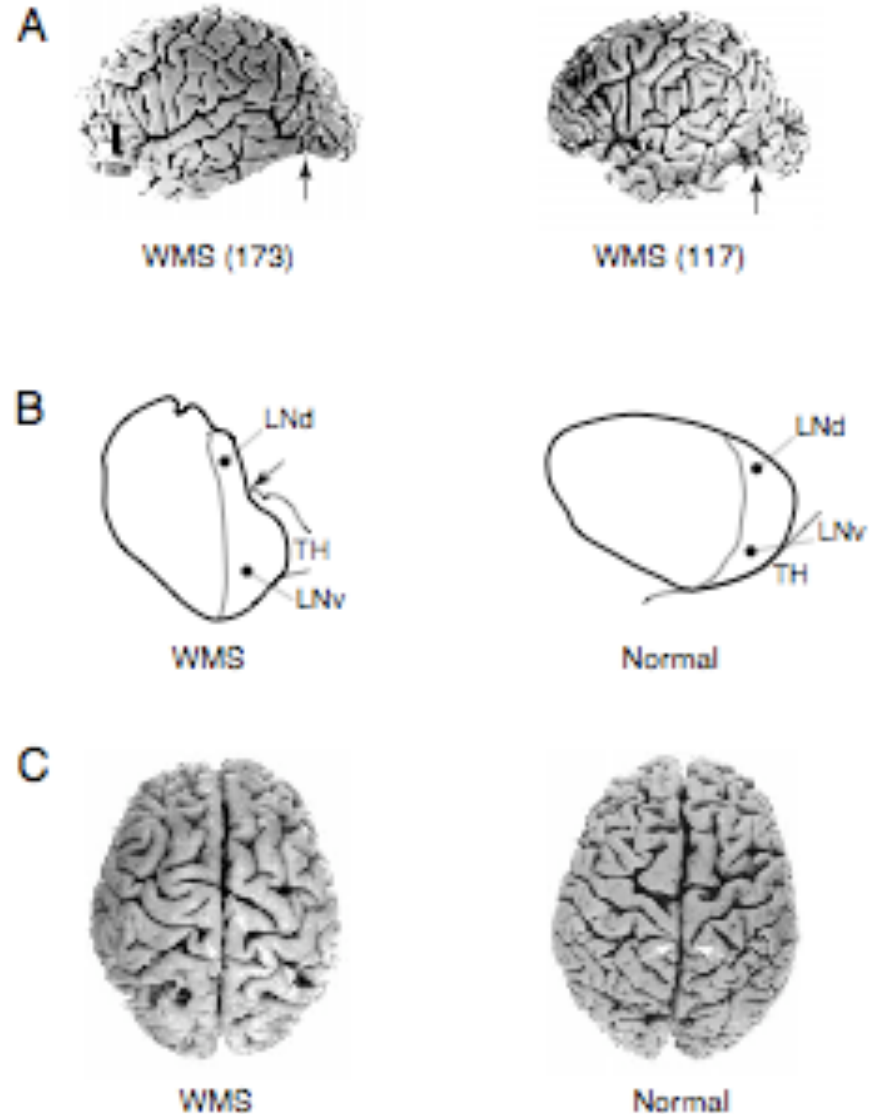
Neuroanatomical profile of WMS

- WMS- normal anterior cortex, spared limbic structures, normal cerebellar size, however neocerebellar lobules are larger
- Intact linguistic function in WMS possibly due to normal development of limbic, frontal and cerebellar structures
- Language subserved by new notion of fronto-cortical-neocerebellar system

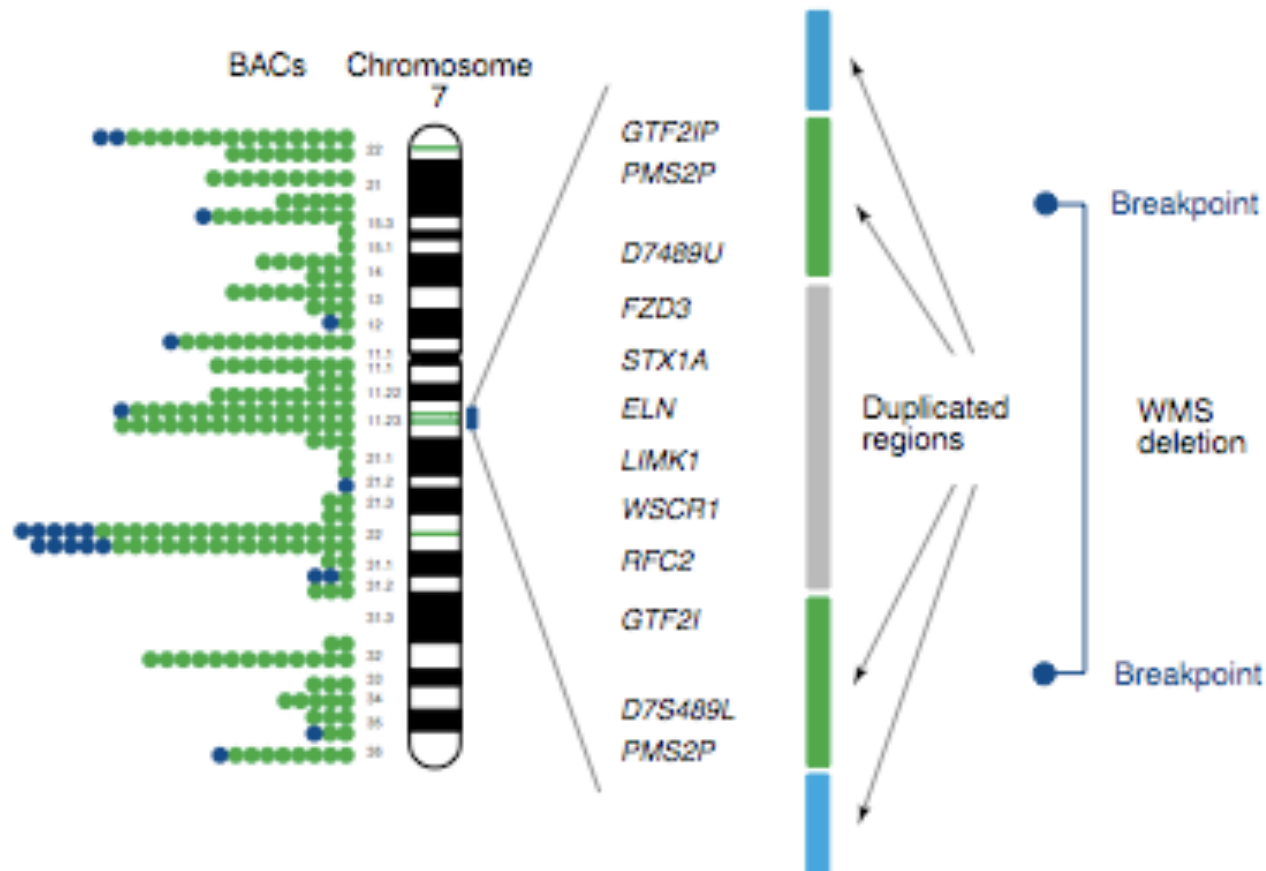


Brain Cytoarchitecture in WMS

- A- small occipital and posterior parietal lobes in 3 out of four brains
- B- decreased amygdala size
- C- central sulcus doesn't reach longitudinal fissure
- Subtle differences due to decreased neuronal population and increased glial population leading to abnormal development



Genetic profile of WMS

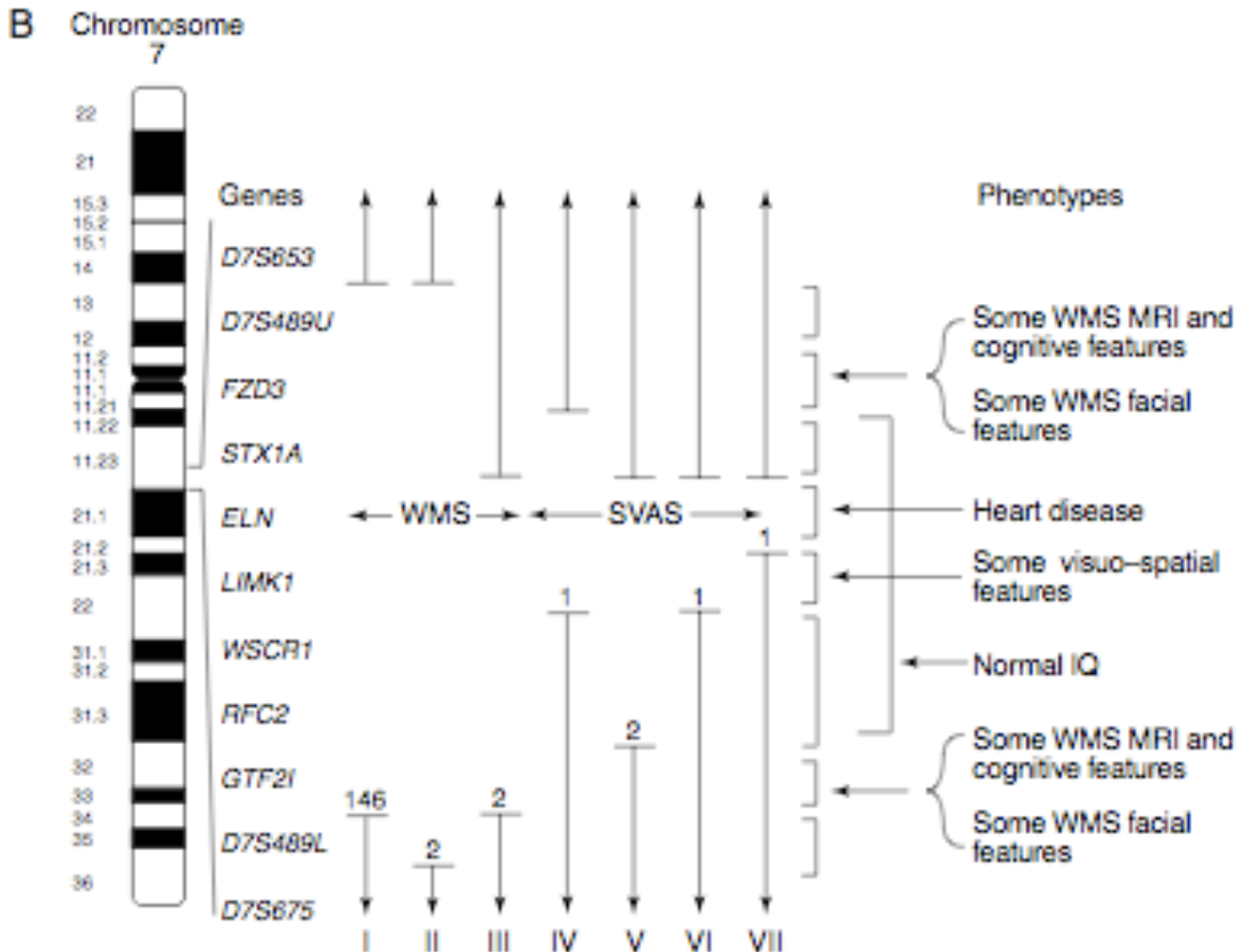


- Deletion on chromosome 7 that includes the gene for elastin, and approximately 20 others
- Gene map of 7q11.2 shows pseudogenes and repeat genes with some single copy genes (elastin)
- Deletion of genes in WMS are usually the same but are located typical points of breaking during meiosis

But what about the uncommon genes?

- Studies of individuals with smaller deletions of uncommon genes not around the breaking point are providing clues for WMS features
- Example of elastin- SVAS
 - frizzled- development of facial, cardiac and mental retardation

How the genes affect phenotype



Summary

- Two possible phenotypic profiles for WMS are emerging
- Neuroanatomy may give insight to development of WMS
- Genetic profile link to phenotypes