Regression (NT & NDDs), the importance of timing and of cross-syndrome comparisons

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NT: Examples of regression/loss of skills in neurotypical development
- Behavioural regression vs representational *progression*
- Balance – synapse strengthening vs pruning weak connections

NDD – Williams syndrome: lack of specialisation/localisation of neural function
possible lack of pruning?

NDD-ASD: Threshold too high – over-aggressive pruning
Regression due to pruning of strong connections,
Sequence of regressive behaviours hypothesized:
sensory -> motor -> language -> executive function

Early differences: ASD-sibs, controls and other NDDs
Behavioural regression vs representational progression in NT language

Past tense/plural marking in early language development:

T-1 Correct: Papa went/Me caught ball/wet feet
Isolated representations

T-2 Behavioural regression: Papa goed/Me catched ball/wet foots
T-2 Representational progression: overgeneralisation of –ed past tense/-s plural patterns

T-3 Correct as at T-1: Papa went/Me caught ball/wet feet
Representations have now become part of a system of morphological markers

Question we must ask of ASD regression:
Is behaviour before regression sustained by same mental reps as behaviour after the regression?
Is child regaining skills, or are the later underlying skills different even if overt behaviour seems the same?
NT loss of skills in infancy: face processing

3-6 month olds: discriminate own-race faces
discriminate other-race faces
discriminate other-species faces

9-10 month-olds: ability lost for other-race/other species
due to pruning of lesser-used connections
and strengthening of used ones

12 months: if experience given at 9 months with faces of
other-race/other species, then ability = retained

Pascalis, Scott, Kelly, Shannon, Nicholson, Coleman & Nelson, 2005
Kelly, Quin, Slater, Lee, Ge & Pascalis 2007
Heron-Delaney, Wirth, & Pascalis, 2011
**NT loss of skills in infancy: speech processing**

<table>
<thead>
<tr>
<th>Age</th>
<th>Ability</th>
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<tbody>
<tr>
<td>3-6 month olds:</td>
<td>discriminate phonemes in native language</td>
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<tr>
<td></td>
<td>discriminate phonemes in non-native languages</td>
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<td>discriminate other-species’ cries??</td>
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Different groups for face/speech. Single *domain-general* mechanism? Need to research faces/speech tasks in *same* infants

**Face and speech processing undergo perceptual narrowing in NT**

**Balance:** strengthening of used connections + pruning of unused connections

*Progressive* specialisation and localisation of neural function

Tees & Werker, 1984  
Nazzi, Jusczyk, & Johnson, 2000  
Maye, Werker & Gerken, 2002  
Best & McRoberts, 2003
Specialization and localisation of brain function are *progressive*.

From de Haan, Pascalis & Johnson, 2002; Halit, de Haan & Johnson, 2005
See, also, Pascalis, deHaan & Nelson, 2002
Hypotheses re NDDs: differences in pruning thresholds and specialisation/localisation of neural function?

NT – Normal pruning threshold
  Balance: strengthening/pruning
  Different timing across neural regions
  Specialisation = experience-dependent, progressive

WS? Under-pruning – imbalance strengthening/pruning?
  Lack of neural specialisation despite behavioural mastery

ASD? Over-pruning – much higher pruning threshold than NT
  Regression seen if development underway, camouflaged if development slow
  Different timing of pruning across neural regions:
    regression: sensori->motor->language->executive function

Huttenlocher & Dabholkar, 1997; Huttenlocher, 2002
Thomas, Knowland, & Karmiloff-Smith, 2011
Hypotheses re NDDs: differences in pruning thresholds and specialisation/localisation of neural function?

NT – Normal pruning threshold
Onset of pruning = timing maturatioanlly constrained (individual differences?)
Different timing across neural regions
Specialisation = experience-dependent, progressive

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Thomas, Knowland, & Karmiloff-Smith, 2011
WS face processing:
behavioural scores “in the normal range”

Different teams worldwide:
WS face processing: ‘in the normal range’
on standarised tasks (Benton, Rivermead)

BUT inversion effect (hallmark of configural processing)
doesn’t emerge developmentally at any age in WS

WS brain signature?

Karmiloff-Smith et al., 2004
Temporal neural signatures for face and car processing in WS

All Ss in “normal range” on standardised face processing tasks

Grice, deHaan, Halit, Johnson, Csibra, & Karmiloff-Smith, 2003
Behavioural scores in normal range… but different *neural* processes

Healthy controls:
Progressive processing restriction of input type

**WS**: failure to specialise

Healthy controls:
Progressive restriction of brain circuits

**WS**: failure to localise

Featural processing
Hypotheses re NDDs: differences in pruning thresholds and specialisation/localisation of neural function?

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Over-pruning hypothesis – ASD?

Not necessarily rare gene mutation but allelic difference in common gene(s) affecting pruning threshold -> exaggeration of normal developmental pruning process - ASD very high pruning threshold means not only weak unused connections are pruned, but also stronger ones -> regression

Pruning occurs at different times in different brain areas (Huttenlocher & Dabholkar, 1997) - Predicts -> first few months, prior to pruning = normal, followed by behavioural symptoms: 1. sensori-motor  2. social/language  3. executive function

Other individual difference factors interact with pruning threshold to create risk, leading to differences in ASD trajectories

Need to consider balance of specialisation vs pruning?  
?NT tasks with at risk ASD infants?

Huttenlocher & Dabholkar, 1997; Huttenlocher, 2002
Thomas, Knowland, & Karmiloff-Smith, 2011
Rogers, 2009; Staples & Reid, 2010
Estes, Zwaigenbaum…IBIS group, 2015
Differences in early development
ASD sibs, controls, other NDDs? What is ASD-specific?

- Atypical saccadic eye movements (WS also)
- Shorter fixation times to social and non-social scenes (Wass et al., 2015) (DS also)
- Attention to eyes declines between 2-6 months (Jones & Klin, 2013) (Rett/FXS?)
- Atypical face processing in infants/adults (featural vs configural) (D’Souza et al. 2015) (WS also)
- Follow head shift but not eye gaze shift (Thorup et al., 2016) (WS also)
- Lack of triadic attention (WS also)
- ERPs to dynamic eye gaze differ (Elsabbaghet al., 2012) (NDDs unknown, being tested)
- EEG frontal-occipital hyperconnectivity (Orekhova et al., 2014) (NDDs unknown, being analysed)
- Disengagement problems (Sacrey, Bryson & Zwaigenbaum, 2013) (WS also)
- Lack of attn to/discrimination of speech/pitch stimuli (D’Souza,Karmiloff-Smith, 2016) (FXS also)
- Enhanced visual search (Kaldy, Kraoewr, Carter & Blaser, 2013; Gliga,et al., 2015) (unique)

Similar cross-syndrome exercise re brain differences

More subtle with cross-syndrome than with NT
Concluding thoughts…

**NT:** initially surplus neurocomputational resources to retain flexible response to environment; then strengthening of used connections/pruning of weak connections to save metabolic costs

**NT:** skills not “regained”; change of underlying representations/change of function

**ASD?** Suffice to have a mutation on a common gene with risk allele regulating pruning threshold. More aggressive, so risk of pruning not only under-used connections but also good ones -> regression.

Regression: If behavioural development slow in ASD, then above could happen before behavioural skills emerge and therefore camouflage regression.

Regression should first occur in sensori-motor patterns:
Parents likely to notice language loss, but loss of reaching/pincer grip?

If pruning too rapid/aggressive -> lack of flexible response to environment -> Rigidity/repetitive behaviours?

Need to focus on individual differences and subtle cross-syndrome comparisons rather than group data compared to NT controls.
Joint work mentioned in talk with past and current Colleagues/Postdocs/Students

Mark Johnson
Gaia Scerif
Michelle de Haan
Sarah Grice
Dean D'Souza
Michael Thomas
Victoria Knowland
Cross-syndrome comparison
WS/DS/FXS/Sibs (MA-matched on Mullen)

- 70% standards: /u/ low pitch
- 15% speech deviants: /i/ low pitch
- 15% pitch deviants: /u/ high pitch

/u/ X 10
/i/ X 8
/u/ X 12
Cross-syndrome neural differences: P3a (250-350ms-attentive orientation) to pitch/speech

Mean P3a amplitude (in microvolts)

Control  Sibs  DS  FXS  WS

Speech  Pitch

pitch  speech

D'Souza, Karmiloff-Smith et al., 2016
Behavioural regression vs representational progression in NT vs Down syndrome

5 and 9 year olds

7 year olds

NT

DS

5yrs  7yrs  9yrs

5yrs  7yrs  9yrs

7yrs  9yrs  11yrs

7yrs  9yrs  11yrs