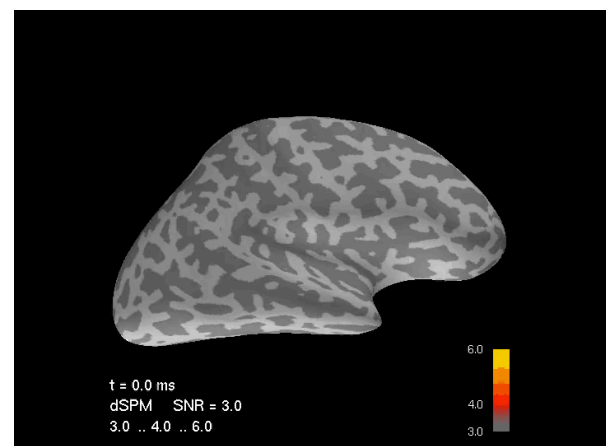
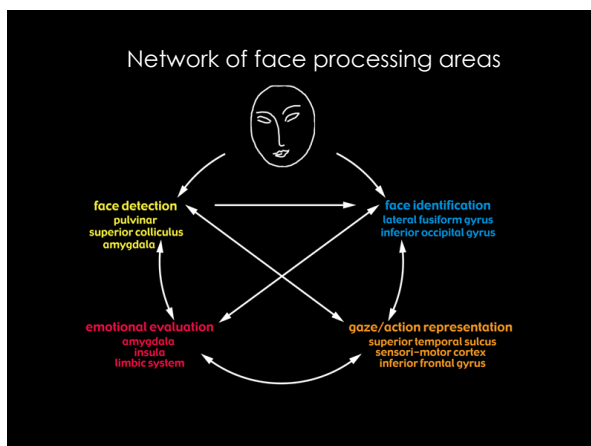
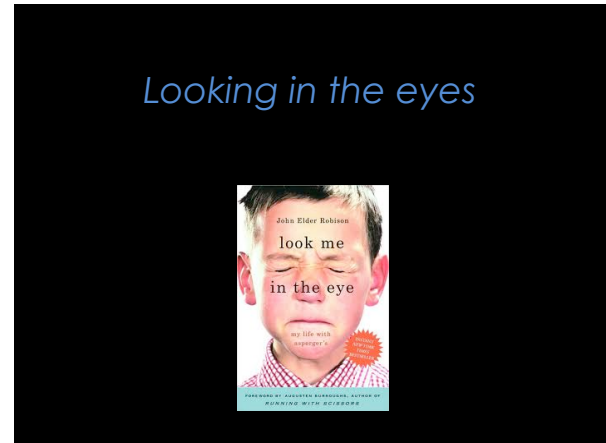
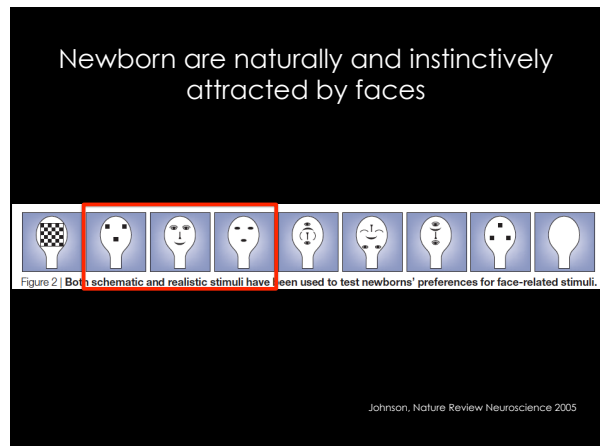
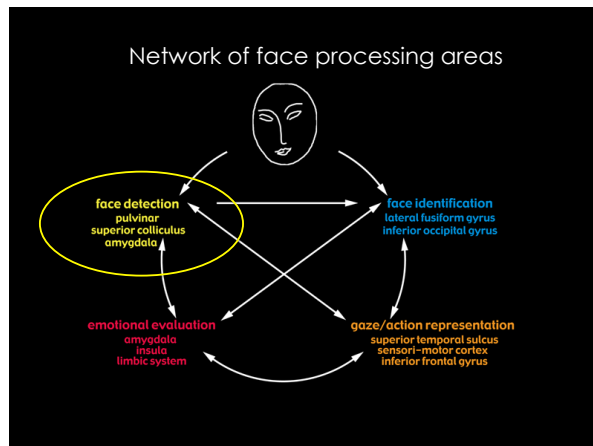


Look me in the eyes – or not?

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 Athinoula A. Martinos Center for Biomedical Imaging  
 Massachusetts General Hospital  
 Harvard Medical School – Boston, USA  
 Gillberg Centrum, Gothenburg, Sweden





Third trimester **fetuses** are instinctively attracted by faces!

Please cite this article as: Reid et al., The Human Fetus Preferentially Engages with Face-like Visual Stimuli, *Current Biology* (2017), <https://doi.org/10.1016/j.cub.2017.05.044>

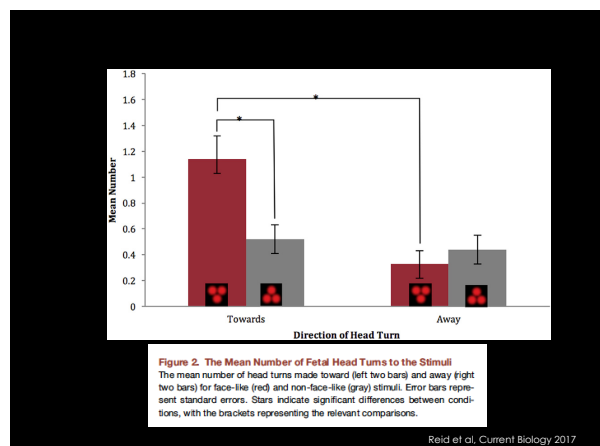
**Current Biology**  
**Report**

**The Human Fetus Preferentially Engages with Face-like Visual Stimuli**

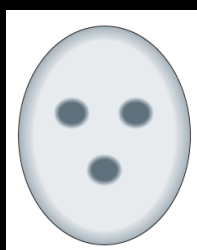
Vincent M. Reid,<sup>1,4,\*</sup> Kirsty Dunn,<sup>1</sup> Robert J. Young,<sup>2</sup> Johnson Amu,<sup>3</sup> Tim Donovan,<sup>4</sup> and Nadja Reissland<sup>1</sup>

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<sup>2</sup>Department of Physics, Lancaster University, Lancaster LA1 4YW, UK  
<sup>3</sup>Department of Obstetrics and Gynaecology, Blackpool NHS Trust, Blackpool FY3 6NR, UK  
<sup>4</sup>Medical and Sports Sciences, University of Cumbria, Lancaster LA1 3JD, UK  
<sup>5</sup>Department of Psychology, Durham University, Durham DH1 3LE, UK

\*Lead Contact  
 \*Correspondence: [v.m.reid@lancaster.ac.uk](mailto:v.m.reid@lancaster.ac.uk)  
<https://doi.org/10.1016/j.cub.2017.05.044>



Stimulus that is optimal to elicit face-related attention in newborns



Johnson, Nature Review Neuroscience 2005

## Newborns have complex face representation!



- In the newborn, it is the SUBCORTICAL system that supports face perception
- Fast pathway
- Enables rapid face detection
- Face detection activates other cortical regions that become important in the adult social brain
- The subcortical route is engaged by eye-contact (both in infants and adults)
- It remains during adult life, and is the basis for blindsight

## The subcortical route

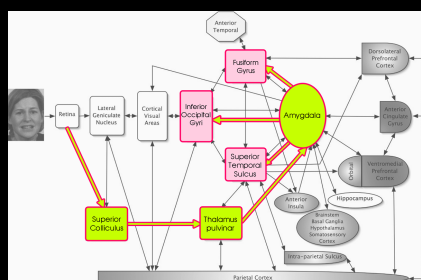
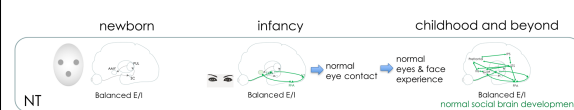


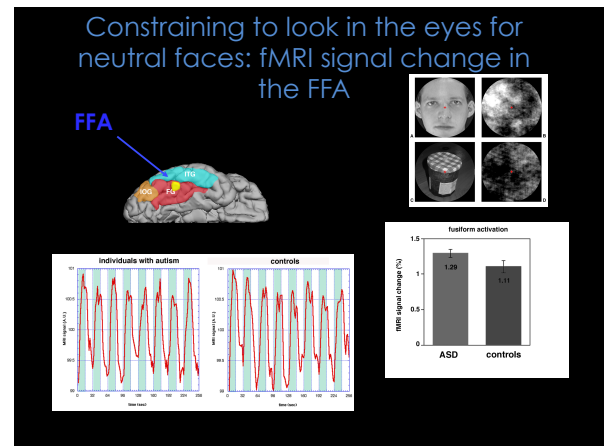
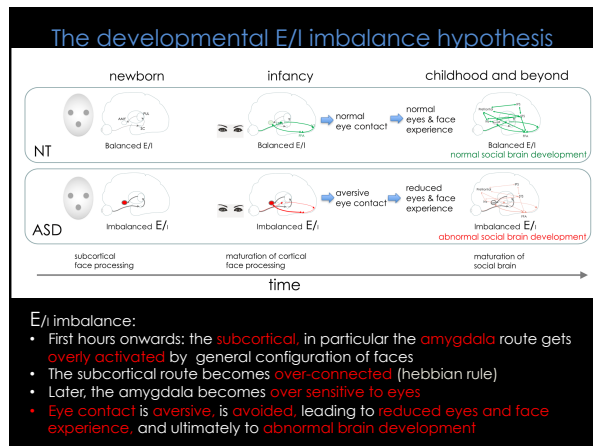
Figure modified from Palermo & Rhodes, Neuropsychologia 2007

## The developmental E/I imbalance hypothesis

### Normal development



- First hours onwards: the subcortical route gets activated by general configuration of faces
- Overtime, the subcortical route, in particular the amygdala, becomes sensitive to eyes, but not oversensitive
- Normal eye-contact leads to normal eyes, gaze and face experience and normal social brain development



Activation of the FFA depends on where they look!

### Gaze fixation and the neural circuitry of face processing in autism

Kim M Dalton<sup>1,2</sup>, Brendon M Nacewicz<sup>2</sup>, Tom Johnstone<sup>2</sup>, Hillary S Schaefer<sup>2</sup>, Morton Ann Gernsbacher<sup>1,3</sup>, H H Goldsmith<sup>1,2</sup>, Andrew L Alexander<sup>1,2,4</sup> & Richard J Davidson<sup>1-4</sup>

Diminished gaze fixation is one of the core features of autism and has been proposed to be associated with abnormalities in the neural circuitry of affect. We tested this hypothesis in two separate studies using eye tracking while measuring functional brain activity during facial discrimination tasks in individuals with autism and in typically developing individuals. Activation in the fusiform gyrus and amygdala was strongly and positively correlated with the time spent fixating the eyes in the autistic group in both studies, suggesting that diminished gaze fixation may account for the fusiform hypoactivation to faces commonly reported in autism. In addition, variation in eye fixation within autistic individuals was strongly and positively associated with amygdala activation across both studies, suggesting a heightened emotional response associated with gaze fixation in autism.

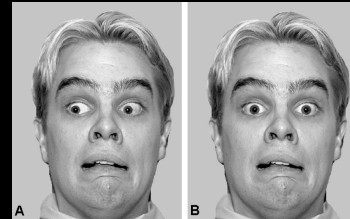
Evidence for an abnormality of the subcortical pathway



"Pointing with the eyes – brain imaging of joint attention deficits in ASD"



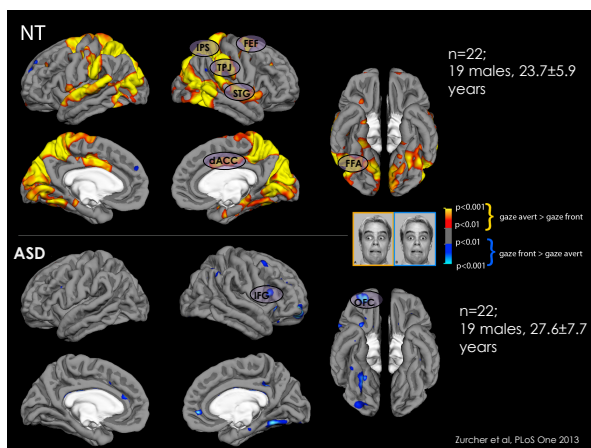
Zurcher et al. PLoS One 2013



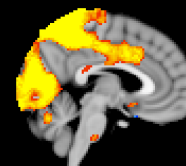
• Making 'theory of mind' inferences by integrating social cues in faces is essential

• In a fearful face, averted gaze signals the presence of a danger, whereas direct gaze is more ambiguous

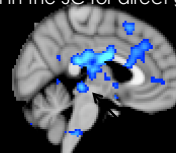
• How do participants with ASD perceive fearful faces gazing towards an unseen danger?



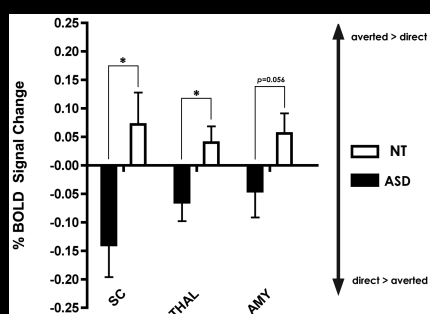
NT: More activation for averted gaze in fearful face



ASD: Almost similar activation for both conditions – more activation in the SC for direct gaze



Zurcher et al. PLoS One 2013



Zurcher et al. PLoS One 2013

Hypersensitivity to low intensity fearful faces in autism when fixation is constrained to the eyes



Lassalle et al., HBM 2017

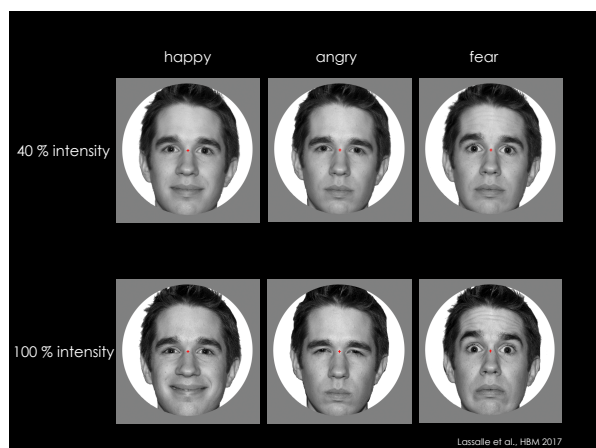
### Constraining to look in the eyes for emotional faces

- Previous studies examining brain activation in ASD for emotional faces did not control that participants looked in the eyes
- They all used very exaggerated expressions

Lassalle et al., HBM 2017

### Ekman emotional faces



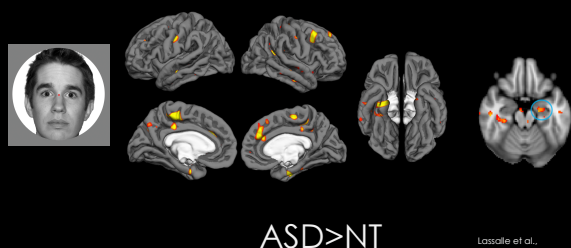


## Experimental design

- ASD:  $n=27$ ;  $23.6 \pm 9.9$  years
- NT:  $n=21$ ;  $19.7 \pm 7.7$  years
- Stimuli presented in blocks, pseudo-random order
- 16 blocks, with 8 different identities in each
- Happy 40%, Happy 100%, Angry 40%, Angry 100%, Fear 40%, Fear 100% and Neutral
- Each stimulus shown for 300ms, followed by 1200 ms red fixation cross
- In  $\frac{1}{2}$  of the blocks, red fixation cross turned blue in one trial, and participants had to press a button (to control for attention)

Lassalle et al., HBM 2017

ASD have **more** activation than NT for low intensity fear



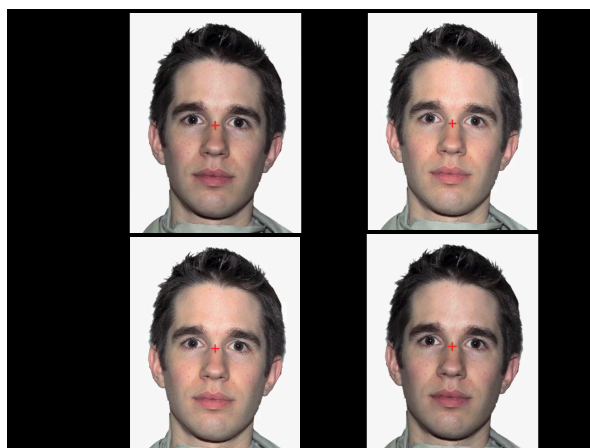
Hyperactivation of the subcortical system in ASD when constrained to look at the eyes

Hadjikhani et al., Nature Scientific Reports 2017

## Experimental design

- ASD:  $n=23$ ;  $22.6 \pm 1.8$  years
- NT:  $n=20$ ;  $23.3 \pm 1.8$  years
- 24 movies created from NimStim database (Happy, Angry, Fear and Neutral)
- Each stimulus lasts 5 seconds: 3 dynamic + 2 static with final expression
- Red fixation cross between movies for 1 second – press if blue
- One version with central cross (CROSS), one without (NO CROSS)
- 2 runs, half participants saw NO CROSS first

Hadjikhani et al., Sci Rep 2017

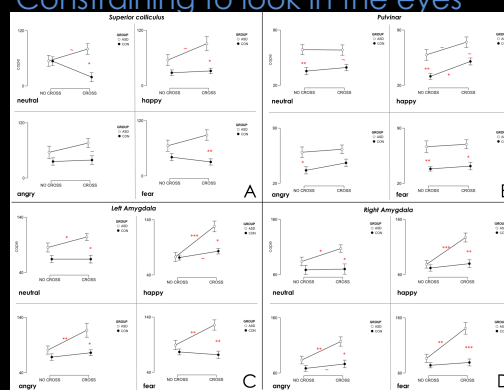


## Experimental design

- For each participant, first compare CROSS vs NO CROSS condition
- Then average of CROSS vs. NO CROSS in ASD and in NT
- Compare groups in regions of interest: subcortical system
  - SUPERIOR COLLICULUS
  - THALAMUS PULVINAR
  - AMYGDALAS

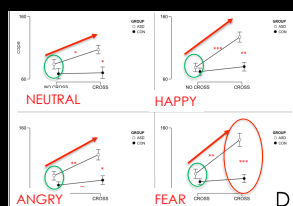
Hadjikhani et al., Sci Rep 2017

## Constraining to look in the eyes



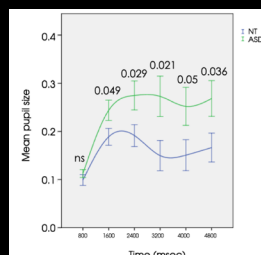
Hadjikhani et al., Nature Scientific Reports 2017

## Amygdala



Hadjikhani et al., Nature Scientific Reports 2017

## Data from eye-tracking



Constraining to look at eyes results in greater pupil dilation in ASD, meaning greater arousal

Work done in collaboration with Daniel Hovey and Jakob Åsberg @ GNC

## Conclusions

- Aberrant activation in the subcortical pathway in ASD when constrained to look in the eyes
- Eye contact is experienced as stressful
- Even for positive emotions

ASD individuals are oversensitive to eye contact, and their avoidance is to reduce over arousal!

Hadjikhani et al., Nature Scientific Reports 2017

## Empathy

- Autism is often reported as a disorder of empathy
- The term empathy is confusing, as it refers to two different concepts: cognitive and affective

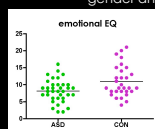
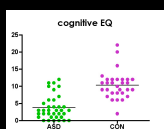
## Empathy

- Cognitive empathy = taking someone else's perspective, put oneself in their shoes; Theory of Mind
  - Medial prefrontal cortex, right TPJ, STS
- Affective empathy = share the feelings of another
  - Pain matrix

## Empathy

- Cognitive empathy is affected in ASD
- Affective empathy is not

## Empathy



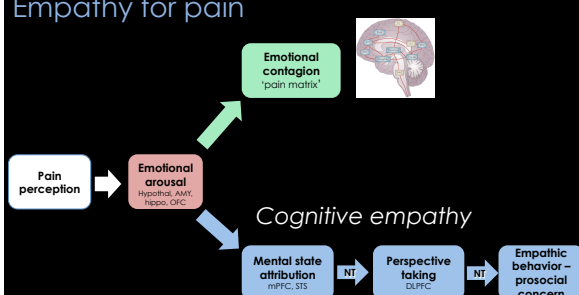
36 adolescents and adults with ASD (33 ♂; 23.5 ± 8.7 (mean age ± SD))  
31 controls, matched for age, gender and IQ

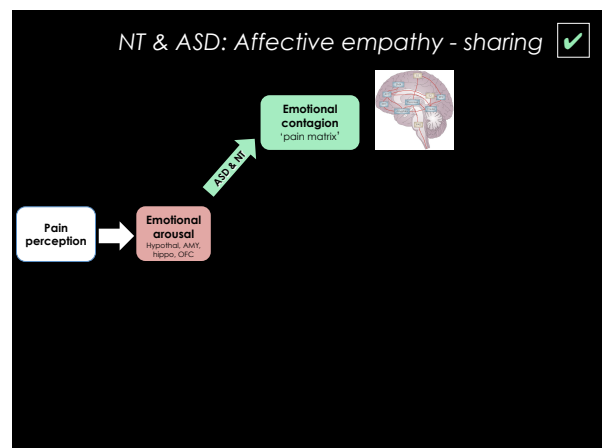
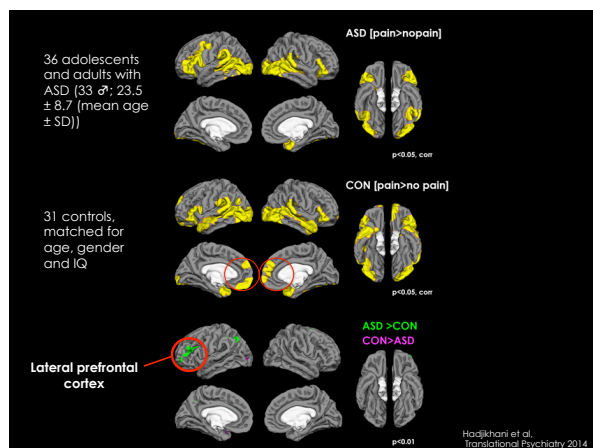
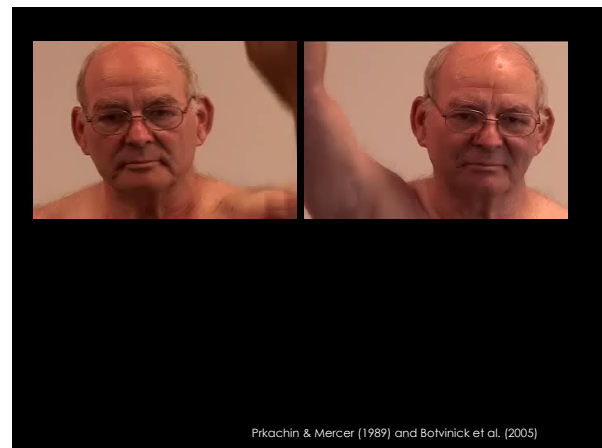
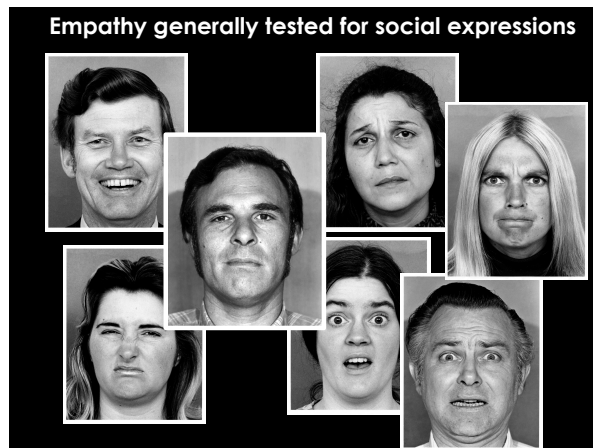
Cognitive empathy (cognitive EQ): perspective taking/theory of mind. Ex: I can tell if someone is masking their true emotion

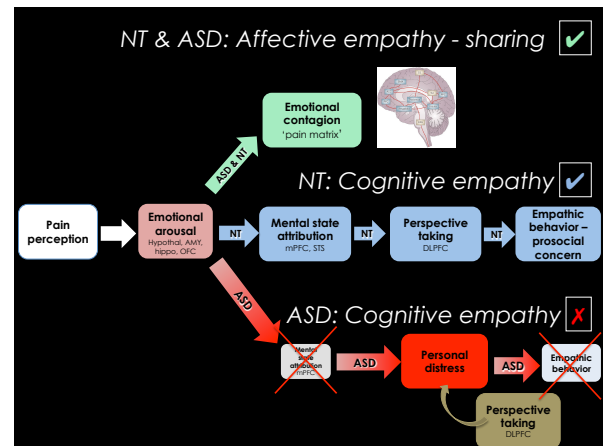
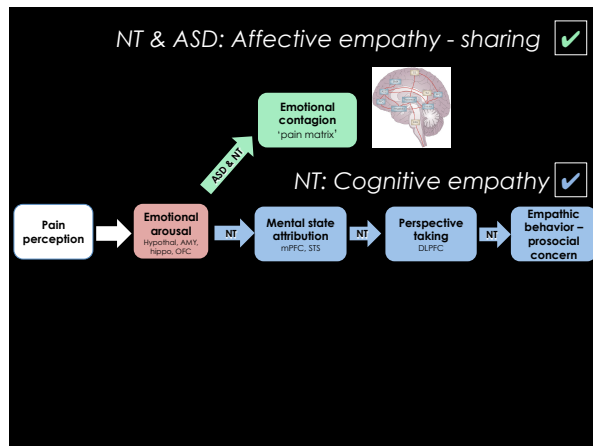
Affective empathy (emotional EQ): I get upset if I see people suffering on news programs

## Empathy for pain

Affective empathy - sharing

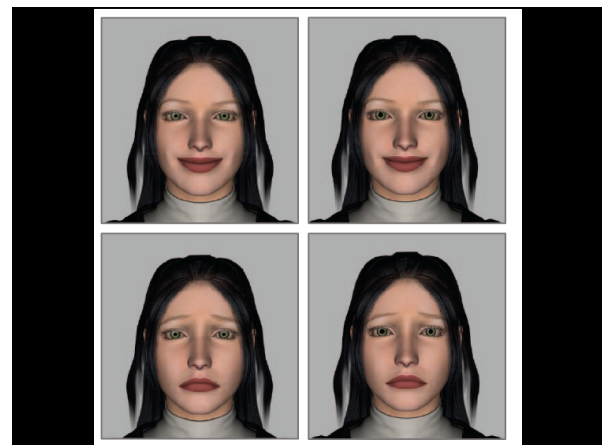




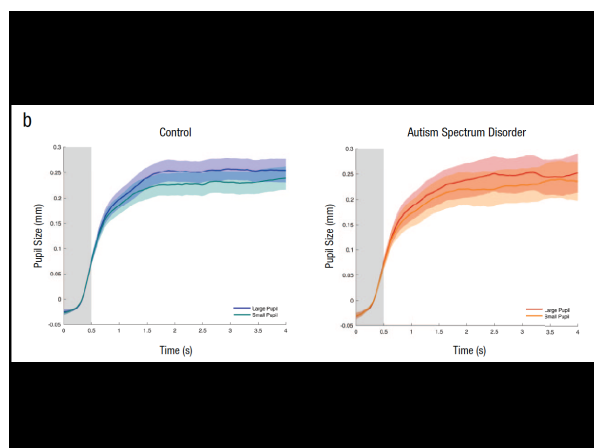


## Pupillary contagion

- Pupillary contagion is an involuntary change in pupil size in response to the pupil size of another person
- Important mechanism for transfer of arousal
- Represents affective empathy contagion
- Present in adults, infants, and even in chimpanzees
- Depends on autonomous nervous system, brainstem pupillary control nuclei (Edinger-Westphal)
- Is it present in autism?







## Pupillary contagion - conclusion

- Is present in ASD
- Even with a shorter duration of fixation in the eyes
- Supports over arousal hypothesis in ASD

Improving emotional face perception in ASD with a diuretic (bumetanide): behavioral and fMRI data

## Why a diuretic ?

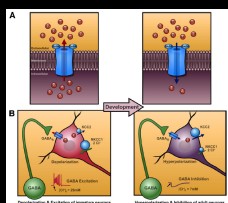
- Evidence for neuronal excitability dysfunction in ASD – high prevalence of epilepsy (~30%) and abnormal EEG in about 60%
- Anecdotal reports of paradoxical effect of GABA agonist Valium on ASD
- GABA – excitatory role during pregnancy, but becomes inhibitory at birth

## Why a diuretic ?

Switch from excitatory to inhibitory linked to decrease in the amount of intracellular chloride

Switch also linked to oxytocin  
Q: Are neurons in ASD reacting as immature neurons?

What will happen if we 'force them to behave as mature' by removing intracellular chloride, with a diuretic, bumetanide?



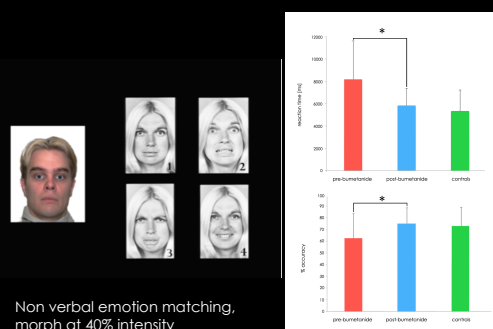
## Improving autism symptomatology with a bumetanide

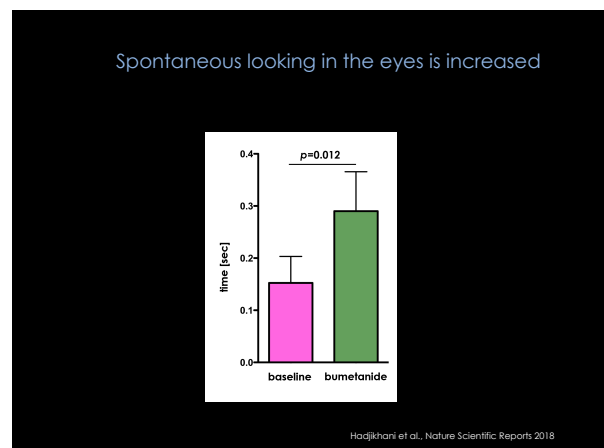
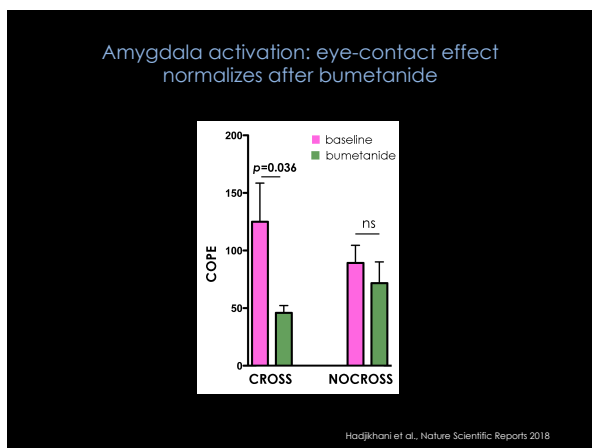
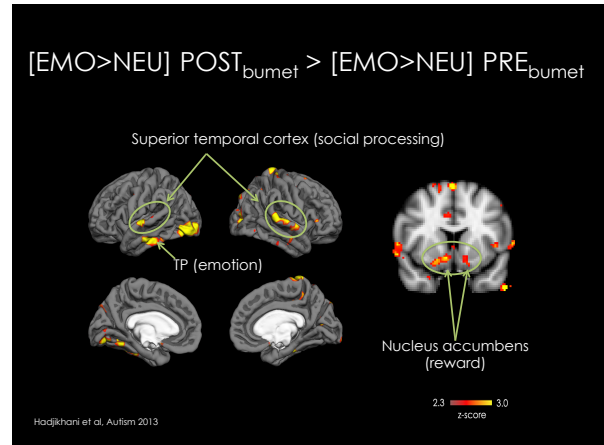
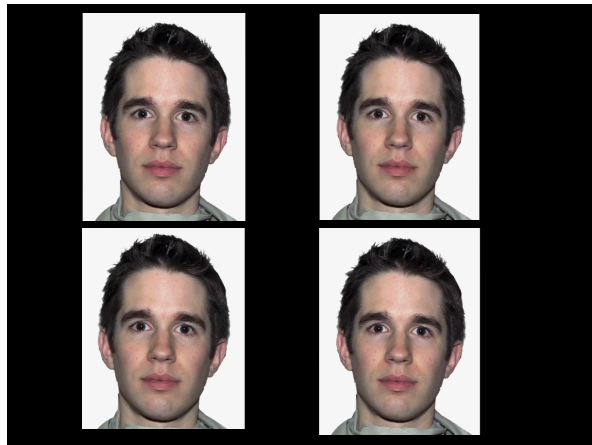
- 2010: pilot open-label study on 5 patients, behavioral improvement with very little side effects (Lemonnier & Ben-Ari, *Acta Paediatrica* 2010)
- 2012: double blind cross over study on 60 participants: significant improvement in autistic symptomatology (Lemonnier et al., *Translat Psy* 2012)
- 2013: proof of concept pilot behavioral and imaging study on 9 (7+2) adolescents before and after 10 months of treatment (Hadjikhani et al, *Autism* 2014)
- 2017: Multicenter phase 2b in children and adolescents: 88 ASD participants (2-18 year old) (Lemonnier et al, *Translational Psychiatry*)
- 2018: Second proof of concept study with brain imaging, showing reduced eye-contact aversion (Hadjikhani et al, *Scientific Reports*)

## Proof of concept pilot studies

- 9 participants with ASD, 7 with treatment and 2 without
- Age at first exam:  $19.3 \pm 4.6$
- Second exam after 10 months of bumetanide treatment (1mg/day)
- Behavioral and fMRI testing at each exam

## Behavioral study – RT and accuracy





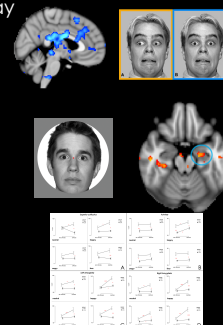
## Bumetanide

- Novel, safe and **etiology-driven** therapy available for a large proportion of ASD.
- The guiding hypothesis is that although a variety of genetic and environmental insults are linked to ASD, **disturbed chloride homeostasis is a common contributing mechanism to pathological brain activity** in ASD and can be treated with the chloride transporter antagonist bumetanide.
- This therapy is safe, given the extensive experience with this drug as a diuretic treatment in children and adults. Side effects are well known: **hypokaliemia and enuresis**.
- In contrast with other existing treatments, the application of bumetanide is etiologically driven and **will not affect the central nervous system in neurons in which chloride homeostasis is unaffected**.

## Conclusions

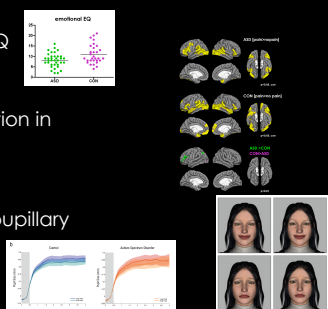
There are evidence of abnormalities in the subcortical pathway

- Abnormal activation in response to gaze cues of danger
- Hypersensitivity to low intensity fearful faces
- Hyperactivation of the subcortical pathway when constrained to look at the eyes

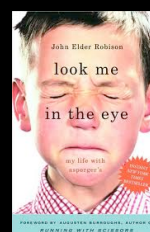


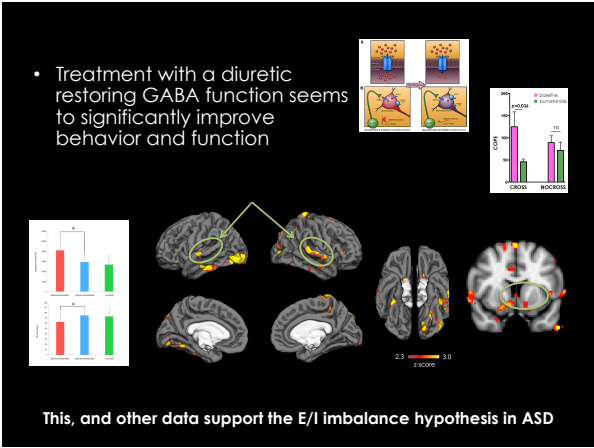
There are evidence of intact affective empathy together with oversensitivity to eye contact

- Normal emotional EQ
- Normal brain activation in response to pain
- Normal involuntary pupillary contagion



- Forcing ASD individuals to look in the eyes may not be such a great idea...





Thank you to:

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And you for your attention!