

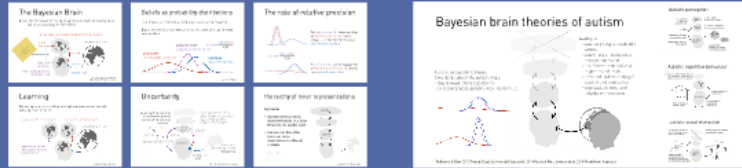
New theories ...

... to explain autism

Research to do

The Bayesian Brain

A computational framework of cognition



Collect evidence

- Apply the theory to existing empirical data
- post-hoc interpretation
- Theory-driven patient studies

Computational Psychiatry

Perception

Action

Perception	Interests	Behaviour	Communication
<ul style="list-style-type: none"> • represent perceptual data • represent uncertainty about perceptual data • represent perceptual data in a way that is useful for action • represent perceptual data in a way that is useful for action • represent perceptual data in a way that is useful for action 	<ul style="list-style-type: none"> • represent interests as a form of uncertainty • represent interests as a form of uncertainty • represent interests as a form of uncertainty • represent interests as a form of uncertainty • represent interests as a form of uncertainty 	<ul style="list-style-type: none"> • represent behaviour as a form of uncertainty • represent behaviour as a form of uncertainty • represent behaviour as a form of uncertainty • represent behaviour as a form of uncertainty • represent behaviour as a form of uncertainty 	<ul style="list-style-type: none"> • represent communication as a form of uncertainty • represent communication as a form of uncertainty • represent communication as a form of uncertainty • represent communication as a form of uncertainty • represent communication as a form of uncertainty

Weak central coherence (Happé & Frith 2006)
 Reduced social motivation (Chevallier et al., 2012)
 Theory of mind deficit (Baron-Cohen et al. 1995)
 Reduced social salience (Hiri et al. 2020)
 Executive dysfunction (Owen et al. 2011)

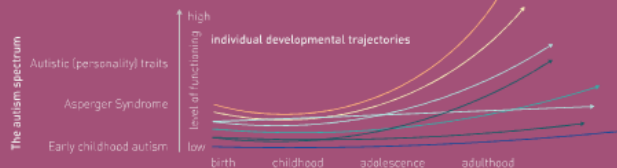
Previous theories

a lack of a pathomechanistic model and superficially defined diagnostic criteria
 fail to capture the huge variance in developmental trajectories

Past

Autism

Autism Spectrum	Asperger Syndrome	High Functioning Autism	Autism	Autism Spectrum	Autism Spectrum
IQ > 70	IQ > 70	IQ > 70	IQ > 70	IQ > 70	IQ > 70
IQ < 70	IQ < 70	IQ < 70	IQ < 70	IQ < 70	IQ < 70



Current clinical problems

Diagnosis	Behavioural Phenotype	Pathophysiology
Autism	Autism	Autism
Autism	Autism	Autism

Present

Understanding and explaining the huge variance, to affected, to relatives, to clinicians, ...

Diagnosing quick, easy to apply, reliable tests

Treating mechanistically informed psychotherapeutic and pharmacological concepts

Potential benefits

Future





Translational Neuromodeling Unit

Autism

Current clinical problems
and how they can benefit from computational psychiatry

Computational Psychiatry Course
Zürich, 29. August 2016

Helene Haker (haker@biomed.ee.ethz.ch)
Translational Neuromodeling Unit, Zürich



Universität
Zürich^{UZH}

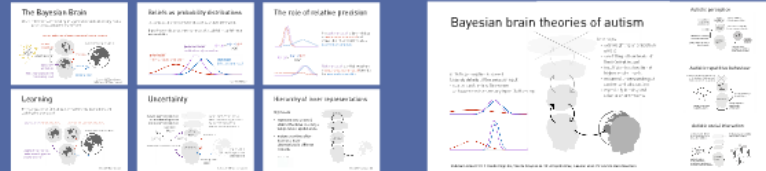
ETH

Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

New theories ...

The Bayesian Brain

A computational framework of cognition



... to explain autism

Research to do

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- post-hoc interpretation

- Theory-driven patient studies

Computational Psychiatry

Perception

Action

Perception	Interests	Behaviour	Communication
<ul style="list-style-type: none"> • sensory processing • sensory prediction • sensory prediction error • sensory prediction error • sensory prediction error • sensory prediction error • sensory prediction error • sensory prediction error • sensory prediction error • sensory prediction error 	<ul style="list-style-type: none"> • reduced attention to social interaction • reduced attention to social interaction • reduced attention to social interaction • reduced attention to social interaction • reduced attention to social interaction • reduced attention to social interaction • reduced attention to social interaction • reduced attention to social interaction • reduced attention to social interaction • reduced attention to social interaction 	<ul style="list-style-type: none"> • repetitive behaviours • repetitive behaviours • repetitive behaviours • repetitive behaviours • repetitive behaviours • repetitive behaviours • repetitive behaviours • repetitive behaviours • repetitive behaviours • repetitive behaviours 	<ul style="list-style-type: none"> • reduced social interaction • reduced social interaction • reduced social interaction • reduced social interaction • reduced social interaction • reduced social interaction • reduced social interaction • reduced social interaction • reduced social interaction • reduced social interaction

Weak central coherence
Happé & Frith 2006

Reduced social motivation
Charlier et al. 2012

Theory of mind deficit
Baron-Cohen et al. 1995

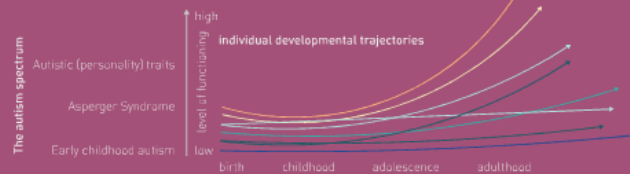
Reduced social salience
Klin et al. 2002

Executive dysfunction
Ozonoff et al. 1991

Previous theories

a lack of a pathomechanistic model and superficially defined diagnostic criteria fail to capture the huge variance in developmental trajectories

Autism



Current clinical problems



Understanding and explaining the huge variance, to affected, to relatives, to clinicians, ...

Diagnosing quick, easy to apply, reliable tests

Treating mechanistically informed psychotherapeutic and pharmacological concepts


Potential benefits

Past

Present

Future





 Translational Neuroimaging 08


Autism
 Current clinical problems
 and how they can benefit from computational psychiatry

Computational Psychiatry Course
 Zürich, 29. August 2016

Helene Mader (hmader@translational.unizh.ch)
 Translational Neuroimaging Unit, Zürich

 Universität Zürich  ETH Zürich

Autism

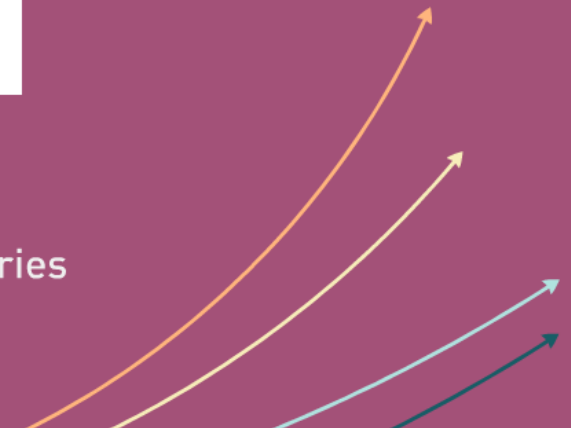
Autism Spectrum Disorders	Diagnostic criteria ICD-10	Perception	Interests	Behaviour	Communication
	F81 Disorders of psychological development F81.0 Pervasive developmental disorders Linking <ul style="list-style-type: none"> • difficulties in social interaction • difficulties in communication • restricted, repetitive behaviour Asperger syndrome (F84.0) vs. childhood autism (F84.0) <ul style="list-style-type: none"> • no general cognitive retardation (IQ > 70) • no retardation of language development 	<ul style="list-style-type: none"> • sensory peculiarities • enhanced sensations (e.g. sounds, visual detail) • reduced (e.g. temperature) • reduced habituation to continuous stimuli • distractibility • focus on details vs. the „big picture“ • focus on formal aspects vs. meaning 	<ul style="list-style-type: none"> • reduced attraction by social/emotional stimuli • focus on inanimate environment (facts) • rationally understandable • stable and predictable • pleasure by repetition of well known thing/actions • reduced exploration of new thing/actions 	<ul style="list-style-type: none"> • clumsy motor skills • difficulties with: <ul style="list-style-type: none"> • complex action sequences • e.g. delay routines (interference game) • intuitive actions • read previously social interactions (not predictable) • compensation by fixed routines („rituals“) • resistance against change 	<ul style="list-style-type: none"> • avoid seems forms lacking verbal communication • reduced non-verbal communication <ul style="list-style-type: none"> • reduced storage possibly, memory, gesture • apical communication style <ul style="list-style-type: none"> • they say what they mean • concerned facts, truth, reality • (less on behavioural, need and the other)

spectrum

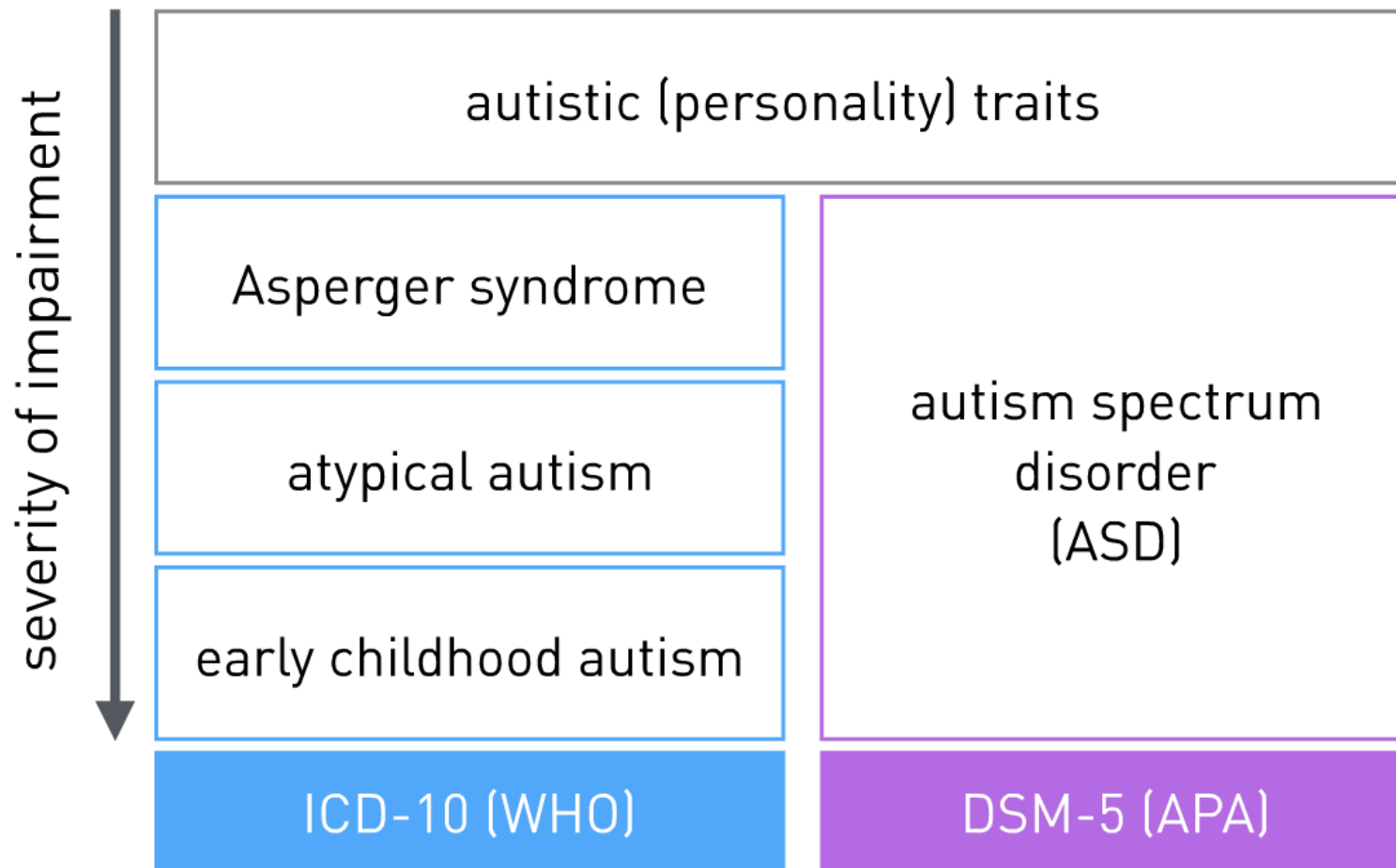
Autistic (personality) traits

high
functioning

individual developmental trajectories



Autism Spectrum Disorders



Diagnostic criteria ICD-10

F8 Disorders of psychological development

F84 Pervasive developmental disorders

Lifelong

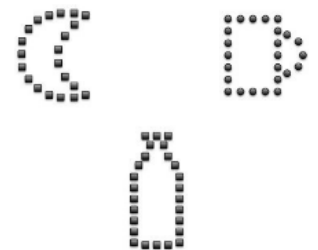
- difficulties in **social interaction**
- difficulties in **communication**
- restricted, **repetitive behaviour**

Asperger syndrome (F84.5) vs. childhood autism (F84.0):

- no general cognitive retardation (IQ >70)
- no retardation of language development

Perception

- sensory peculiarities
 - enhanced sensations (e.g. sounds, visual detail)
 - reduced (e.g. temperature)
- reduced habituation to continuous stimuli
 - distractability
- focus on details vs. the „big picture“
- focus on formal aspects vs. meaning





Interests

- reduced attraction by social/emotional stimuli
- focus on inanimate environment (facts)
 - rationally understandable
 - stable and predictable
- pleasure by repetition of well known things/actions
- reduced exploration of new things/actions

Behaviour

- clumsy motor skills
- difficulties with
 - complex action sequences
e.g. daily routines (interference prone)
 - intuitive actions
most prominently: social interactions (not predictable)
- compensation by fixed routines („rituals“)
- resistance against change

Communication

- most severe forms: lacking verbal communication
- reduced non-verbal communication
 - reduced/strange prosody, mimics, gestures
- explicit communication style
 - they say what they mean
 - oriented on facts, truth, reality
(less on the emotional reaction of the other)

Autism

Autism Spectrum Disorders



Diagnostic criteria ICD-10

- F84 Disorders of psychological development**
F84.0 Pervasive developmental disorders
- Autism**
- Difficulties in social interaction
 - Difficulties in communication
 - Restricted, repetitive behaviour
- Asperger syndrome (F84.1) vs. childhood autism (F84.0)**
- no general cognitive retardation (IQ > 70)
 - no retarded oral language development

Perception

- sensory peculiarities
- enhanced sensations (e.g. sounds, visual detail)
- reduced (e.g. temperature)
- reduced habituation to continuous stimuli
- distractibility
- focus on details vs. the „big picture“
- focus on formal aspects vs. meaning

Interests

- reduced attraction by social/personal stimuli
- focus on inanimate environment (facts)
- rationally understandable
- stable and predictable
- pleasure by repetition of well known things/actions
- reduced exploration of new things/actions

Behaviour

- stereotyped skills
- rituals with
- complex action sequences (e.g. rote routines, interference proof)
- obsessive actions
- social (preference) social interactions (not and visual)
- compulsions (fixed routines, rituals)
- resistance against change

Communication

- most severe forms: lacking verbal communication
- reduced non-verbal communication
- reduced language fluency, syntax, semantics
- explicit communication style
- pragmatic language skills
- semantic fluency, syntax, semantics (less on the individual function of the other)

The autism spectrum

Autistic (personality) traits

Asperger Syndrome

Early childhood autism

high

level of functioning

low

individual developmental trajectories

birth

childhood

adolescence

adulthood

Current clinical problems

Diagnosis

- Gold standard diagnostic procedures (ADOS/ADI-R)
- are well established only for severely affected young children
- are time consuming and rely on expert knowledge
- No individual operationalized diagnostic procedure for less severely affected and older individuals
- careful clinical observation by experienced clinicians
- time consuming
- experts are still scarce

Behavioral-/Psychotherapy

- Well established treatment concepts exist
- for severely affected young children (ABA)
- for less severely affected teenagers (social training)
- But lack
- for severely affected adults (without spoken language)
- for hidden symptoms, e.g. sensory affected adults
- for the action-specific treatment of associated disorders (e.g. anxiety disorders, psychosis, ...)

Pharmacotherapy

- No pharmacologically grounded pharmacotherapy
- with weak effect of developmental trajectory
- No individual prediction of treatment response
- for treatment of symptoms in adulthood (behavioural traits, and disorders, ...)

Diagnosis

- Gold-standard diagnostic procedures (ADOS/ADI-R)
 - are well validated **only for severely affected young children**
 - are time consuming and rely on specifically trained staff
- **No (validated) operationalized diagnostic procedure for less severely affected and older individuals**
 - careful clinical exploration by experienced clinicians
 - time consuming
 - experts are (still) rare

Behavioral-/Psychotherapy

- Well established treatment concepts exist
 - for severely affected young children (ABA)
 - for less severely affected teenagers (social training)
- but lack
 - for severely affected adults (without spoken language)
 - for hidden symptoms in less severely affected adults
 - for the autism-specific treatment of comorbidities (depression, addiction, eating disorders, psychoses, ...)

Pharmacotherapy

- No pathomechanistically grounded pharmacotherapy
 - with studied effect of developmental trajectory
- No individual prediction of treatment response
 - for treatments of symptoms in adulthood
(with stimulants, antidepressants, ...)

Autism

Autism Spectrum Disorders



Diagnostic criteria ICD-10

- F84 Disorders of psychological development**
F84.0 Pervasive developmental disorders
- Asperger syndrome**
- Difficulties in social interaction
 - Difficulties in communication
 - Restricted, repetitive behaviour
- Asperger syndrome (F84.0) vs. childhood autism (F84.0)**
- no general cognitive retardation (IQ > 70)
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Perception

- sensory peculiarities
- enhanced sensations (e.g. sounds, visual detail)
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- focus on details vs. the „big picture“
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Interests

- reduced attraction by social/personal stimuli
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Behaviour

- stereotyped skills
- rituals with
- complex action sequences (e.g. rote routines, interference proof)
- obsessive actions
- social (preference) social interactions (not and visual)
- compulsions (fixed routines, rituals)
- resistance against change

Communication

- most severe forms: lacking verbal communication
- reduced non-verbal communication
- reduced language proficiency, syntax, semantics
- explicit communication style
- poor conversational skills
- monotonous, high-pitched, noisy (less on the emotional function of the other)

The autism spectrum

Autistic (personality) traits

Asperger Syndrome

Early childhood autism

high

level of functioning

low

individual developmental trajectories

birth

childhood

adolescence

adulthood

Current clinical problems

Diagnosis

- Gold standard diagnostic procedures (ADOS/ADI-R)
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- for severely affected adults (without spoken language)
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- for the action-specific treatment of associated disorders (e.g. anxiety disorders, psychosis, ...)

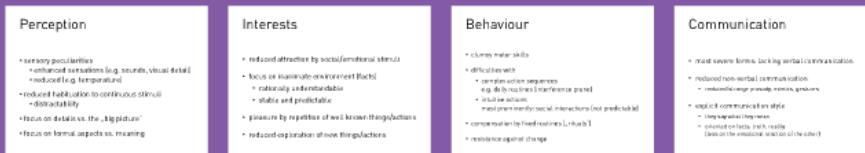
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Perception

Action



Weak central coherence
Happé & Frith 2006

Reduced social motivation
Chevallier et al. 2012

Theory of mind deficit
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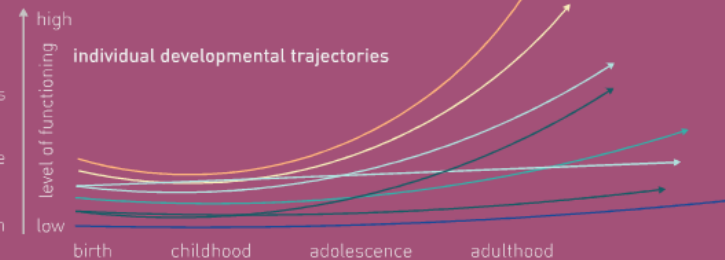
Past

Autism



The autism spectrum

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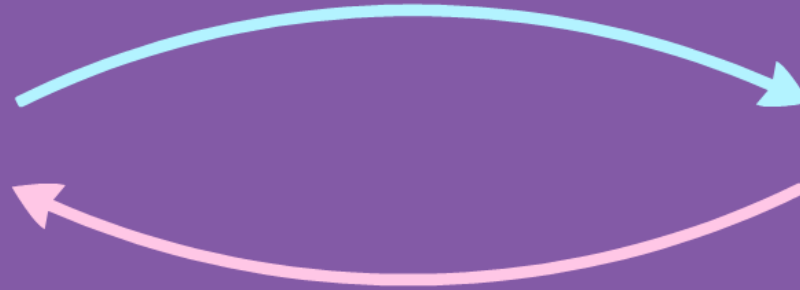


Current clinical problems



Present

Perception



Action

Perception

- sensory peculiarities
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 - reduced (e.g. temperature)
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 - distractability
- focus on details vs. the „big picture“
- focus on formal aspects vs. meaning

Interests

- reduced attraction by social/emotional stimuli
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 - rationally understandable
 - stable and predictable
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Behaviour

- clumsy motor skills
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 - they say what they mean
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(less on the emotional reaction of the other)

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Executive dysfunction

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Previous theories

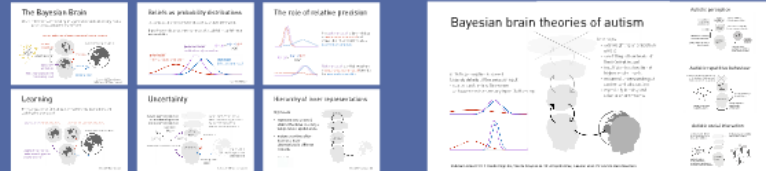
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... to explain autism

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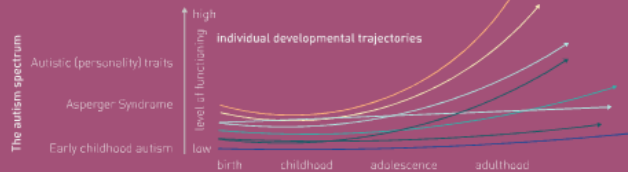
Computational Psychiatry

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Past

Present

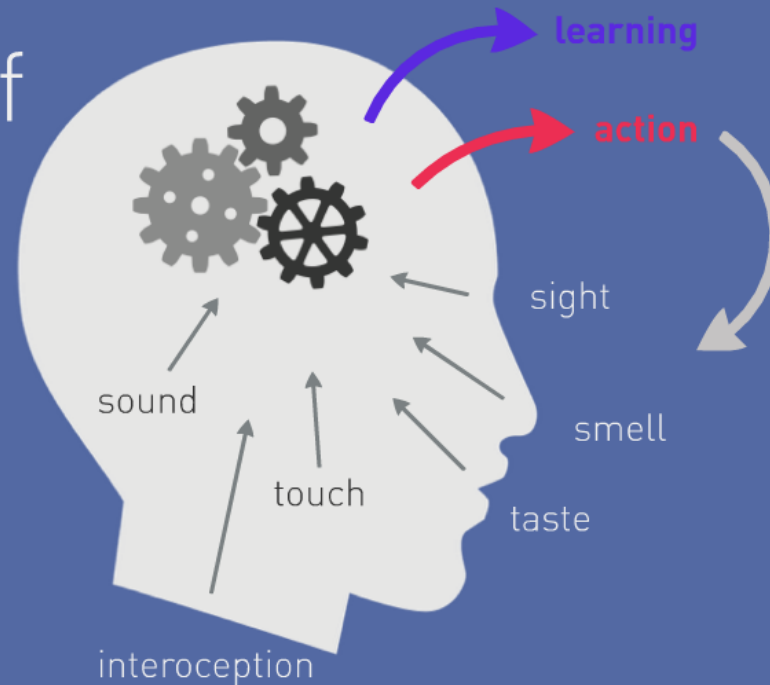
Future



New theories ...

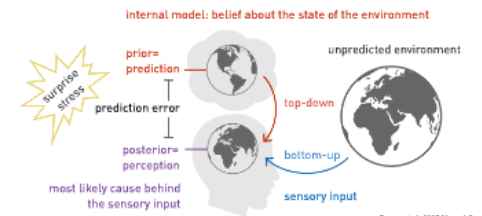
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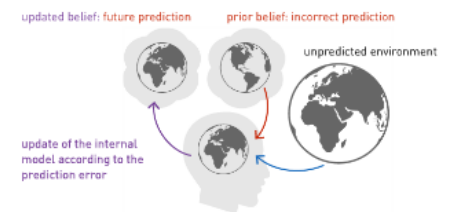
The Bayesian Brain

Brain: inference machine, resting on a generative model of sensory inputs, which are caused by the environment



Learning

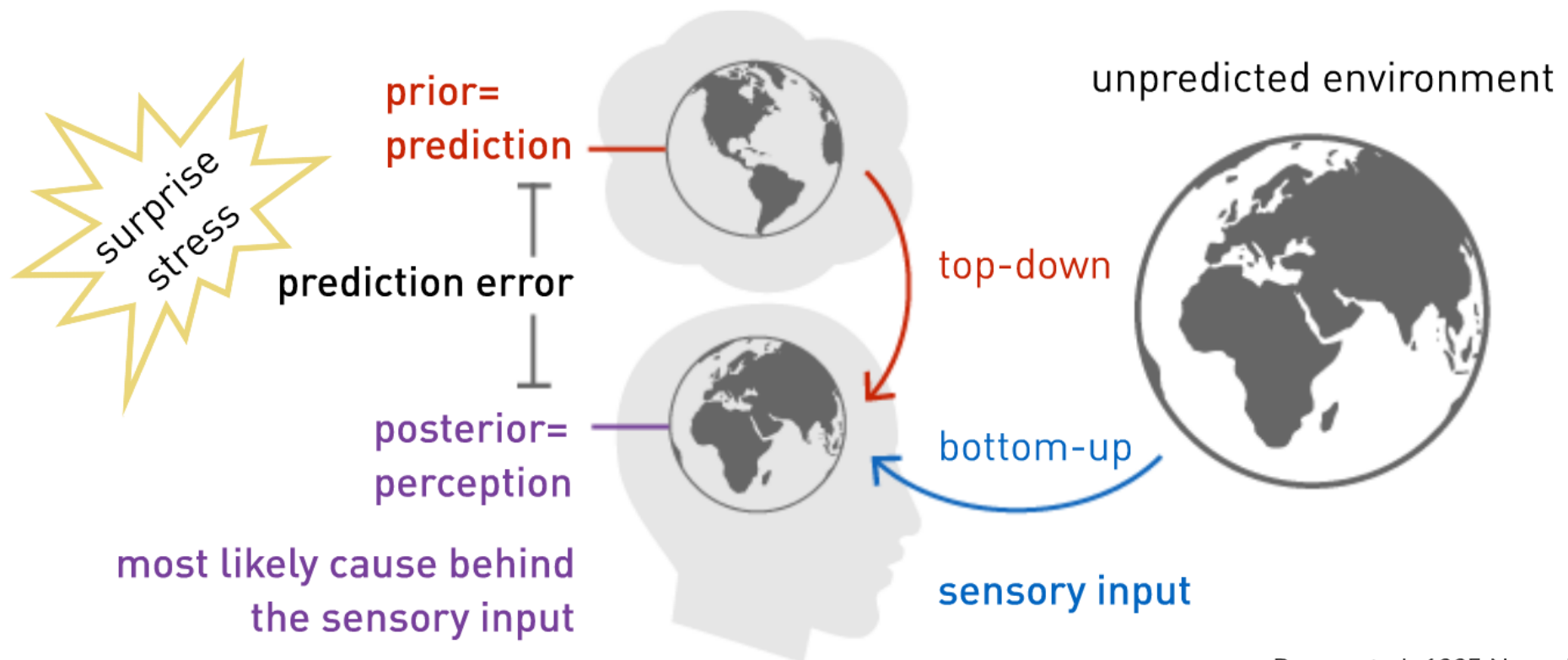
Minimizing surprise [stress] by learning from new observations and updating the prior belief



The Bayesian Brain

Brain: inference machine, resting on a generative model of sensory inputs, which are caused by the environment

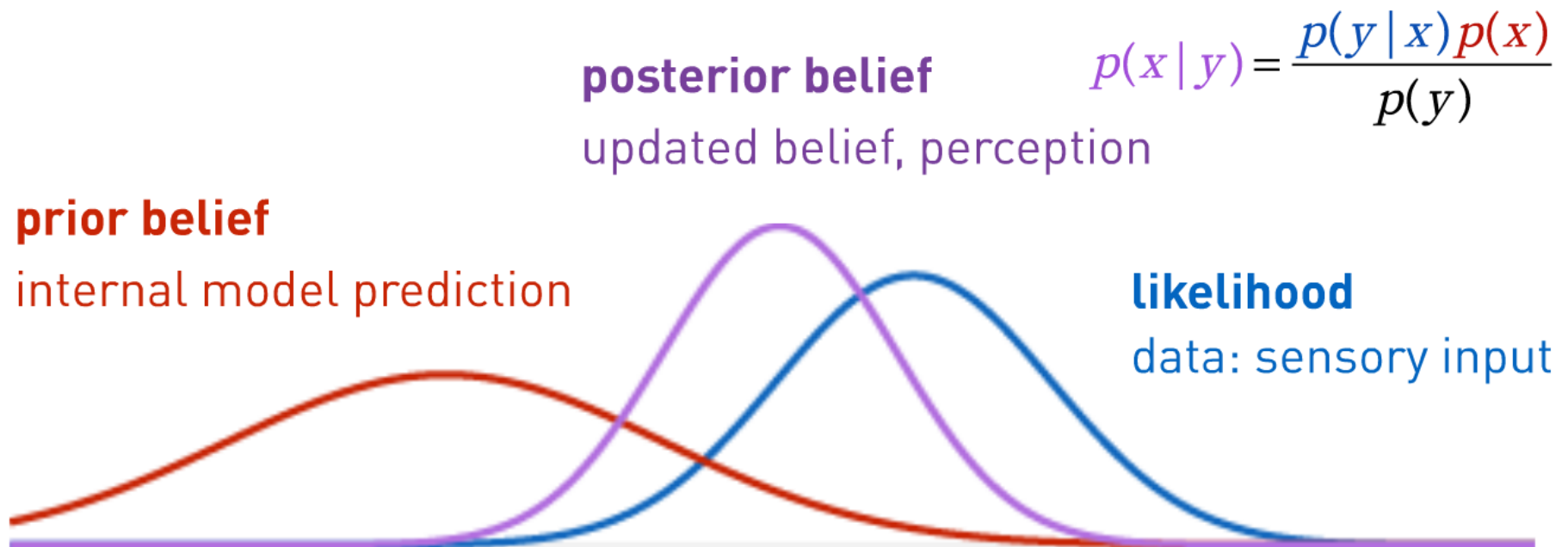
internal model: belief about the state of the environment



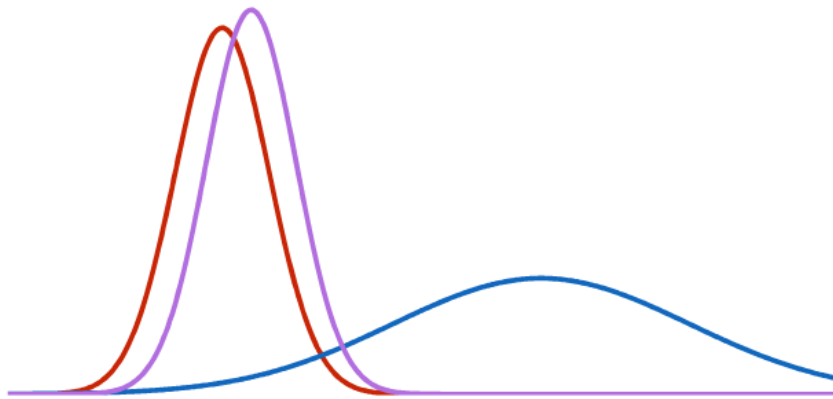
Beliefs as probability distributions

i.e. a probabilistic representation of a particular state of the world.

Bayes theorem describes how a prior belief is updated in light of newly observed data

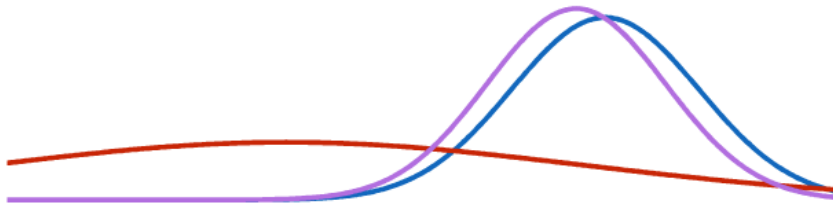


The role of relative precision



The **posterior belief** is dominated by an **overprecise prior belief** and shows little influence of the actual **observed sensory data**

$$p(x|y) = \frac{p(y|x)p(x)}{p(y)}$$



Posterior belief is shifted away from a **very unprecise prior belief** towards the **observed sensor data**

Learning

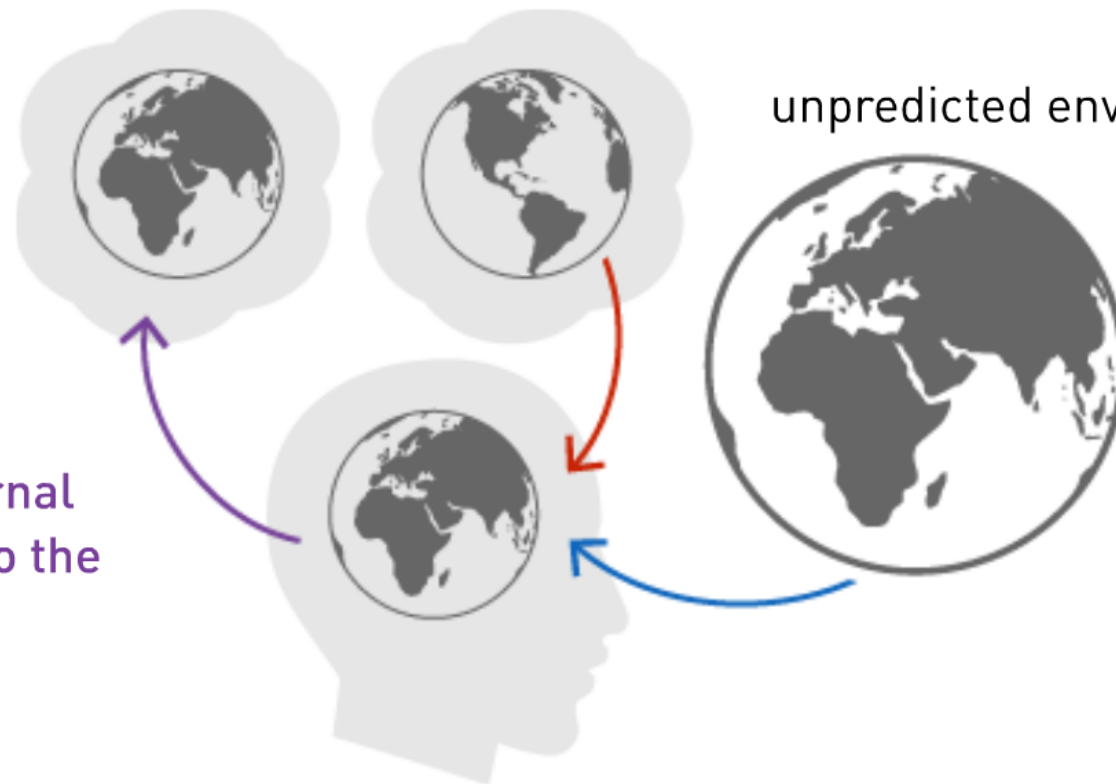
Minimizing surprise (stress) by learning from new observations and updating the prior belief

updated belief: future prediction

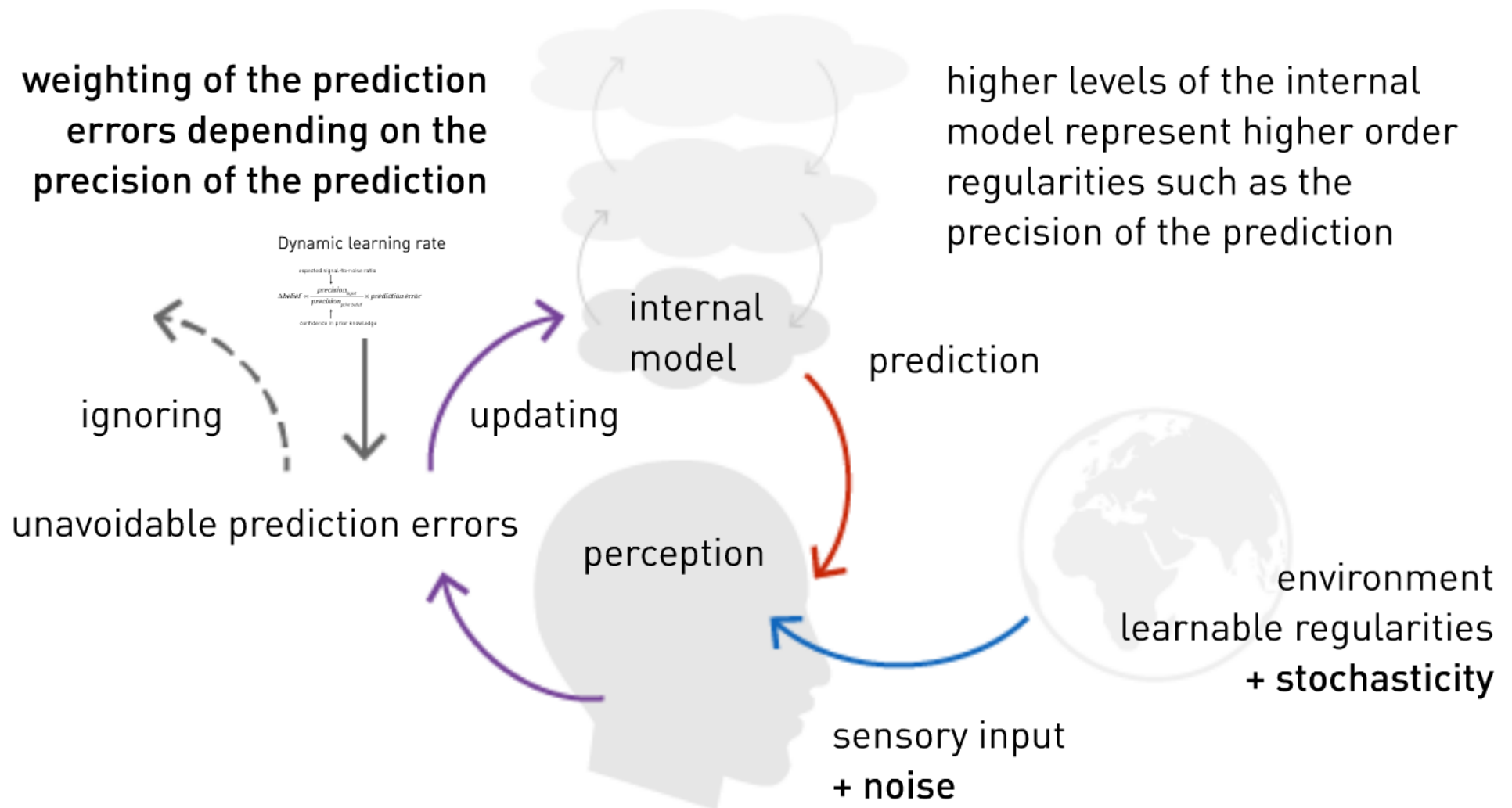
prior belief: incorrect prediction

unpredicted environment

update of the internal model according to the prediction error



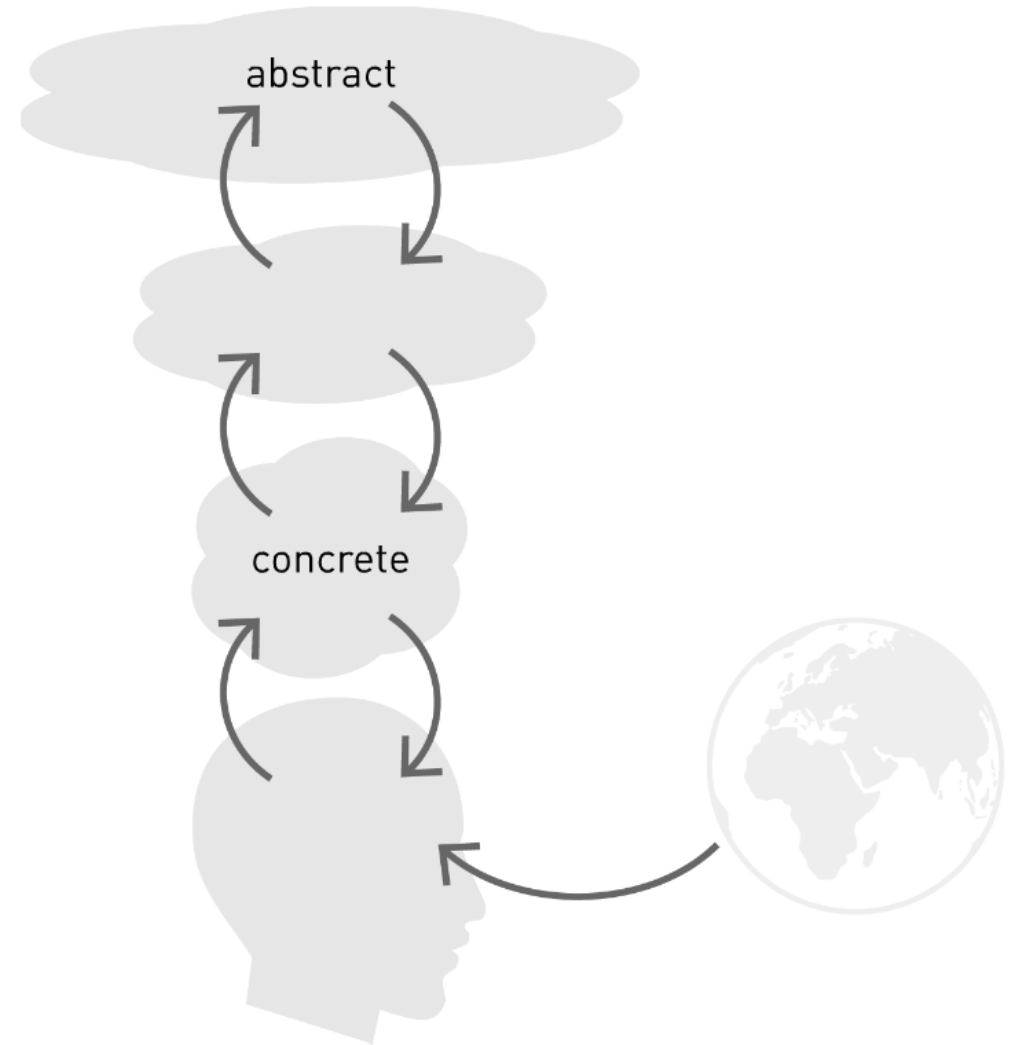
Uncertainty



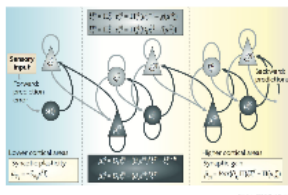
Hierarchy of inner representations

high levels

- represent very general, abstract features on a large temporal and spatial scale
- mature over time after more and more observations in different contexts



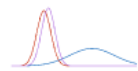
Biological implementation ...



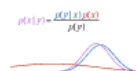
... to explain autism

utions
world.
ght of newly
 $p(z|x)p(x)$
 $p(x)$
of
sensory input
2017 Front Hum Neurosci

The role of relative precision



The posterior belief is dominated by an overprecise prior belief and shows little influence of the actual observed sensory data



Posterior belief is shifted away from a very unprecise prior belief towards the observed sensory data

Hierarchy of inner representations

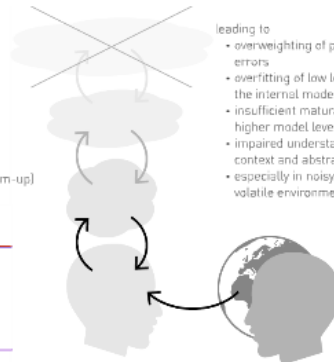
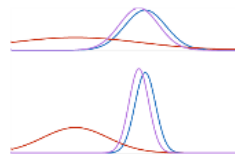
- high levels
- represent very general, abstract features on a large temporal and spatial scale
- mature over time after more and more observations in different contexts



Primer 2009 Public Comput Biol

Bayesian brain theories of autism

Autistic perception is biased towards details of the sensory input
- due to weak priors (top-down)
- or to overprecise sensory input (bottom-up)



- leading to
- overweighting of prediction errors
 - overfitting of low levels of the internal model
 - insufficient maturation of higher model levels
 - impaired understanding of context and abstraction
 - especially in noisy and volatile environments

Pellicano & Burr 2012 Trends Cogn Sci; Van de Cruys et al. 2014 Psychol Rev; Lawson et al. 2014 Front Hum Neurosci

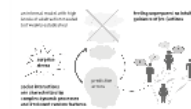
Autistic perception



Autistic repetitive behaviour



Autistic social interaction

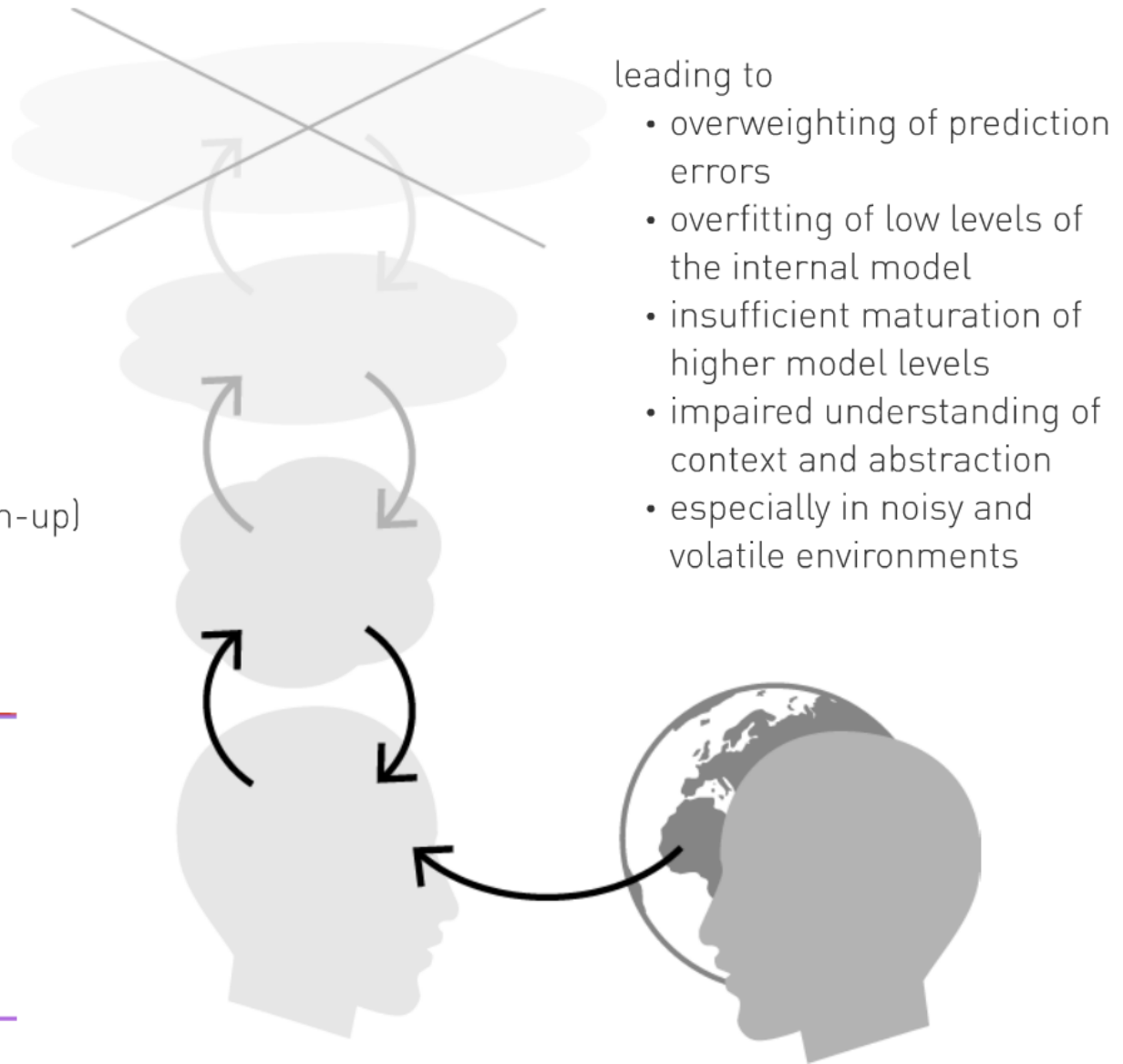
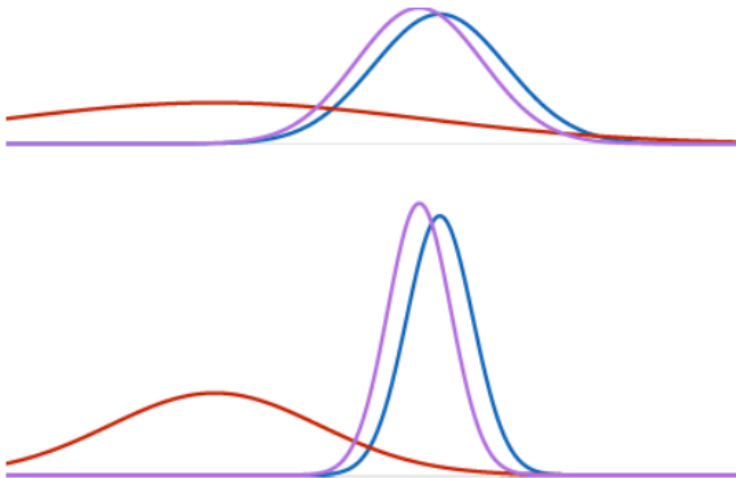


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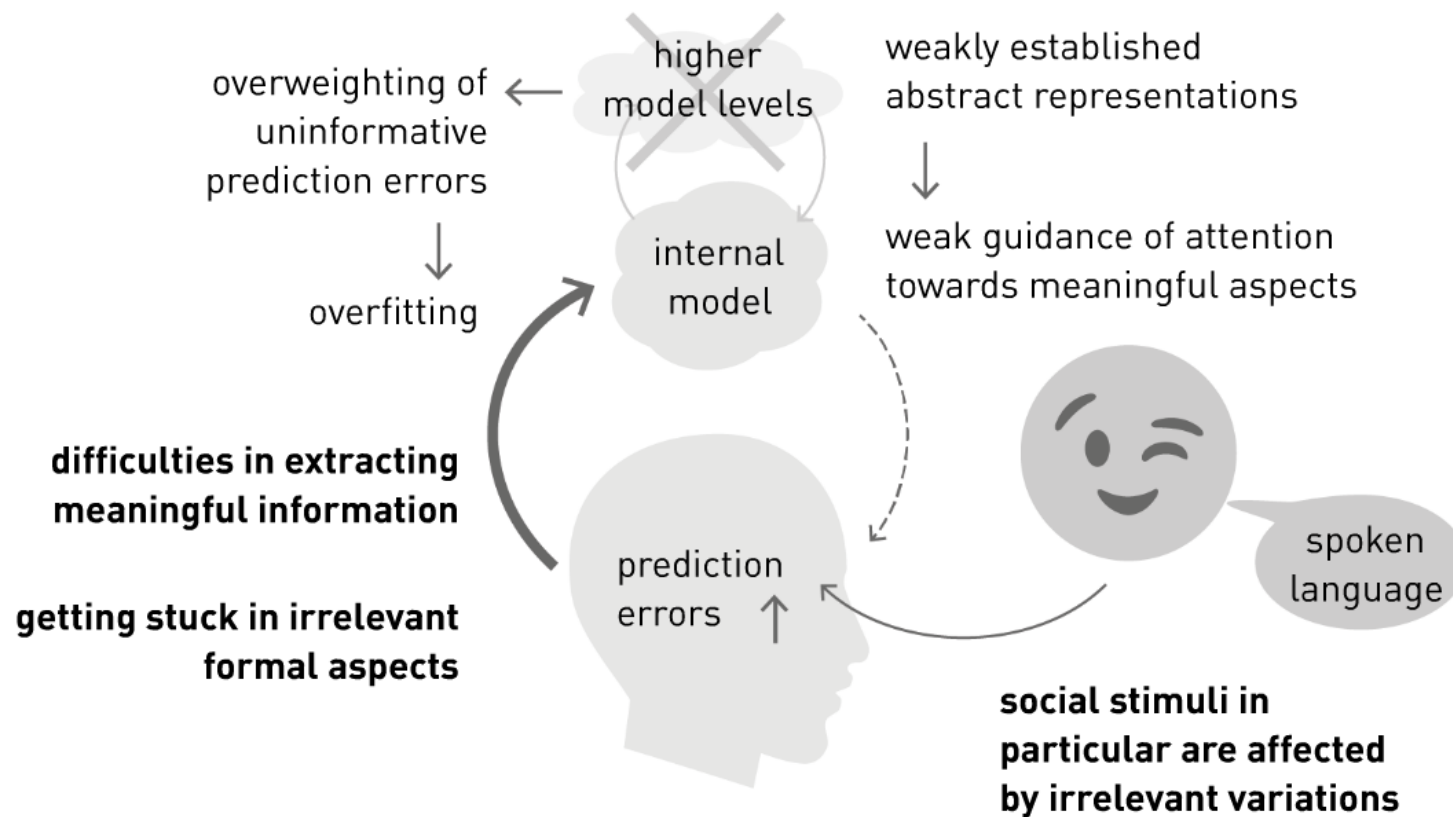
Bayesian brain theories of autism

Autistic perception is biased towards details of the sensory input

- due to weak priors (top-down)
- or to overprecise sensory input (bottom-up)



Autistic perception



Autistic repetitive behaviour

an internal model lacking higher levels of abstraction is able to represent stable environments very precisely



**known environment,
repetitive actions**



perfect predictions, no
cognitive stress

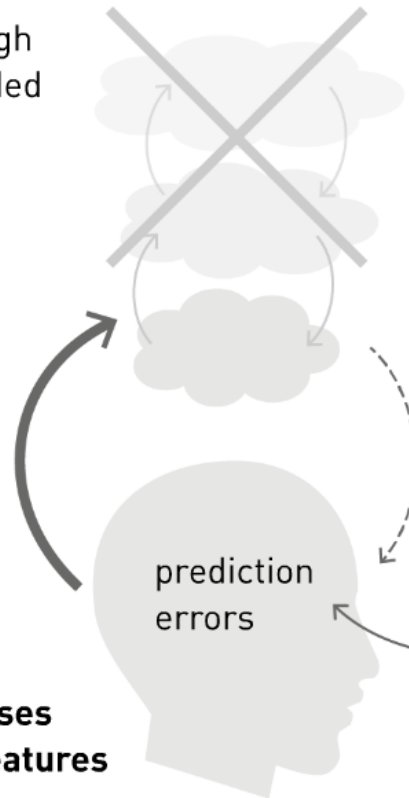
**moving away from
unpredictable
environments**

Autistic social interaction

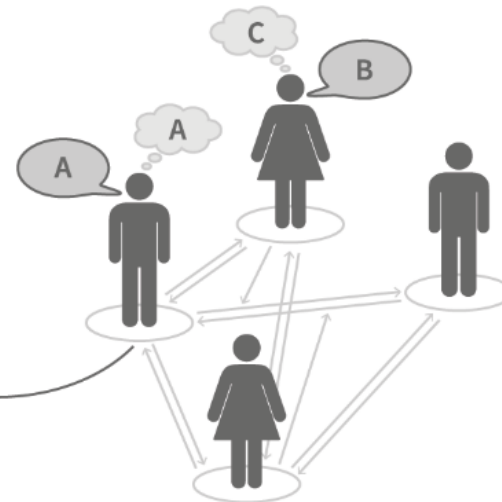
an internal model with high levels of abstraction needed but weakly established



social interactions are characterized by complex dynamic processes and irrelevant random features



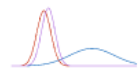
feeling unprepared no intuitive guidance of (re-)actions



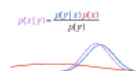
... to explain autism

utions
world.
ght of newly
 $p(z|x)p(x)$
 $p(x)$
of
sensory input
2017 Front Hum Neurosci

The role of relative precision



The posterior belief is dominated by an overprecise prior belief and shows little influence of the actual observed sensory data



Posterior belief is shifted away from a very unprecise prior belief towards the observed sensory data

Hierarchy of inner representations

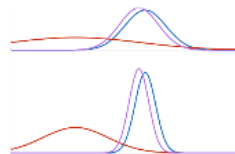
- high levels
- represent very general, abstract features on a large temporal and spatial scale
 - mature over time after more and more observations in different contexts



Primer 2009 Public Comput Biol

Bayesian brain theories of autism

Autistic perception is biased towards details of the sensory input
- due to weak priors (top-down)
- or to overprecise sensory input (bottom-up)



- leading to
- overweighting of prediction errors
 - overfitting of low levels of the internal model
 - insufficient maturation of higher model levels
 - impaired understanding of context and abstraction
 - especially in noisy and volatile environments

Pellicano & Burr 2012 Trends Cogn Sci; Van de Cruys et al. 2014 Psychol Rev; Lawson et al. 2014 Front Hum Neurosci

Autistic perception



Autistic repetitive behaviour



Autistic social interaction



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Research to do

Collect evidence

- Apply the theory to existing empirical data
 - post-hoc interpretation

Pellicano & Burr 2012 Trends Cogn Sci; Van de Cruys et al. 2014 Psychol Rev; Lawson et al. 2014 Front Hum Neurosci

- Theory-driven patient studies

Modeling cognition

- Design learning tasks to study peculiarities in hierarchical inference in individuals
 - high levels of sensory noise
 - hierarchical uncertainty

Mattar & Tenenbaum 2007; Tenenbaum & Mattar 2007; Tenenbaum & Mattar 2007

Modeling neurophysiology

- Use individual learning parameters for model-based imaging analysis (e.g. EEG, fMRI)
- ... for model-based connectivity analysis (DCM for EEG, fMRI)
- Modeling individual medication effects on learning parameters

Cross-sectional patient studies

Open research questions:

- Do individuals with and without a current diagnosis of ASD (children, adults) differ in learning parameters?
 - ... first step toward the development of **diagnostic tests**
- Do individual learning parameters correlate with symptom clusters
 - ... definition of **mechanistically defined subgroups**

Longitudinal patient studies

- Are specific constellations of individual characteristics of Bayesian learning related to specific developmental trajectories in children?
 - ... **prognostic tests**?
- Do specific learning parameters predict the response to a pharmacological intervention?
 - ... **treatment selection tests**?

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Reynolds & Griffiths 2007; Griffiths & Reynolds 2009; Griffiths & Tenenbaum 2009

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Understanding and explaining
the huge variance, to affected, to relatives, to clinicians, ...

Diagnosing
quick, easy to apply, reliable tests

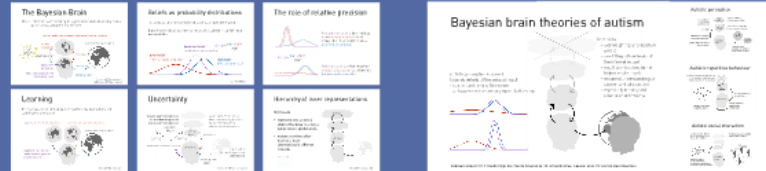
Treating
mechanistically informed psychotherapeutic
and pharmacological concepts

Potential benefits

New theories ...

The Bayesian Brain

A computational framework of cognition



... to explain autism

Research to do

Collect evidence

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- Theory-driven patient studies

Computational Psychiatry

Perception

Action

Perception	Interests	Behaviour	Communication
<ul style="list-style-type: none"> • sensory processing • sensory processing • sensory processing • sensory processing • sensory processing 	<ul style="list-style-type: none"> • reduced attention to social/functional stimuli • focus on immediate sensory input • sensory processing • sensory processing • sensory processing 	<ul style="list-style-type: none"> • repetitive behaviours • repetitive behaviours • repetitive behaviours • repetitive behaviours • repetitive behaviours 	<ul style="list-style-type: none"> • reduced social interaction • reduced social interaction • reduced social interaction • reduced social interaction • reduced social interaction

Weak central coherence
Happé & Frith 2006

Reduced social salience
KS et al. 2002

Reduced social motivation
Charlier et al. 2012

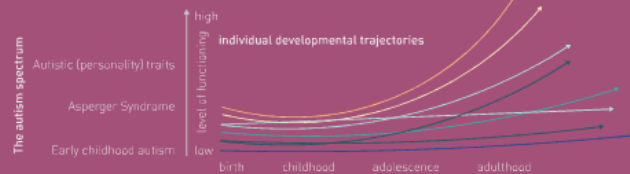
Executive dysfunction
Goyette et al. 1991

Theory of mind deficit
Baron-Cohen et al. 1985

Previous theories

a lack of a pathomechanistic model and superficially defined diagnostic criteria fail to capture the huge variance in developmental trajectories

Autism



Current clinical problems



Understanding and explaining the huge variance, to affected, to relatives, to clinicians, ...

Diagnosing quick, easy to apply, reliable tests

Treating mechanistically informed psychotherapeutic and pharmacological concepts

Potential benefits

Past

Present

Future

