Identification of clinical high risk of psychosis: special requirements in children and adolescents

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The author declares no conflict of interest.

Background

Prevalence: lifetime prevalence of 0.2-3.5% with an annual incidence of 0.01-0.035%; rising numbers in Europe: 3.7 Mill. adults (0.8%) in 2005 and 5 Mill. (1.2%) in 2011

Age at onset: mainly striking first in early adulthood; approx. 10-15% are *early-onset psychoses* (EOP) starting before age 18; approx. 1-3% are *very-early-onset psychoses* (VEOP) starting before age 13

Course: psychoses, in particular schizophrenias, frequently take an unfavourable course with longterm cognitive and functional impairments even when positive symptoms have remitted

Unfavourable course commonly associated with a longer duration of untreated psychosis (DUP) and illness (DUI), both commonly particularly long in EOP. Assumed more negative course of EOP not present when DUP/DUI are taken into account

Background

Costs: the often chronic course of psychoses is a main cause of why these infrequent disorders account for the 6th highest share of *disability-adjusted life years* (DALYs) in European adults and for the 3rd highest of all disorders of the brain worldwide; only dementias and affective disorders cause higher direct and indirect costs.

Despite the low prevalence of VEOP and EOP, schizophrenias are already a main cause of DALYs already in children and adolescents.

Global burden of disease in young people aged 10–24 years: a systematic analysis

Fiona M Gore, Paul J N Bloem, George C Patton, Jane Ferguson, Véronique Joseph, Carolyn Coffey, Susan M Sawyer, Colin D Mathers

Lancet 2011; 377: 2093–102
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DOI:10.1016/S0140-6736(11)60512-6

	Males		Females		Total	
	Cause	Total DALYs (100 000s) (%)	Cause	Total DALYs (100 000s) (%)	Cause	Total DALYs (100 000s) (%)
10–14 years						
1	Road traffic accidents	15 (6·0%)	Lower respiratory infections	15 (6·3%)	Unipolar depressive disorders	28 (5·7%)
2	Unipolar depressive disorders	14 (5·4%)	Unipolar depressive disorders	14 (6·1%)	Lower respiratory infections	28 (5·6%)
3	Lower respiratory infections	13 (4·9%)	Asthma	12 (5·1%)	Road traffic accidents	26 (5·2%)
4	Asthma	10 (4·1%)	Migraine	11 (4·8%)	Asthma	23 (4·6%)
5	Drownings	10 (3·8%)	Road traffic accidents	10 (4·2%)	Refractive errors	19 (3·8%)
6	Refractive errors	10 (3·7%)	Refractive errors	9 (3·8%)	Iron-deficiency anaemia	17 (3·4%)
7	Falls	9 (3·4%)	Iron-deficiency anaemia	8 (3·5%)	Falls	16 (3·2%)
8	Iron-deficiency anaemia	9 (3·4%)	Falls	7 (2·9%)	Migraine	16 (3·2%)
9	Schizophrenia	6 (2·5%)	Diarrhoeal diseases	6 (2·7%)	Drownings	14 (2·9%)
10	Lymphatic filariasis	6 (2·5%)	Fires	6 (2·5%)	Diarrhoeal diseases	12 (2·4%)
15–19 years						
1	Unipolar depressive disorders	34 (8·0%)	Unipolar depressive disorders	53 (11·7%)	Unipolar depressive disorders	86 (9·9%)
2	Road traffic accidents	33 (7·8%)	Schizophrenia	23 (5·2%)	Schizophrenia	46 (5·3%)
3	Alcohol use	30 (7·2%)	Bipolar disorder	22 (4·9%)	Road traffic accidents	46 (5·3%)
4	Schizophrenia	23 (5·4%)	Abortion	17 (3·8%)	Bipolar disorder	44 (5·1%)
5	Bipolar disorder	23 (5·3%)	Panic disorder	16 (3·5%)	Alcohol use	34 (4·0%)
6	Violence	21 (5·1%)	Maternal sepsis	14 (3·1%)	Violence	26 (3·0%)
7	Drug misuse	11 (2·7%)	Self-inflicted injuries	13 (3·0%)	Self-inflicted injuries	24 (2·8%)
8	Asthma	11 (2·6%)	Road traffic accidents	13 (2·9%)	Panic disorder	23 (2·7%)
9	Self-inflicted injuries	11 (2·6%)	Chlamydia	10 (2·3%)	Asthma	18 (2·0%)
10	Drownings	10 (2·5%)	Iron-deficiency anaemia	9 (2·1%)	HIV/AIDS	17 (2·0%)

The ultra high risk (UHR) criteria: detecting imminent risk of psychosis

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Attenuated Psychotic Symptoms: **APS**

- ideas of reference
- odd beliefs or magical thinking
- perceptual disturbancwes
- odd thinking and speech
- paranoid ideation

Symptom should deviate significantly from normal

Transient Psychotic Symptoms: **B(L)IPS**

- hallucination
- delusion
- formal thought disorder

Duration of each symptom is short, before resolving spontaneously

Trait plus State Risk Factors

first-degree relative with psychosis or schizotypal personality disorder

plus

change in mental state or functioning

(Yung et al. 1998)

Basic symptom at-risk criteria
COPER & COGDIS

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‘Cognitive-Perceptive Basic Symptoms‘: **COPER**

≥1 basic symptom of at least weekly frequency (SPI ≥ ‚3‘) within past 3 months and first occurrence or significant increase in frequency at least 12 months ago:

- thought interference
- thought perseveration
- thought pressure
- thought blockages
- dist. of receptive speech
- decreased ability to discriminate between ideas and perception, …
- unstable ideas of reference
- derealisation
- visual perception dist.
- acoustic perception dist.

'Cognitive Disturbances’: **COGDIS**

≥2 basic symptoms of at least weekly frequency (SPI ≥ ‚3‘) within past 3 months :

- inability to divide attention
- thought interference
- thought pressure
- thought blockages
- dist. of receptive speech
- dist. of expressive speech
- dist. of abstract thinking
- unstable ideas of reference
- captivation of attention by details of the visual field

(Klosterkötter et al. 2001; Schultze-Lutter et al. 2007)

Age at onset of symptoms and early course

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(Schultze-Lutter, Rahman et al., 2015; Soc Psychiatry Psychiatr Epidem)

		Onset before age 18 (EOFS; n=45)	Onset at / after age 18 (AOFS; n=81)	Statistics
DUI, total in mths: Mdn (range); mean±SD		156 (35-398); 165±90	53 (0-331); 65±59;	U=562.0, Z= -6.418, **p<0.001**
DUP in mths.: Mdn (range); mean±SD		21 (0-244); 46±65	5 (0-131); 17±27	U=1214.0, Z= -3.106, **p=0.002**
Phases (n,%):	only DUP	3 (6.7%)	**14 (17.3%)**	$\chi^2_{(3)}$=14.964, **p=0.002**
	DUI-UPS+DUP	11 (24.4%)	**40 (49.4%)**	
	DUI-ARMS+DUP	**13 (28.9%)**	10 (12.3%)	
	all 3 phases	**18 (40.0%)**	17 (21.0%)	
Help-seeking (n,%):	prior to first PS	13 (28.9%)	16 (19.8%)	$\chi^2_{(1)}$=1.363, p=0.243
	after first PS	32 (71.1%)	65 (80.2%)	
Help-seeking (n,%):	in DUI-UPS	7 (15.[illegible]%)	[illegible].1%)	$\chi^2_{(2)}$=1.381, p=0.501
	in DUI-ARMS	6	[illegible].6%)	
	in DUP	32 ([illegible]	[illegible]80.2%)	
Initiator of help-seeking (n,%):	patient	15 (33.[illegible]	[illegible] (46.9%)	$\chi^2_{(1)}$=2.189, p=0.139
	other person	30 (66.7[illegible]	[illegible] (53.1%)	
First contact point (n,%):	GP	9 (20.0[illegible]	[illegible]4.8%)	$\chi^2_{(3)}$=3.640, p=0.303
	professional	24 (53[illegible]	[illegible]3%)	
	semi-profess.	3 ([illegible]	[illegible]%)	
	other	9 (20.0%)	1[illegible]%)	

Age at onset of symptoms and early course

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(Schultze-Lutter, Rahman et al., 2015; Soc Psychiatry Psychiatr Epidem)

	Onset before age 18 (EOFS; n=45)	Onset at / after age 18 (AOFS; n=81)	Statistics
Initiator × help-seeking (n,%):			
patient × in DUI-UPS	5 (33.3%)	6 (15.8%)	EOFS: $\chi^2_{(2)}$= 7.212, **p=0.027**
patient × in DUI-ARMS	3 (20.0%)	4 (10.5%)	
patient × in DUP	7 (46.7%)	28 (73.7%)	AOFS: $\chi^2_{(2)}$= 2.088, p=0.352;
other × in DUI-UPS	2 (6.7%)	3 (7.0%)	
other × in DUI-ARMS	3 (10.0%)	3 (7.0%)	All: $\chi^2_{(2)}$= 6.840, **p=0.033**
other × in DUP	25 (83.3%)	37 (86.0%)	
Contact point × help-seeking (n,%):			
GP × in DUI-UPS	2 (22.2%)	1 (8.3%)	EOFS: $\chi^2_{(6)}$=2.839, p=0.829;
GP × in DUI-ARMS	2 (22.2%)	3 (25.0%)	
GP × in DUP	5 (5[illegible])	[illegible].7%)	
professional × in DUI-UPS	3 (12[illegible])	[illegible]11.4%)	AOFS: $\chi^2_{(6)}$=6.521, p=0.367;
professional × in DUI-ARMS	3 (12.5%)	(6.8%)	
professional × in DUP	18 (75.0%)	[illegible](81.8%)	
Semi- professional × in DUI-UPS	0	[illegible].1%)	
Semi- professional × in DUI-ARMS	0		All: $\chi^2_{(6)}$=8.605, p=0.197
Semi- professional × in DUP	3 (1[illegible])	[illegible]%)	
other × in DUI-UPS	2 (22.2%)	[illegible]%)	
other × in DUI-ARMS	1 (11.1%)	1 (9.1%)	
other × in DUP	6 (66.7%)	8 (72.7%)	

Age at onset of symptoms and early course

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(Schultze-Lutter, Rahman et al., 2015; Soc Psychiatry Psychiatr Epidem)

- Not only an early onset of positive symptoms but also an **early onset of the prodromal symptoms** was associated to **a longer DUI and DUP**, and thus with a consistent predictor of unfavourable outcome
- Interestingly, an **early onset of prodromal symptoms** was not related to delayed but to an **advanced help-seeking** at contact points comparable to those at later onset.
- This emphasises the **necessity of studies on help-seeking and early detection of psychoses in children and adolescents**.
- Early detection might be impeded by the frequent **insidious onset** in children and adolescents that might be **mistaken for „normal“ changes related to puberty**
- However, ….

A caterpillar is not a small adult butterfly

Development matters

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Developmental considerations of (pseudo)hallucinations

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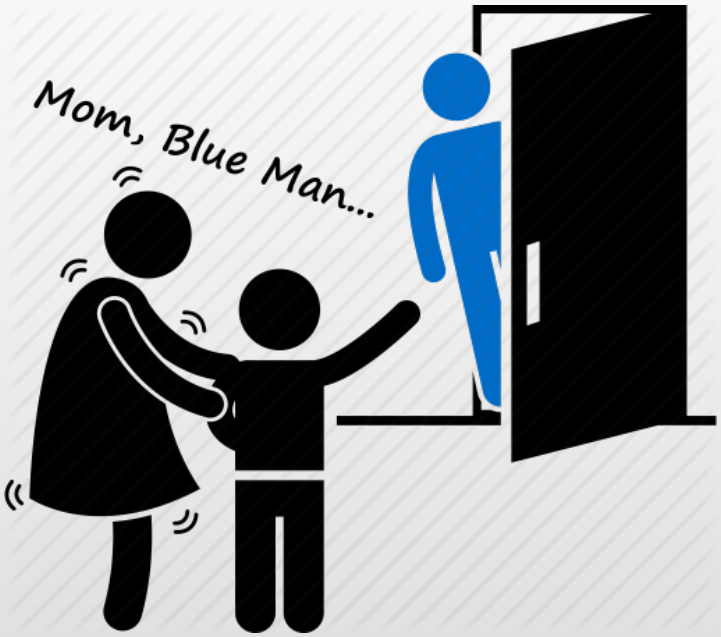
- Hallucinations are perceptions in the absence of external stimuli that are experienced in a fully awake state as real perceptions located in the external objective space
- Pseudohallucinations (unusual perceptual experiences / attenuated hallucinations in terms of APS) are also not under voluntary control, but do not mimic real perception as they are eventually recognized as being generated in one's own mind
- Thus, impaired (or not yet fully matured) source monitoring has been considered to play an important role in the development of positive symptoms, in particular of hallucinations



Developmental considerations of (pseudo)hallucinations II

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- Source monitoring = complex process of making decisions about the source of a memory that requires the availability and coordination of many cognitive skills
- Three source monitoring processes: external source monitoring, internal or self-monitoring and reality monitoring (i.e., discrimination between internal and external sources of information)
- Source monitoring decisions are based on memory characteristics recorded, such as perceptions, contextual information or emotional reactions and heuristic or more controlled judgement processes
- Until approximately age 10, children perform worse than adults on many source-monitoring tasks, possibly because, before that age, the frontal lobe has not matured sufficiently to enable the necessary complex and effortful decisions

Can (pseudo)hallucinations be validly assessed before age 10 ?

(Pseudo)hallucinations in children and adolescents

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(Bartels-Velthuis et al. 2010, 2011a,b)

- In a Dutch study of verbal (pseudo)hallucinations in 7- to 8-year-olds recruited from the general population, 347 of the 3870 interviewees (9%) reported hearing voices within the previous year.
- In only 15% of cases, verbal (pseudo)hallucinations were associated with substantial suffering and problem behaviors.
- 5 years later, verbal (pseudo)hallucinations had remitted in 76% of 170 re-interviewed young adolescents with earlier reports of hearing voices, while they were newly reported by only 9% of the 167 re-interviewed adolescents without such an earlier report.
- Persistence into age 12/13 was predicted by
  - an external attribution of the voices,
  - a multitude of voices,
  - the presence of other psychotic symptoms (in particular odd behavior, unusual thought content, and visual hallucinations),
  - problematic behaviors,
  - lower school performance at baseline,
  - further problem behavior (*also related to new occurrence*)

(Pseudo)hallucinations in children and adolescents

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(Bartels-Velthuis et al. 2010, 2011a,b)

- Another 6 years later, of the 293 re-interviewed young adults (now age 18/19), altogether 18% (n = 6) of those having reported hearing voices at 5-year follow-up (n = 33) and only 6% (n = 9) of those having reported hearing them at baseline (n = 145) still reported verbal (pseudo)hallucinations.
- These were associated with
  - higher levels of other psychotic experiences
  - higher levels of other psychopathology
  - traumatic events,

  but not with
  - high levels of current stress
  - cannabis use

Verbal (pseudo)hallucinations in childhood are mostly transitory, but gain clinical relevance when persisting into adolescence / adulthood and are accompanied by other (attenuated) psychotic symptoms, affective symptoms, and environmental risk factors.

Attenuated hallucinations in children and adolescents

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(Schimmelmann et al. 2015; Schultze-Lutter et al. 2017)

- Swiss, cross-sectional general population study of the effect of age on the prevalence and clinical significance of attenuated psychotic symptoms in 8- to 40-year-olds, assessed as in early detection services
- Altogether, 5% of the 698 interviewees reported perception-related APS, i.e., unusual perceptual experiences in terms of positive features of a schizotypal personality disorder and attenuated hallucinations with insight into their abnormal nature
- A strong age effect on prevalence was detected for two age groups with a split around the age of 16: in 8-to 15-year-olds, perceptive APS were significantly more frequent than in 16- to 40-year-olds, with no difference in frequency within these two age groups
- Finding was confirmed in a clinical sample of 9- to 38-year-old patients of the Bern early detection service (FETZ Bern).

For the interested reader …

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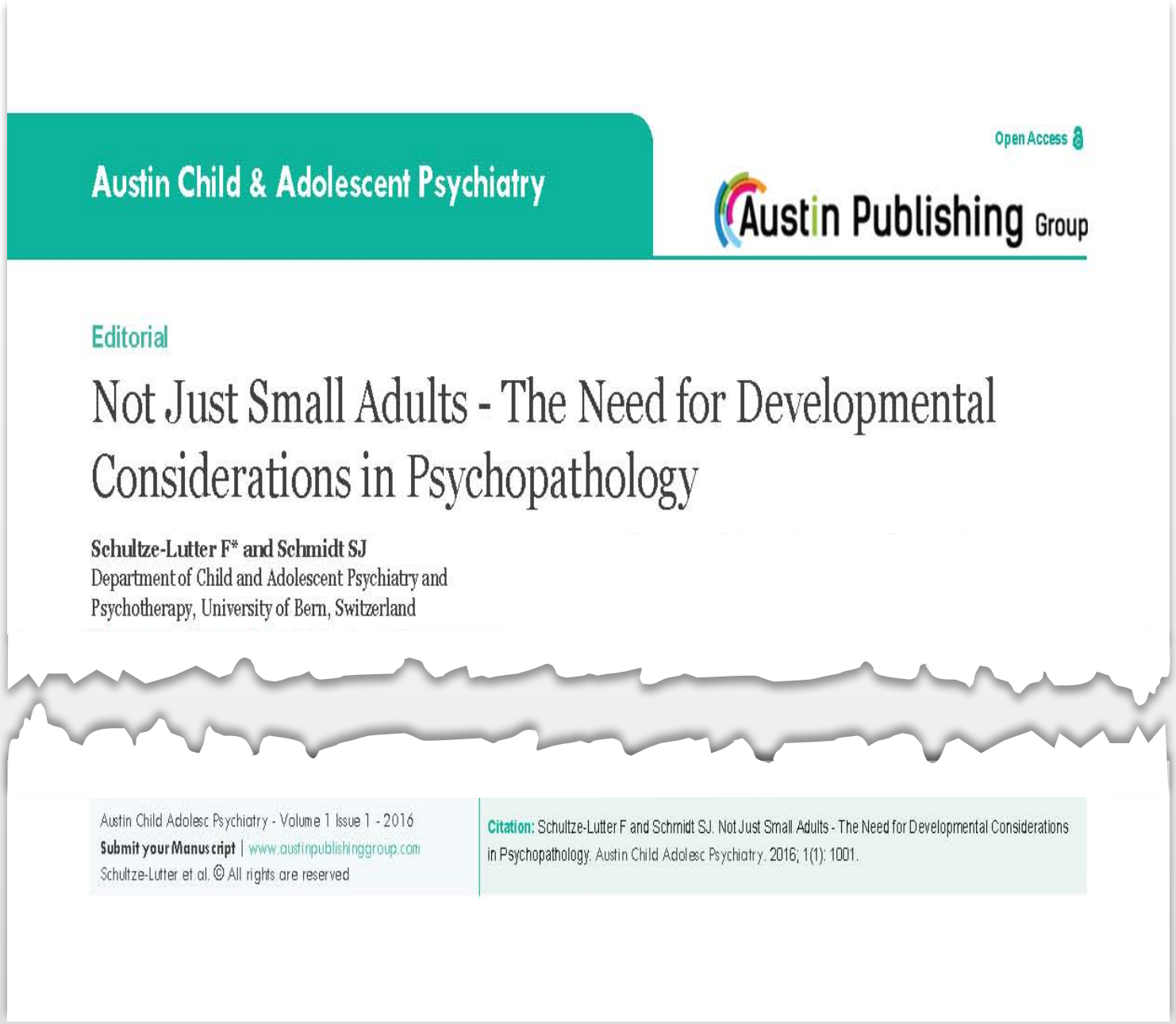

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Editorial

Not Just Small Adults - The Need for Developmental Considerations in Psychopathology

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Developmental considerations of unusual / delusional thought contents

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- Similar to hallucinatory experiences, unusual / delusional thought contents (incl. magical thinking) might be caused by immature source monitoring skills in children younger than age 10
- Additionally, illusion of control over random events (which was linked to positive symptoms in adults) only decreases across childhood and adolescence into adulthood
- Furthermore, magical thinking only becomes suppressed – but never extinguished – in late childhood, its likelihood of occurrence not only varying as a function of age and knowledge acquisition but also of:
  - context and social / cultural support
  - tendency to causally link events close in time and proximity
  - tendency to essentialize (i.e., perceive some underlying essence of similar objects that create some *magical* connection between them)
  - general fantasy orientation
- Magical thinking was related to delusion formation but also, in the sense of thought-action fusion, to anxiety and OC disorders, suggesting a continuity from child- to adulthood in magical thinking in certain clinical populations

Unusual / delusional thought contents in children and adolescents

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(Schimmelmann et al. 2015; Schultze-Lutter et al. 2017)

- Swiss, cross-sectional general population study of the effect of age on the prevalence and clinical significance of attenuated psychotic symptoms in 8- to 40-year-olds, assessed as in early detection services
- Altogether, 6% of the 698 interviewees reported thought content-related APS (paranoid: 3.0%, grandiose: 0.3%, others, incl. magical thinking: 6.0%) with insight into their abnormal nature with **no differences in prevalence rates across ages**
- An age effect showed for the association between presence of unusual thought content and functional impairment but not for the much weaker association between presence of unusual thought content and axis-I disorder.
- Functional impairment in the presence of unusual thought content became more likely with increasing age, indicating **lesser clinical significance of unusual thought contents in children and adolescents**.

Positive psychotic symptoms in children and adolescents

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(Hlastala & McClellan 2005)

- Comparison of psychotic symptoms associated to a psychotic disorder and so-called “atypical “ psychotic symptoms (*unfortunately, no distinction between delusion-like and hallucinatory symptoms*) in a 7- to 18-year-old in-patient sample
- Patients with “atypical” psychotic symptoms, who did not develop frank psychosis over two years, were more likely to report:
  - childhood adversities, in particular physical neglect and abuse
- Their reports of psychotic symptoms were
  - extremely elaborate
  - closely linked to certain situations,
  - clearly directed towards earning secondary gain
  - not accompanied by odd behaviors or disorganized speech and only little reactive and aggressive behaviors
  - accompanied by social problems that mainly involved peers but hardly any social withdrawal and/or social anhedonia

Psychosis-predictive value of UHR criteria and age

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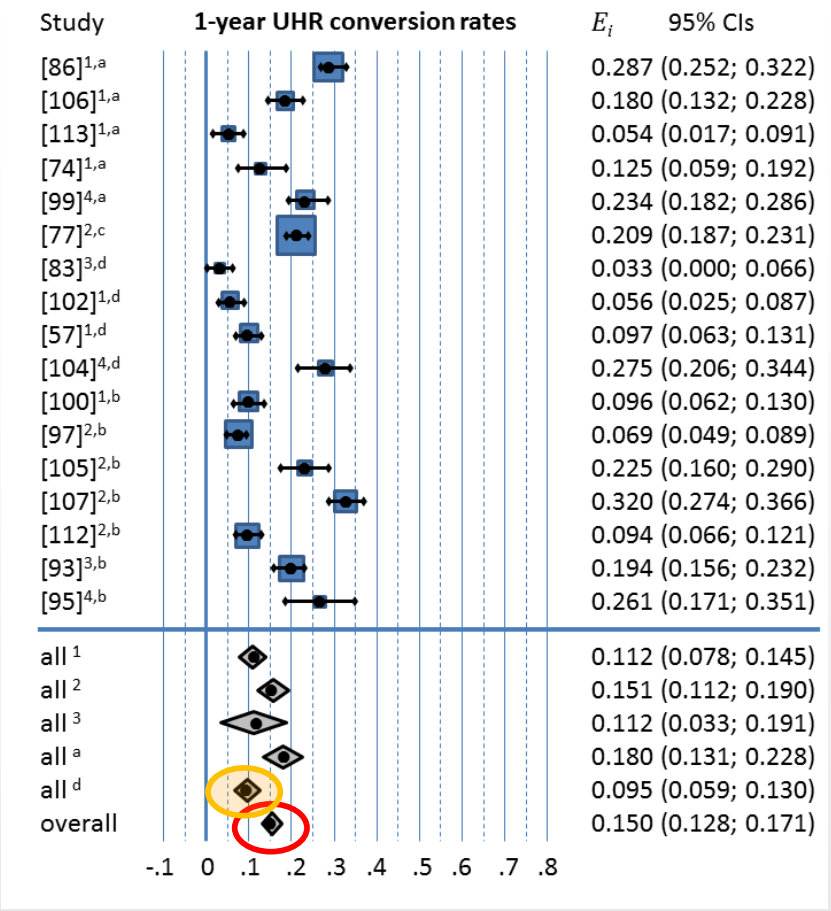
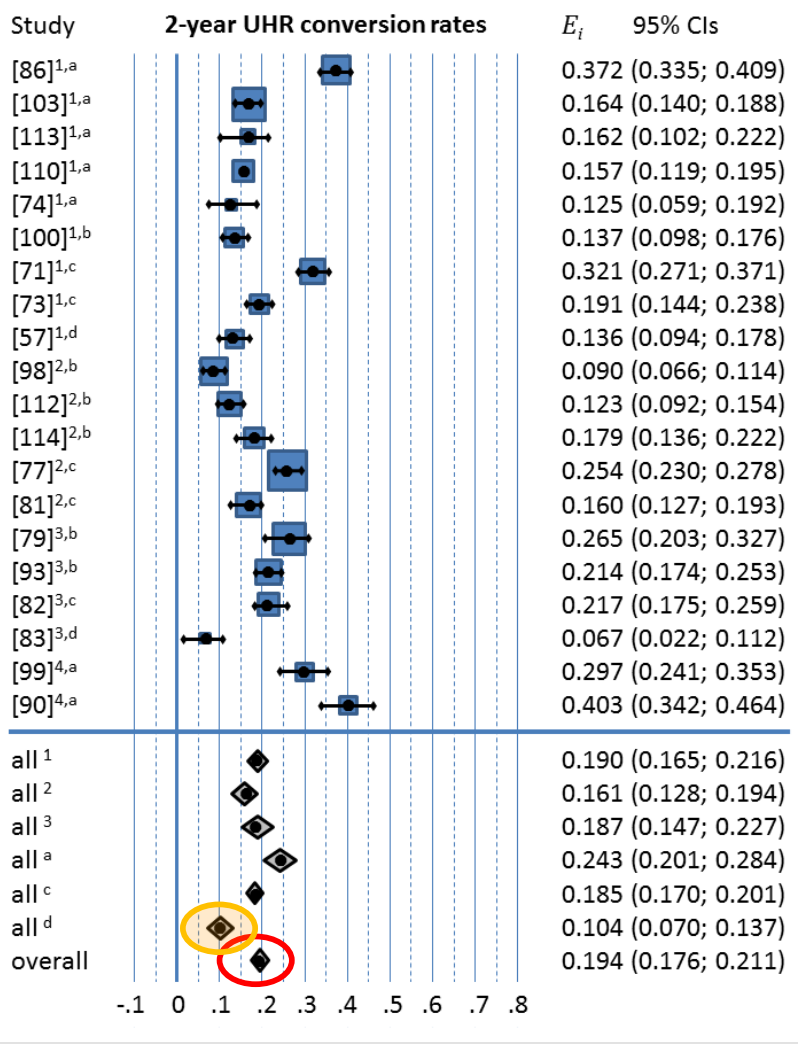
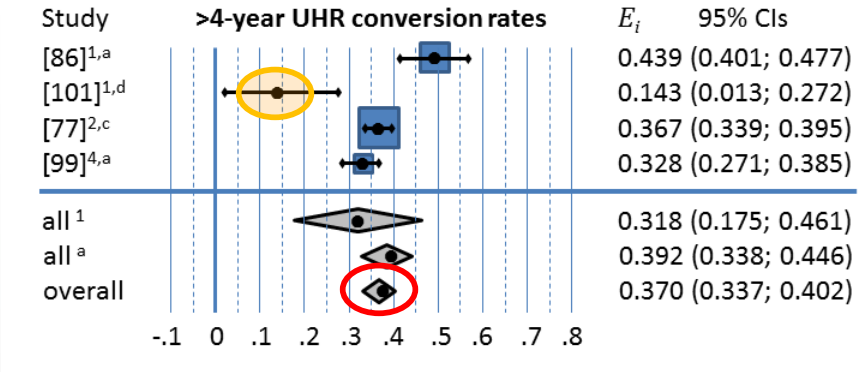




Psychosis-predictive value of UHR criteria and age



- In a study of Cornblatt et al. 2015 on 12- to 18(22)-year-old patients meeting UHR criteria by APS, the conversion rate in 12-14-year-olds was significantly lower than in all other age groups
- No report of type of APS

Basic symptom criteria and age

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(Schultze-Lutter et al. in revision)

- Swiss, cross-sectional general population study of the effect of age on the prevalence and clinical significance of basic symptoms in 8- to 40-year-olds, assessed as in early detection services
- Altogether, 18% of the 698 interviewees reported basic symptoms (perceptive: 5.4%, cognitive: 14.7%), 3.3% met COPER, 1.2% COGDIS
- Perceptive basic symptoms were more prevalent before age 18, cognitive basic symptoms before early twenties
- Basic symptoms by themselves rather than their interaction with age was associated with mental disorder, esp. when rather new and/or frequent.
- In contrast, interactions of (cognitive) basic symptoms with age rather than basic symptoms themselves predicted low functioning. with low functioning always becoming more likely with advancing age – esp. above the age of early twenties.

Conclusion related to age effects in UHR and basic symptoms

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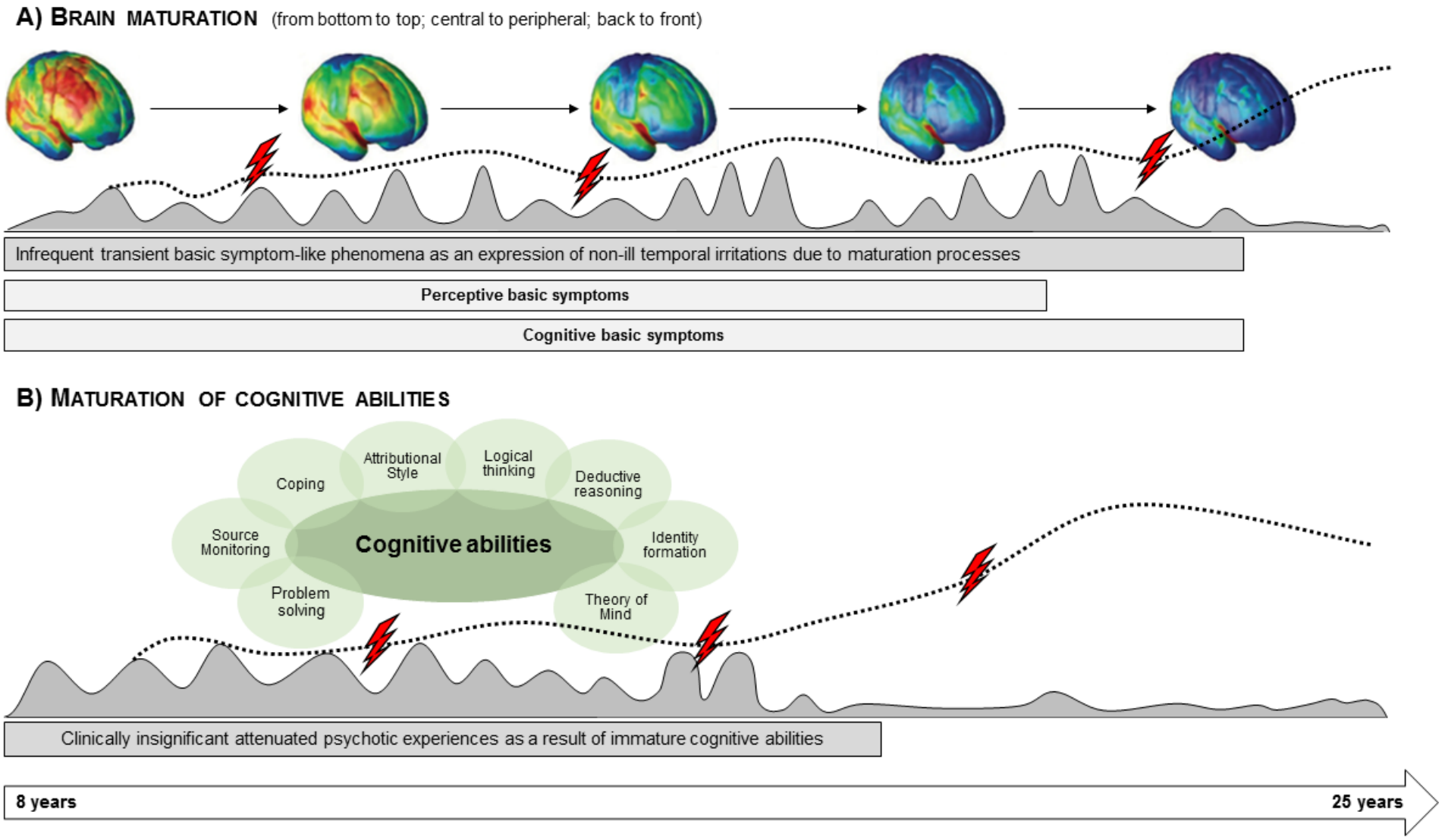
- The BS concept assumes **BS** to be the **most direct expression of the underlying neurobiological aberrations**, …
- … and **APS** and psychotic symptoms to be the **result of dysfunctional coping**.
- In light of this, **APS** would be **affected** primarily by the development of **cognitive abilities**, …
- … while **BS** would be **affected** primarily by **brain maturation**.

➢ **BS-like phenomena** likely occur **temporarily, infrequently and at random as part of major brain maturation processes** without being clinically significant and thus decrease in prevalence once brain maturation steps have arrived at their adult corridor.

Modell of the relationship of between basic symptoms and brain maturation, and APS and maturation of cognitive abilities



Conclusions

- Effects related to cognitive and brain development – and thus to age – clearly play a role in symptoms currently used to predict psychosis
- More research into such age-related aspects and into potential age-differential prediction models are needed – the more so, as no prediction-enhancement in children and adolescents by current studies on additional biological markers can be expected
- However, an early is particularly important in this young age group for the potential devastating effects of treatment delays
- Thus, for the time being, one should follow the recommendations by the EPA

EPA recommendations for clinical high risk states children and adolescents

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(Schmidt et al. 2015; Schultze-Lutter et al. 2015)

*"… CHR criteria should only be used and communicated with outmost care in children and young adolescents in whom they should nevertheless be **assessed and monitored**."*

*"… the current evidence for the psychosis-predictive value of CHR criteria and for the efficacy of psychological and pharmacological interventions in children and young adolescents is **not** sufficient to justify **primarily preventive** interventions."*

"… in children and adolescents, specific psychological interventions with the aim to improve functioning should be provided as part of an overall treatment plan and complemented by interventions for other psychosocial problems and co-morbid mental disorders according to their treatment guidelines. CHR symptoms should be carefully monitored and assessed for a potential progression over an extended period, and the treatment plan should be adapted according to their course."

Thank you for your attention!