Chapter 2

Integrating the 'Broader Autism Phenotype' into General Dimensional Frameworks of Psychopathology.

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Abstract

The concept of a 'Broader Autism Phenotype', a dimensional approach to problems related to Autism Spectrum Disorders (ASD), has received much attention in recent literature. ASD-problems occur frequently in the general population and often co-occur with problems from other domains of psychopathology. In the research presented here these co-occurrence patterns were investigated by integrating a dimensional approach to ASDs into more general dimensional frameworks of psychopathology. Factor Analysis was used to develop models covering multiple domains of psychopathology. A bi-factor model of specific and non-specific features of psychopathology showed the most adequate model fit in three measurement waves of a longitudinal general population sample (N=2230, ages 10-17). The results show that (a) problems traditionally related to the domain of ASDs can be adequately integrated into general population based dimensional models of psychopathology, (b) the 'Broad Autism Phenotype' can be regarded as a specific domain of problems that can be distinguished from the domains of Internalizing, Externalizing and Attention Problems, and (c) specific subdomains of BAP are differently related to INT, EXT and Attention Problems.

Introduction

Autism Spectrum Disorders (ASDs) are characterized by problems from the domains of (1) reciprocal social behavior, (2) language development and communication, or (3) repetitive/stereotypic behavior. Some children with these problems can be diagnosed according to the narrow criteria of 'Autistic Disorder', but a larger group of children show problems from these domains that do not meet these narrow criteria. This observation has led to the idea of a spectrum (Wing & Gould, 1979) which consists of both narrowly defined autistic disorder and milder forms of autistic problems. In DSM-IV some (but not all) children with these milder problems can be diagnosed as suffering from 'Asperger's disorder' or 'Pervasive Developmental Disorder- Not otherwise Specified' (PDD-NOS). PDD-NOS constitutes a residual, catch-all category that does not correspond to a clearly defined disorder and a

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dimensional conceptualization is a promising alternative in capturing the structure of these problems without imposing arbitrary cut-offs. A dimensional approach also accommodates continuity between PDD-NOS, subthreshold symptoms, and normality (Constantino & Todd, 2003). Furthermore, dimensions are in line with the finding that the family members of children with a diagnosis of autism often present with milder symptoms of what has been called the 'Broader Autism Phenotype' (BAP; Bolton, et al., 1994; Folstein & Rutter, 1988).

The research we report here is aimed at testing and expanding the dimensional approach by integrating autism spectrum problems into more general dimensional frameworks of psychopathology. Dimensional models of psychopathology are particularly useful in that they can provide insight into the high comorbidity rates that have been found between ASDs and other domains of psychopathology (de Bruin, Ferdinand, Meester, de Nijs, & Verheij, 2007; Simonoff, et al., 2008). Furthermore, they illuminate the dimensional structure of autism spectrum-problems by testing the hypothesis that they constitute a single coherent spectrum of problems in the general population.

Comorbidity among syndromes is not specific to ASDs, but a general phenomenon in psychiatric classification (Kessler, Chiu, Demler, & Walters, 2005). If syndromes have clearly distinct underlying causal factors, comorbidity indicates the presence of two diseases at the same time. In psychiatry this is seldom the case and comorbidity may indicate that the syndrome categories used do not adequately capture the underlying causal structures from which problems emerge (Krueger & Markon, 2006a; Meehl, 2001). For understanding comorbidity in psychiatry it is therefore useful to reconsider and remodel the way psychopathology is conceptualized. Research on general population data shows that many cross-diagnostic correlation patterns can be captured by a structure with two higher-order-factors, generally referred to as the Internalizing (INT) and Externalizing (EXT) spectrum (Krueger, et al., 1998; Krueger, et al., 2003; Vollebergh, et al., 2001). This work builds on work by Achenbach and colleagues who were the first to propose this distinction between Internalizing and Externalizing problems in child psychiatry (Achenbach, 1966). Recently, a similar model has been found to fit data on child- and adolescent DSM-IV syndromes (Lahey, et al., 2008).

Comorbidity in these higher-order models may be interpreted in many other ways than the idea of 'two diseases at the same time' and has resulted in new theories about the causal structure of psychopathology (e.g. Krueger & Markon, 2006b). Comparable, but slightly different from the higher order factor models are models of specific and non-specific features of psychopathology (Weiss, Susser, & Catron, 1998). In these models comorbidity is interpreted as indicating that part of the problems are non-specific, i.e. not indicating a syndrome-specific latent structure, and therefore their variance is primarily related to non-specific variation in the amount of problems. Variance not captured by this component is interpreted as indicating a more specific latent structure related to broad domains like INT or EXT, or specific domains like

'Depression' or 'Aggression'. These models have been applied by using contrasts (Essex, et al., 2006; Weiss, et al., 1998) or Principal Component Analysis (Noordhof, Oldehinkel, Verhulst, & Ormel, chapter 4 of this thesis). For the research reported here we used Confirmatory Factor Analysis (CFA), because it allows for a direct comparison with the aforementioned higher-order models (Patrick, Hicks, Nichol, & Krueger, 2007; Yung, Thissen, & McLeod, 1999).

ASDs show high comorbidity with other DSM-IV syndromes (de Bruin, et al., 2007; Simonoff, et al., 2008). Furthermore, behavioral-genetic studies have shown substantial shared additive genetic variance of the BAP and other domains of psychopathology (Hoekstra, Bartels, Hudziak, van Beijsterveldt, & Boomsma, 2007; Reiersen, Constantino, Grimmer, Martin, & Todd, 2008; Ronald, Simonoff, Kuntsi, Asherson, & Plomin, 2008). Thus, BAP problems are both phenotypically and genotypically related to other domains of psychopathology. Integration of these problems into the general INT and EXT dimensional models of psychopathology described above may offer new insights into the phenotypic structure. A second rationale for the integration of BAP into existing dimensional models is to understand whether the higher order structure of BAP problems is appropriately conceptualized as a single dimension. Some authors have found that the first principal component captured a major part of variance in ASD-problems (Constantino, et al., 2004). Others, using other instruments, have found solutions with three or more correlated factors (e.g. Boomsma, et al., 2008; Hoekstra, Bartels, Cath, & Boomsma, 2008; Luteijn, Luteijn, Jackson, Volkmar, & Minderaa, 2000; Volkmar, et al., 1988). Happe and Ronald (2008) have argued that the correlations between the different subdomains within the BAP are actually quite low and suggestive of a 'fractionable autism triad'. This triad is proposed to consist of relatively independent subdomains which are related to different specific underlying (biological) mechanisms. In a recent review Mandy and Skuse (2008) concluded that only a few studies have directly addressed the hypothesis that the social (i.e. reciprocal behavior, social information processing) and non-social (i.e. restricted interest, repetitive behavior) problems are strongly related and that most of the evidence does not support a strong link between these domains. Nevertheless, the authors conclude that completely abandoning the idea of a 'Broad Autism Phenotype' is premature, given the inconclusiveness of the evidence and the fact that the loose covariance between sub domains is still a finding that deserves research attention. Some authors have proposed a higher-order model (Bolton, et al., 1994) in which BAP subscales load on one higher-order factor. However, it is not certain that a BAP factor will actually emerge as a distinct factor, in joint analysis with subscales from other domains of psychopathology. Therefore, the present joint analysis of BAP, Internalizing, and Externalizing subscales in the general population can also be used to further test the hypothesis that the multiple subdomains that are considered part of the BAP constitute a distinct and coherent dimension which can be differentiated from INT and EXT.

To summarize, dimensional conceptualization of problems that are traditionally referred to as the 'Broader Autism Phenotype' offers a promising approach to increase

understanding of the latent structure of these problems in the general population. Integration into more general dimensional frameworks may offer insight into the structure of psychopathology in general and the structure of ASD-problems in particular. To this end, we developed and tested several factor analytic models in a general population cohort of (pre)adolescents. On the one hand these analyses can be regarded as an exploration of the covariance structure underlying these multiple problem domains. On the other hand these models allowed us to test the specific hypothesis that INT, EXT and BAP constitute three, correlated, problem domains in the general population, or alternatively, that covariance between problems from these domains is either suggestive of a more simple structure (e.g., BAP problems can be fully captured by INT and EXT factors) or a more complex structure. (e.g., BAP problems cannot be captured by a single higher order factor).

Methods

Sample

Subjects were participants in the 'Tracking Adolescents' Individual Lives Survey' (TRAILS), a prospective multi-cohort study of Dutch (pre)adolescents. The study involved a representative sample from the general population and is described in detail in Huisman et al.(2008). Briefly, the target sample involved all 10- to 11-year-old children living in the three largest cities and some rural areas in the North of The Netherlands. Of the eligible children, 76.0% (n=2230, mean age = 11.09, SD =0.55) were enrolled in the study. Responders and non-responders did not differ regarding the prevalence of teacher-rated problem behavior and associations between sociodemographic variables and mental health indicators (De Winter, et al., 2005). To date, the population cohort has been assessed three times (T1: March 2000- July 2001, T2: September 2003- December 2004, T3: September 2005-December 2007). Participation rates were 96.4% at T2 (mean age= 13.55, SD = 0.53), and 81.4% at T3 (mean age= 16.25, SD = 0.73). After complete description of the study to the subjects, written informed consent was obtained from the parents at each assessment wave and from the adolescents at T2 and T3. T1, T2, and T3 data are used in the present study.

Instruments

- *CBCL*

The Dutch version of the Child Behavior Checklist (CBCL; Achenbach, 1991a; Verhulst, van der Ende, & Koot, 1996) was used to assess Internalizing, Externalizing and Attention problems. The CBCL is a 112-item questionnaire on which parents rate descriptions of emotions and behaviors on a 3-point scale (not [0], sometimes [1], or very often [2]). The period over which they are asked to report is the last six months. In the TRAILS-study the questionnaire was completed by one of the parents, which was the mother in most cases. Factor analysis on these items revealed a structure of eight syndrome scales (Achenbach, 1991a). Three of the CBCL scales are related to the

Internalizing domain (INT): Anxious-Depressed (13 items, α=0.78), Somatic complaints (11 items, α=0.69), and Withdrawn-Depressed (8 items, α=0.71). Two are related to the Externalizing domain (EXT): Aggressive Behavior (18 items, α=0.88) and Rule-Breaking behavior (17 items, α=0.68). The other three scales are Attention Problems (10 items, α=0.82), Social Problems (11 items, α=0.78), and Thought Problems (15 items, α=0.63). In a study by Hartman et al. (1999) the distinction between an INT and EXT factor was replicated quite well, although they found no significant difference in model fit between a 2-factor and an 8-factor solution.

The scales Thought Problems and Social Problems are generally not regarded part of either the INT or EXT domain. Integration of these diverse items into INT, EXT or more comprehensive dimensional models may be interesting for its own sake, but was regarded too complex within the context of the current paper. The Attention Problems scale is also not part of INT or EXT in the CBCL. However, this scale is related to ADHD, which is part of the EXT-spectrum in other studies (e.g. Lahey, et al., 2008) and which is strongly comorbid with ASDs (Simonoff, et al., 2008). Therefore the Attention Problems scale was included in the analysis.

• *CSBQ*

The parent-rated Child Social Behavior Questionnaire (Luteijn, Jackson, Volkmar, & Minderaa, 1998) was used to assess problems that are commonly found in children diagnosed with an ASD. The instrument has a 3-point rating-scale that is equal to the CBCL-format (not [0], sometimes [1], or very often [2]). The CSBQ differs from the CBCL in that the questions refer to a two-month period. Originally, the instrument consisted of 96 items covering the full range of problems, with an emphasis on the milder variants seen in PDD-NOS (Luteijn, et al., 1998). Hartman, Luteijn, Serra, & Minderaa (2006) refined and shortened the CSBQ to 49 items and found a 6-factor structure with Exploratory Factor Analysis (EFA): Behavior/Emotions not Optimally Tuned to the Social Situation (Not tuned, 11 items, α=0.84), Reduced Contact and Social Interests (Reduced Contact, 12 items, α=0.76), Orientation Problems in Time, Place or Activity (Orientation, 8 items, α=0.78), Difficulties in Understanding Social Information (Social Understanding, 7 items, α=0.75), Stereotyped Behavior (Stereotyped, 8 items, α=0.69), and Fear and Resistance to Change (Fear of Change, 3 items, α=0.74).

Statistical analyses

MPlus version 5.2 was used to explore and test latent variable models of the subscales of the CBCL and the CSBQ. All scales were skewed and some scales were extremely skewed (skewness coefficient > 2): CBCL Rule-Breaking, and CSBQ Orientation, Social Understanding, Stereotyped, and Fear of Change. To accommodate for this, we transformed all variables by taking their natural logarithms.[1]

[1] *We added 1 to the scores before taking the natural logarithm, because the natural logarithm of zero is undefined.*

Furthermore, we used maximum likelihood estimation with robust standard errors (MLR), because of its relative robustness to deviations from normality. We used the Root Mean Square Error of Approximation (RMSEA) and Comparative Fit Index (CFI) as indicators of absolute model fit. The Bayesian Information Criterion (BIC) was used to compare different models with satisfactory RMSEA and CFI. We started by developing models on T2-data and then replicated these model for the younger (T1) and older (T3) measurement waves.

First, a higher-order model was developed on the basis of T2-data. To this end we used both CFA and EFA. We started with testing the higher-order model illustrated in Figure 1, which corresponds to the hypothesis that INT, EXT and BAP are three different, correlated, domains of psychopathology. Subsequently, we explored and tested multiple alternative models, which will be described in more detail in the results-section. Finally, we selected those models that showed adequate model fit for replication in T1 and T3 data.

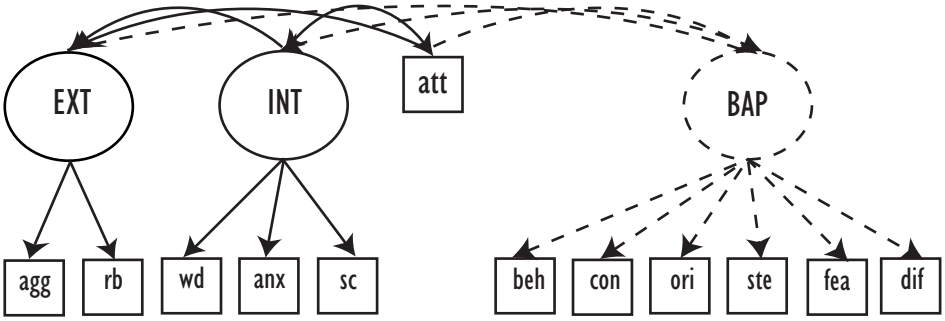

Figure 1. Higher order model with and without inclusion of a factor related to the 'Broader Autism Phenotype' (indicated by dotted lines).
Note: EXT = Externalizing,; *INT* = Internalizing; *BAP* = Broader Autism Phenotype; *Agg* = Aggressive Behavior; *Anx* =Anxious-Depressed; *Rb* = Rule-Breaking Behavior; *Sc* = Somatic Complaints; *Wd* = Withdrawn-Depressed; *Att* = Attention Problems; *Beh* = Behavior and Emotions Not Optimally Tuned to The Social Situation; *Dif* = Difficulties in Understanding Social Information; *Fea* = Fear of and Resistance to Changes; *Ori* = Orientation-problems in time, place, or activity; *Con* = Reduced Contact and Social Interests; *Ste* = Stereotyped behavior.

Second, a bi-factor model was developed. A bi-factor model corresponds to the hypothesis that part of the variance in problem behavior consists of non-specific (NS) covariance between all subscales. Covariance that is not captured by this NS-factor is hypothesized to be related to a specific problem domain. In contrast with higher-order models, bi-factor model factors are orthogonal (i.e. the factors are not correlated). Instead, the correlations between the factors in the higher-order model are assumed to be captured by the NS-factor in the bi-factor model. We tested multiple alternative

bi-factor models and selected those that showed adequate model fit for replication in T1 and T3 data.

Third, we evaluated whether the selected models could be replicated in different measurement-waves within the same sample. We compared fit indices of the multiple alternative models in T1, T2, and T3 in order to test whether the same model was superior in all measurement waves.

Results

Developing a higher-order model on T2-data

We developed higher-order models by fitting CFA-models on the one hand and exploring possible improvements using EFA on the other. This approach allowed us to test specific hypotheses regarding BAP and its co-occurrence with other problem domains and develop a well-fitting integrative higher-order model. The analysis proceeded in five steps and resulted in the selection of two adequate models to be replicated on T1 and T3 data. All fit indices of these analyses are shown in Table 1.

In step one, we tested the basic hypothesis that the CSBQ-scales measure a single distinct problem domain (BAP) and that comorbidity of BAP with Internalizing and Externalizing problems can be captured by correlations with the INT and EXT higher-order factors. To this end the 'basic higher-order model' (Figure 1) was tested with the use of CFA. In this model Attention Problems was regarded as a different problem domain indicated by only one subscale and correlated with the three higher order factors. An adequate fit of this model would support the strategy of simply investigating INT, EXT and BAP as three distinct domains of psychopathology measured by two different instruments. However, as shown in Table 1, this model did not fit well to the T2-data (RMSEA>.05; CFI<.95). This implies that the covariance between CSBQ- and CBCL-scales cannot be regarded as simply reflecting correlations between broad domains of psychopathology and should be investigated in more detail, which was done in step two and three.

In step two, we explored the relation between subscales in more detail, using EFA to model the covariance structure of CSBQ and CBCL-scales. A well-fitting 5-factor model (RMSEA<.05; CFI>.95) was found with a lower BIC-value than the 4-factor model (see Table 1). The 6-factor model did not converge, so we used the factor loadings of the 5-factor model. Factor loadings of the 5-factor model are shown in Table 2.

Table 1. *Fit indices for CFA and EFA-models developed on T2-data and replicated on T1 and T3 data.*

Data	Model	Step[a]	Figure[b]	RMSEA	CFI	BIC
T2	Higher-order	1	1	0.12	0.86	37886
	EFA					
	4 factor	2		.047		41656
	5 factor			.03		41588
	6 factor			nc		
	Higher-order					
	Refined	3	2	0.05	0.98	36710
	Without BAP	4	2	0.12	0.86	37899
	Third-order	5	3	0.06	0.98	36730
	Bi-factor					
	Refined	1	4	0.05	0.98	36655
	Without BAP* [c]	2	4	0.08	0.95	36943
	Without F4*	3	5	0.06	0.98	36726
T1	Higher order					
	Refined		2	0.05	0.98	41954
	Third-order		3	0.05	0.97	41963
	Bi-factor					
	Refined		4	0.04	0.99	41863
	Without F4*		5	0.05	0.98	41937
T3	Higher-order					
	Refined		2	0.06	0.97	29127
	Third-order		3	0.06	0.97	29142
	Bi-factor					
	Refined		4	0.05	0.99	29042
	Without F4*		5	0.05	0.98	29099
	Without F4*		5	0.05	0.98	29099

Note: *RMSEA* = Root Mean Square Error of Approximation; *CFI* = Comparative Fit Index; *BIC* = Bayesian Information Criterion; *EFA* =Exploratory Factor Analysis; *BAP* = Broader Autism Phenotype; *F4* = Factor from previous EFA.

[a] Refers to the analytic steps described in the results-section.

[b] Refers to the Figure in which the model is shown.

[c] A * refers to factors in the bi-factor models which correspond to, but are not equivalent to, the factors with the same names in the higher-order models.

Table 2. *Loadings of subscales in 5-factor Exploratory Factor Analysis-solution.*

	F1	F2	F3	F4	F5
Agg		0.88			
Anx	0.80				
Rb		0.53		0.31	
Sc	0.48				
Wd	0.38		0.69		
Att				0.64	
Beh		0.71			0.34
Dif				0.32	0.40
Fea	0.34				0.42
Ori				0.58	0.42
Con			0.46		0.46
Ste				0.21	0.44

Note: Only loadings >.2 are reported. Factor Fx refers to the x-th factor derived in the EFA-solution; *Agg* = Aggressive Behavior; *Anx* =Anxious-Depressed; *Rb* = Rule-Breaking Behavior; *Sc* = Somatic Complaints; *Wd* = Withdrawn-Depressed; *Att* = Attention Problems; *Beh* = Behavior and Emotions Not Optimally Tuned to The Social Situation; *Dif* = Difficulties in Understanding Social Information; *Fea* = Fear of and Resistance to Changes; *Ori* = Orientation-problems in time, place, or activity; *Con* = Reduced Contact and Social Interests; *Ste* = Stereotyped behavior.

In step three, we constructed a 'refined higher-order model' in order to model the more specific relations between CBCL- and CSBQ-scales that were suggested by EFA. A first refinement was to include loadings of CSBQ-scales on the higher-order factors INT and EXT. Based on the EFA-factors F1 and F2, free loadings were added of the CSBQ-scale Fear of Change on INT and Not Tuned on EXT. This indicates that in the refined model these two CSBQ-scales are interpreted as partly related to the INT and EXT domain rather than only related to the BAP domain. As a second refinement, a free correlation was added between the residual variances of the CSBQ-scale Reduced Contact and that of the CBCL-scale Withdrawn-Depressed, because the EFA-factor F3 suggested a specific covariance between these two scales.

The third refinement was to add the fourth EFA-factor to the model by specifying a higher-order factor F4 with loadings of five subscales. The EFA-factor F4 captures covariance between two CBCL (Rule-Breaking Behavior, and Attention Problems) and three CSBQ-scales (Orientation, Stereotyped, and Social Understanding). These three additions resulted in the 'refined higher-order model' illustrated in Figure 2. As shown in Table 1, this model fitted well to the T2-data (RMSEA=.05, CFI>.95) and had a lower BIC-value than the basic model. This means that the EFA-based improvements were sufficient to adequately capture the covariance between CBCL and CSBQ in a higher-order model.

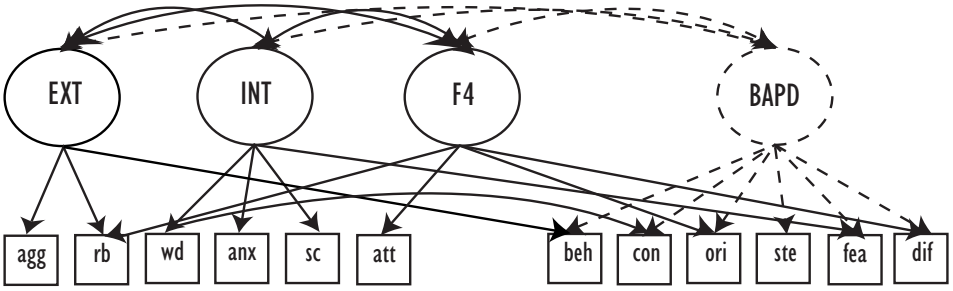

Figure 2. Refinement of the higher order model on the basis of interpretation of EFA.
Note: Abbreviations are explained in figure 1.

In step four, we tested the hypothesis that the six CSBQ-scales had to be modeled as a separate domain in the general population. For this aim we tested whether a model without a BAP-factor fitted the data. This was not the case (Table 1: RMSEA>.05; CFI<.95) and the BIC-values were even lower than those for the basic model. This shows that it was necessary to include a BAP-factor, which implies that the six CSBQ subscales constitute a specific domain that can be distinguished from INT and EXT.

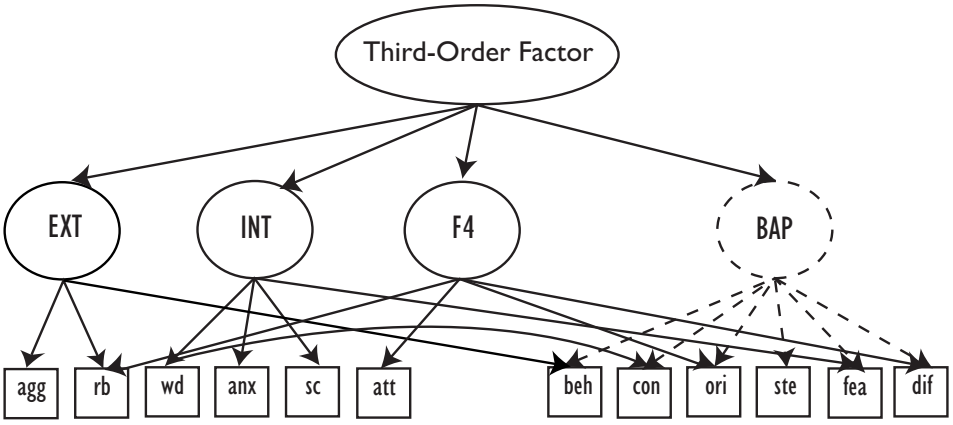

Figure 3. The refined higher order model with inclusion of a third-order factor.
Note: Abbreviations are explained in figure 1; *F4* = Factor from previous Exploratory Factor Analysis.

In step five, we tested the hypothesis that the covariance between the four higher-order domains (INT, EXT, BAP and F4) could be captured by a single third-order factor (see Figure 3). As described in the introduction section of this paper, this model can be conceptually and statistically distinguished from the way between-domain covariance is captured in a bi-factor model (see next paragraph). Fitting both models to T2-data allowed for a direct comparison between their fit indices. Including a third-order factor resulted in slightly worse fit indices (see Table 1). This shows that covariance between the four higher-order factors could not be fully captured by a single third-order factor.

On the basis of these five analyses, the 'refined higher-order model' with inclusion of a BAP-factor (step 3) was chosen as the most adequate model and selected for replication in T1 and T3-data. The model with addition of the third-order general factor (step 5) was also selected for replication, because the fit indices of this model were only slightly worse.

Developing a bi-factor model on T2-data

The bi-factor model was developed as an alternative to the higher-order models. This was done to compare two different interpretations of the covariance between INT, EXT and BAP-problems. In the higher-order models, covariance between these domains is interpreted as a correlation between higher-order factors (Figure 2) or as an expression of an underlying, more general, third-order factor (Figure 3). In a bi-factor model the correlation between domain-specific factors is fixed at zero and a non-specific factor is introduced on which all subscales may have loadings. Therefore, between-domain covariance is interpreted as 'non-specific' covariance between subdomains rather then as correlation between higher-order factors. We developed a bi-factor model in three steps.

In the first step, the 'refined higher-order model' (Figure 2) was 'translated' into a bi-factor model to allow for a direct comparison of model fit between these two models. To this end we simply added a NS-factor and fixed all correlations between factors at 0 (see Figure 4).[2] This model showed adequate model fit (RMSEA=.05, CFI=.98).

In the second step, we tested the effect of removing the BAP*-factor from the model. Removal of the BAP-factor had resulted in completely inadequate model fit for the higher-order model (see step 4 above). However, this does not automatically generalize to the bi-factor model, because the NS-factor may capture part of the covariance between the six CSBQ subscales, which is captured by the BAP-factor in the higher-order model. A bi-factor model without BAP* did not show adequate fit indices (RMSEA= .08, CFI= .95), which supports the presence of covariance between all six CSBQ-scales that is not captured by the non-specific covariance between all CBCL and CSBQ-scales.

[2] *Because of introducing the NS-factor and orthogonality, the factors in the bi-factor are not the same as those in the higher-order model. To distinguish between the two a * is added to the factors of the bi-factor model.*

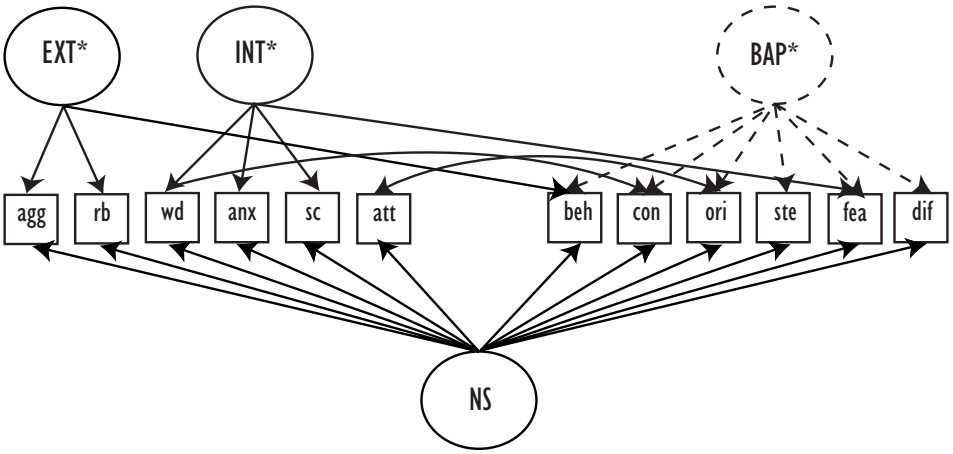

Figure 4. The bi-factor model based on adding an NS-factor to the 'refined higher-order model' and fixing correlations between factors at zero.
Note: Abbreviations are explained in figure 1. A * refers to a factor in the bi-factor that corresponds to, but is not equivalent to, the factor with the same name in the higher-order models; *F4* = Factor from previous Exploratory Factor Analysis.

The third step was based on an exploratory finding from observing the factor loadings of the bi-factor model with an additional F4* factor (Figure 4). It was found that the scales Social Understanding and Stereotyped had very low loadings (<.15) on this F4* factor. The loading of the Rule-Breaking scale was also rather low (.22). On the basis of this observation, we developed an alternative model, which includes a correlation between the Attention Problems and the Orientation scale rather than an F4*-factor. The model is illustrated in Figure 5. Fit indices for this model were only slightly inferior (RMSEA=.06, CFI=.98).

On the basis of these three analyses the 'refined bi-factor model' (Figure 4) was selected for replication, because the fit indices for this model were best. Furthermore, the model with only a correlation between Attention and Orientation Problems (Figure 5), rather than an F4* factor, was selected as it showed only slightly worse fit indices.

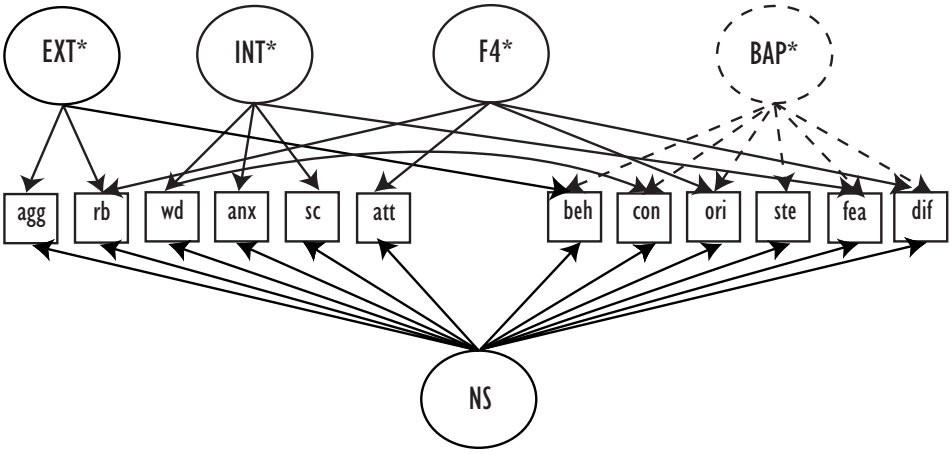

Figure 5. Alternative bi-factor model in which factor F4* is replaced by a free correlation between Att and Ori.
Note: Abbreviations are explained in figure 1.

Fitting models on T1 and T3 data

After having selected two higher-order models (Figure 2 and 3) and two bi-factor models (Figure 4 and 5), we tested the same models in different measurement waves of the sample. This was done to test whether the findings replicated in a younger (T1) and older (T3) age group, and to compare the models and test whether the same model showed superior fit indices at T1, T2 and T3.

As shown in table 1, CFI fit indices were adequate for all models (CFI>.95). Only the refined bi-factor model with F4* showed completely satisfactory RMSEA indices (RMSEA<.05). Furthermore, for this model BIC-values were lowest at all occasions. These results show that the bi-factor model shown in figure 4 is preferable to the other models in terms of model fit, but the differences shown in Table 1 are only modest. Factor loadings and residual variances of this model in the T2-data are shown in table 3.[3] This model includes the three specific factors INT*, EXT*, and BAP*. Furthermore, it includes two exploratory findings. First, a free correlation between the Withdrawn-Depressed and the Reduced Contact subscales. Second, the factor F4*, which is dominated by the subscales Attention Problems and Orientation. These two exploratory findings will be interpreted in the discussion.

[3] *In view of the limited space for this article we do not report the loading-patterns for T1 and T3 data. These were very comparable, but not exactly equal. These results can be obtained from the authors upon request.*

Table 3. *Factor loadings of the final bi-factor model for T2-data and explained variance for each subscale.*

	NS		EXT* [a]		INT*		F4*		BAP*		R^2
Agg	1.00	*0.77*	1.00	*0.55*							0.89
Anx	0.71	*0.63*			1.00	*0.56*					0.71
Rb	0.67	*0.64*	0.52	*0.35*			1.15	*0.22*			0.58
Sc	0.41	*0.40*			0.47	*0.35*					0.25
Wd	0.60	*0.59*			0.56	*0.29*					0.47
Att	0.41	*0.68*					1.00	*0.33*			0.57
Beh	0.88	*0.70*	0.74	*0.42*					1.00	*0.26*	0.74
Dif	0.68	*0.65*					0.71	*0.13*	1.01	*0.31*	0.53
Fea	0.30	*0.45*			0.33	*0.31*			0.76	*0.37*	0.43
Ori	0.58	*0.58*					2.40	*0.48*	1.27	*0.41*	0.73
Con	0.63	*0.55*							1.39	*0.39*	0.46
Ste	0.36	*0.45*					0.53	*0.13*	0.88	*0.35*	0.34

Residual Correlation Wd with Con = *0.56* [b]

Note: Standardized loadings are shown in italics; *NS* = Non Specific; *EXT** = Externalizing; *INT** = Internalizing; *F4** = Factor modeled on the basis of the fourth factor in the earlier Exploratory Factor Analysis; *BAP** = Broader Autism Phenotype; Other abbreviations are explained in table 2.

[a] A * refers to factors in the bi-factor models which correspond to, but are not equivalent to, the factors with the same names in the higher-order models.

[b] Residual correlation between Wd and Con was freely estimated.

Discussion

This study shows that ASD problems can be adequately integrated into dimensional frameworks of psychopathology. Support was found for the concept of a 'Broader Autism Phenotype' (BAP; Bolton, et al., 1994; Folstein & Rutter, 1988) in the general population that can be distinguished from the Internalizing and Externalizing spectrum. We also found support for the importance of subscale specific processes, as emphasized in the idea of a 'Fractionable Autism Triad' (Happe & Ronald, 2008). More generally, the study provides insight into the co-occurrences of BAP and its subdomains with other domains of psychopathology. Before discussing these insights, we will highlight some limitations of the study and discuss some precautions in interpreting the results.

Limitations

This is the first study that fully integrated BAP into higher-order and bi-factor models of Internalizing and Externalizing problems. The generalizability of the results may therefore be limited by the specifics of our study and replications are necessary before reaching more definite conclusions. These specifics include sample (Northern

part of the Netherlands), age (11-17), measures (CSBQ and CBCL), and informant (parent).

A second limitation is that the models are based on subscales rather than items. The drawback is that covariance between subscales of the CSBQ and CBCL may in some cases result from overlapping item content. Such item overlap is suggested by an EFA by Hartman et al. (2006). A full-scale bottom-up analysis of the two instruments could be used to resolve this issue. However, that is a computationally and conceptually complex project, which was beyond the scope of the current paper.

Finally, the research is limited by the fact that we only used factor analysis. Therefore, all the models we compared assumed normally distributed latent variables with linear relations to the observed variables. There may be underlying phenomena in our data that are better captured by non-linear relations or categorical variables. In future studies categorical latent variables may be studied by employing the techniques of latent class analysis or factor mixture modeling (Lubke & Muthen, 2005).

Interpreting the bi-factor model

The best fitting model was a bi-factor model. Before interpreting the specific factors in this model one may wonder what the 'non-specific' factor (NS) is. First, analyses of subscales that are all positively correlated will generally result in a first unrotated factor on which all subscales load substantially, which is the primary reason to call it non-specific. Second, systematic biases and specific viewpoints of the informant may result in increased correlations between subscales in non-specific ways and therefore contribute to the variance of the NS-factor. Third, by face-value inspection of the items and intuitive thinking one can think of many different ways in which these problems can be causally related in the development of a child and how multiple biological and social systems may interact in this development. A manifold of small positive causal effects crossing the borders of specific domains of psychopathology can result in the positive correlations that are found between subscales and therefore result in a large NS-factor (van der Maas, et al., 2006).

Our findings are much in line with the conclusion drawn in a recent review by Mandy and Skuse (2008) that, although subscale specific processes may be of primary importance, abandoning the concept of a 'Broader Autism Phenotype' is premature and neglects the modest coherence that is found between subdomains. The finding of a BAP-factor independent of NS, INT and EXT supports this conclusion. Yet the results also show that BAP cannot be understood well if it is studied as a single trait in the general population (Happe & Ronald, 2008; Mandy & Skuse, 2008). Subscales of the CSBQ are differentially related to other domains of psychopathology, and may involve different traits in the general population rather than just one single problem domain. In what follows, the relation of BAP-subdomains with the Internalizing, Externalizing and Attention Problems domains and implications for understanding comorbidity will be discussed.

BAP and the Internalizing Domain

Children with ASD often meet criteria for an anxiety disorder, specifically Social Anxiety Disorder (de Bruin, et al., 2007; Simonoff, et al., 2008). These children seldom meet criteria for a depressive disorder (de Bruin, et al., 2007; Simonoff, et al., 2008), but others have reported higher rates of co-occurrence between depression and ASDs (see Ghaziuddin, Ghaziuddin, & Greden, 2002). Brereton, Tonge, and Einfeld (2006) showed that prevalence of depressive symptoms increased with age, so the finding of a low co-occurrence may be specific for children. The other way around, ASD-symptoms have been found to be substantially elevated in children with diagnoses of Internalizing disorders and most strongly in mood disorders (Pine, Guyer, Goldwin, Towbin, & Leibenluft, 2008; Towbin, Pradella, Gorrindo, Pine, & Leibenluft, 2005). The current study shows two specific factors that may improve understanding of comorbidity.

First, the scale Reduced Contact was specifically correlated with Withdrawn-Depressed, but did not load on the INT-factor. Reduced Contact contains several items specifically related to core features of ASDs (e.g. 'makes little eye contact', 'dislikes physical contact' and 'does not look up when spoken to'). These results suggest a dimension related to reduced social interaction that is not specifically related to the Internalizing spectrum, but also not fully captured by the 'Broader Autism Phenotype'. This is very much in line with the idea that the social and non-social aspects of BAP should be studied as separate traits rather than as a single dimension (Happe & Ronald, 2008). Reduced social interaction may be specifically relevant to understand comorbidity with Social Anxiety Disorder and may also be related to possible (future) comorbidity with depressive disorders.

Second, the scale Fear of Change loaded on the INT-factor. This subscale consists of only three items, which have low prevalence in the general population and are related to strong emotional reactions to change, which is typical for some children with ASDs. A speculative hypothesis derived from this finding is that these strong reactions to (social) change underlie or are risk factors for Internalizing problems.

BAP and the Externalizing Domain

Children with ASD often meet criteria for Oppositional Defiant Disorder (ODD), and less often for Conduct Disorder (CD; de Bruin, et al., 2007; Simonoff, et al., 2008). The other way around, ASD-problems are highly prevalent in children with ODD or CD (Gilmour, Hill, Place, & Skuse, 2004; Luteijn, et al., 2000). The current study suggests one specific source that may contribute to this comorbidity.

The scale Not Tuned loaded on EXT. This can be explained by the fact that the items of this scale are clearly related to aggressive and disobedient behaviors. Nevertheless, the scale contains items on a specific kind of problems that are not fully captured by EXT and the CBCL-scales, as the scale also loads on the BAP-factor. The hypothesis that can be derived from this is that the subscale reflects a source of disobedience and opposition that is specifically related to social deficits, difficulties in

social information processing or strong reactions to change. The question to be answered is whether overlap between problems from the syndromes ODD/CD and ASDs is specifically related to the factor Not Tuned and what underlying mechanisms influence this specific covariance. It may be relevant for understanding and diagnosing Externalizing behaviors to distinguish between children who have a lot of social deficits and poorly understand social conventions and those who don't, because they may differ with regard to their motives and triggers for aggression and opposition, and in their response to interventions (Gilmour, et al., 2004).

BAP and ADHD

Children with an ASD often meet criteria for ADHD (de Bruin, et al., 2007; Simonoff, et al., 2008). The other way around, autism symptoms are often found in children with ADHD (Bishop & Baird, 2001; Mulligan, et al., 2009). To understand this phenomenon it may be important to distinguish between two aspects of ADHD: attention problems on the one hand and impulsivity/hyperactivity on the other (Ronald, et al., 2008). This distinction was found important in a recent study by Lahey, et al. (2008) and has been supported by a recent Latent Class Analysis by Volk, Henderson, Neuman, and Todd (2006), which distinguished three types: Severe Inattention, Severe Combined and Mild Combined. The results of the current study suggest two specific sources of co-occurrence between ASD-symptoms and ADHD.

First, the scales Attention Problems and Orientation both loaded strongly on the same factor of the bi-factor model (F4* in figure 4). Similarly, in an EFA by Hartman et al. (2006) items from these scales loaded on the same factor. This points to the possibility that one specific source of comorbidity between ADHD and ASD-symptoms is related to attention, executive functioning, and information processing difficulties. Children with ADHD and PDD-NOS have been shown to perform very similarly on a number of tasks measuring executive functioning (Gomarus, Wijers, Minderaa, & Althaus, 2009). The factor F4* may be specifically related to these problems in executive functioning and to the 'inattention' aspect of ADHD, which may constitute as specific subdomain of problems that can be distinguished from BAP, INT and EXT.

Second, the CBCL-scale Attention problems does not capture the 'hyperactivity and impulsivity' component of ADHD. Items regarding this component are found in the Aggressive Behavior scale. This scale loads on the EXT factor and so does the Not Tuned scale of the CSBQ. This suggests that a second source of co-occurrence between ADHD and ASD-symptoms may involve a specific Externalizing feature of both syndromes. This idea is very similar to the hypothesis we developed for the overlap between ODD and ASD-symptoms and results in a more general hypothesis that similar underlying (EXT-related) mechanisms may be implicated in the comorbidity between these three syndromes. One such common mechanism may involve deficient social problem solving (Matthys, Cuperus, & Van Engeland, 1999), which can increase the chance to get into conflicts with others.

Implications for diagnosis and clinical practice

Understanding the latent structure underlying multiple problem domains can be crucial for advancing diagnostic systems over time. The current study points to some important ways in which clinical diagnosis may be improved.

First, measuring BAP and its subdomains may not only be relevant in the context of diagnosing ASDs, but also in the context of other, more prevalent, DSM-IV diagnoses. The current study shows that treating BAP as a completely distinct domain of psychopathology may neglect important relations between BAP-subscales and other domains of psychopathology. It is counterintuitive to assume that ASD-symptoms are only relevant if severe enough to meet criteria for a DSM-IV syndrome.

Second, the study provides a method to eliminate the unsatisfying heterogeneous residual category PDD-NOS. From the bi-factor model a stepwise approach to diagnosis may be derived: First, a diagnostician would use a measure of non-specific amount of problems. Second, he or she would investigate scores on specific problem domains (for example, INT, EXT, Attention, Reduced Contact, BAP). Third, in some cases, a more detailed analysis of the subscales of these domains may add specific diagnostic information. In such a diagnostic procedure that follows a dimensional model of common and specific features, the category PDD-NOS can be replaced by a broad BAP-dimension with more specific subscales. This approach, which is similar to a recent proposal of Watson (2005) regarding the Mood and Anxiety Disorders, has several advantages, among which (a) decreased artificial comorbidity, (b) more attention to both general and specific aspects of diagnosis, (c) an emphasis on the gray areas between current categorical syndromes and thereby (d) a closer link to the covariance structure of problems in the general population. Furthermore, if categories are preferred for clinical practice they can be derived on the basis of carefully chosen cut-points on a dimensional structure (e.g. Kamphuis & Noordhof, see chapter 3).

Third, the results are in line with a recent tendency in research and clinical practice to place more emphasis on trans-diagnostic processes as opposed to focusing on predefined syndromes. Even if syndrome boundaries would "neatly carve nature at its joints" (Waller, 2006), underlying processes and successful interventions may be shared between multiple problem domains. Since it is well-know that the actual situation is one of overlapping domains and gray arrays between them the issue of trans-diagnostic processes is even more relevant and neglecting it can result in suboptimal treatment.

Conclusion

This study shows that (a) problems traditionally related to the domain of ASDs can be adequately integrated into general population based dimensional models of psychopathology, (b) the 'Broad Autism Phenotype' can be regarded as a specific domain of problems that can be distinguished from the domains of Internalizing, Externalizing and Attention Problems, and (c) specific subdomains of BAP are differently related to INT, EXT and Attention Problems.