

Deriving Biologically Grounded Dimensions of Social Functioning in Autism: Results from the Autism Biomarkers Consortium for Clinical Trials (ABC-CT)



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Background

Caregiver-report questionnaires are widely used to assess social functioning in autistic children, often serving as primary outcomes in clinical trials and endpoints in studies of genetic, physiological, and neurobiological markers. Yet, many existing measures aggregate distinct social abilities into broad composites, assess only a limited subset of these abilities, or rely on poorly validated factor structures – limiting the precision with which candidate biomarkers can be linked to specific aspects of social functioning.

The Research Domain Criteria (RDoC)¹ framework parses social functioning into fine-grained domains that are supported by interconnected neural systems and measurable across units of analysis, from brain to behavior. RDoC-aligned questionnaires may better capture underlying mechanisms and facilitate biomarker discovery by enabling more precise links between specific social functioning domains and neurobiological systems.

Objectives

To determine whether RDoC-aligned domains of social functioning can be derived from existing caregiver-report questionnaires in autism and to assess their associations with EEG and eye-tracking biomarkers.

Methods

A secondary analysis was conducted on Autism Biomarkers Consortium for Clinical Trials (ABC-CT) data collected across five U.S. sites².

Caregiver-report questionnaires were available for 480 autistic children ($M_{age}=8.53$ years, $SD=1.61$; 76% male; 66% White), with EEG and eye-tracking data available for a subset ($n=204$; $M_{age}=8.53$ years, $SD=1.58$; 75% male; 63% White).

1. Item Selection

Item content from questionnaires was reviewed to identify candidate items relevant to RDoC social functioning constructs:

- Aberrant Behavior Checklist (ABC)
- Autism Impact Measure (AIM)
- Child and Adolescent Symptom Inventory, 5th Edition (CASI-5)
- Pervasive Developmental Disorder Behavior Inventory (PDDBI)
- Social Responsiveness Scale, 2nd Edition (SRS-2)

2. Integrated Item Pool

The final item pool comprised 58 items.

3. Item-Domain Assignment

Five theoretical factors were formulated based on conceptual analysis of item content:

- Attachment and Affiliation
- Production of Facial Communication
- Production of Non-Facial Communication
- Reception of Communication (Facial and Non-Facial)
- Understanding Mental States

4. Structural Modelling

The hypothesized five-factor structure was evaluated through confirmatory application of exploratory structural equation modeling (ESEM). Correlated factor and bifactor models were iteratively estimated and compared.

5. Biomarker Associations

Spearman or Pearson partial correlations were computed between the resulting RDoC constructs and candidate EEG and eye-tracking biomarkers within the ABC-CT. Child age, sex, and full-scale IQ were included as covariates, with false discovery rate (FDR) correction applied for multiple comparisons.

Results

The five-factor correlated factors model showed good fit ($CFI=.933$, $TLI=.919$, $RMSEA=.046$ [.044–.049], $SRMR=.050$). Due to cross-loadings between Production of Facial and Non-Facial Communication items, these were combined into a single Production of Communication factor. The revised four-factor correlated factors model showed good fit ($CFI=.935$, $TLI=.920$, $RMSEA=.057$ [.053–.060], $SRMR=.051$), with improved fit for a bifactor solution ($CFI=.955$, $TLI=.941$, $RMSEA=.049$ [.045–.052], $SRMR=.042$) (**Figure 1**).

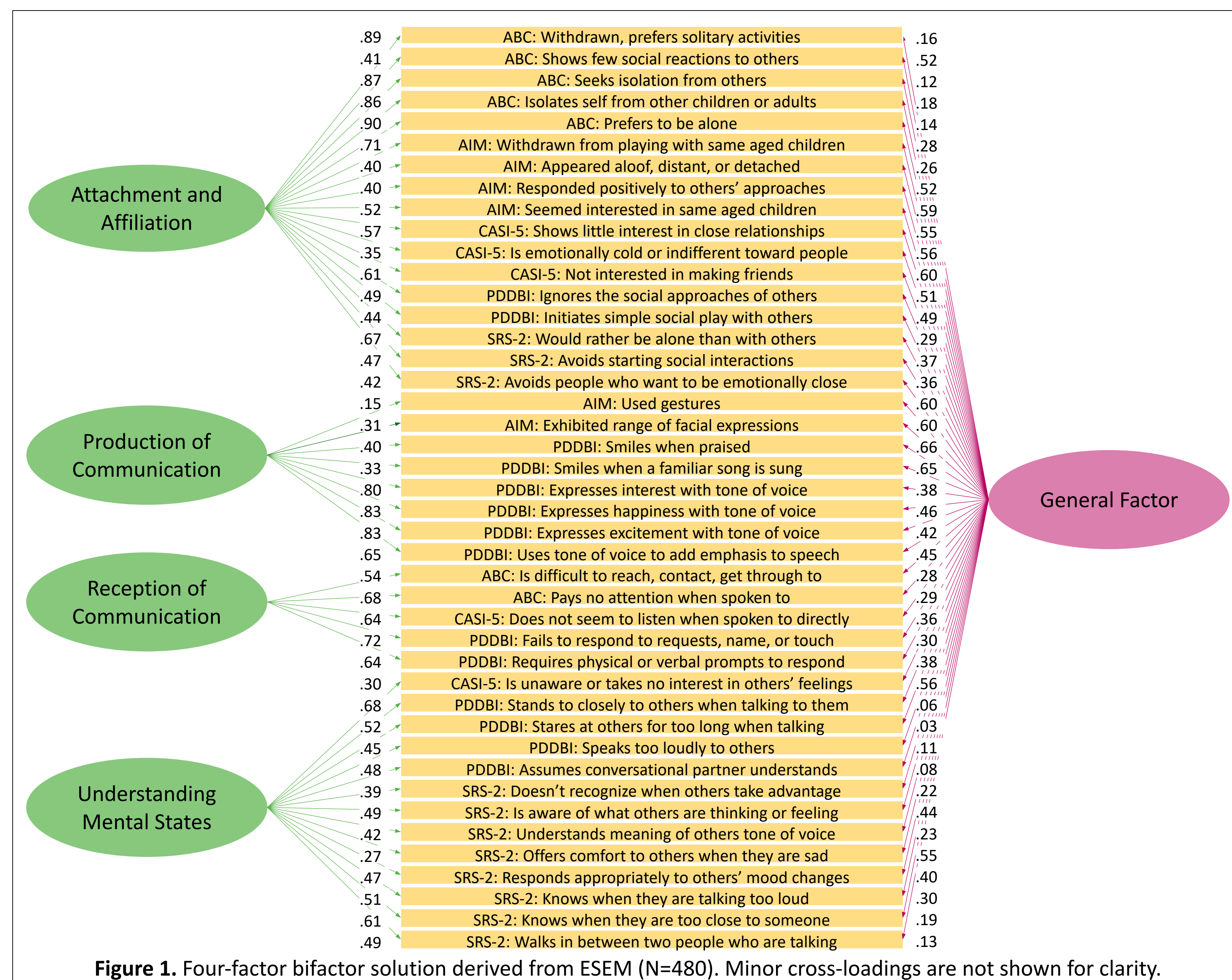


Figure 1. Four-factor bifactor solution derived from ESEM (N=480). Minor cross-loadings are not shown for clarity.

RDoC factors showed distinct correlations with EEG and eye-tracking biomarkers (**Table 1**), generally stronger than those reported for standard composite scores^{3,4}.

Table 1. Partial Correlations between RDoC Factor Scores and EEG and Eye-Tracking Biomarkers (N=204)

	General Factor	Attachment and Affiliation	Production of Communication	Reception of Communication	Understanding Mental States
EEG					
Faces N170 Amplitude	.045	-.010	-.032	-.064	-.003
Faces N170 Latency	.137*	-.044	-.019	.046	-.025
Faces P100 Amplitude	-.019	-.119	-.114	-.142*	-.178*
Faces P100 Latency	-.037	-.027	.036	.049	.044
VEP N1 Amplitude	-.018	-.011	-.028	.015	-.088
VEP P100 Amplitude	.023	-.104	-.147*	-.091	-.073
VEP P100 Latency	-.079	-.012	-.161*	.090	.015
Slope	.022	-.046	.018	-.093	.053
Alpha	.022	.005	.013	-.065	-.085
Beta	.048	-.032	-.019	-.113	-.079
Theta	.001	-.014	.017	-.075	-.007
Eye-Tracking					
PLR Latency	.011	.054	.070	.035	.013
PLR Amplitude	.103	-.004	.026	.074	.073
AM % Activity	-.026	-.016	-.016	.056	.161**
AM % Heads	-.127*	-.023	-.068	-.184**	-.087
SI % Activity	-.01	.118	.094	.092	.142*
SI % Heads	-.033	-.143*	-.065	-.222***	-.129*
SS % Activity	-.066	-.139*	-.059	-.095	-.044
SS% Face	-.051	-.087	-.064	-.108	-.110
OMI	-.089	-.118	-.077	-.195**	-.122

Note. Partial correlations controlling for age, sex, and full-scale IQ. Underlined values survived multiple comparison correction. AM = Activity Monitoring; OMI = Oculomotor Index; SI = Social Interactive; SS = Static Scenes. * $p<.05$. ** $p<.01$. *** $p<.001$.

Conclusions

RDoC-aligned domains of social functioning show distinct and meaningful associations with EEG and eye-tracking biomarkers, suggesting the utility of a fine-grained, biologically aligned approach to behavioral measurement. Nevertheless, effect sizes were modest, indicating that this approach does not fully account for variability in neurobiological measures and should be complemented by additional multimodal assessments.

References

¹Insel et al. (2010) *American Journal of psychiatry*, 167(7), 748-751.; ²McPartland et al. (2020) *Frontiers in integrative neuroscience*, 14, 16; ³Webb et al., (2023) *American Journal of Psychiatry*, 180(1), 41-49; ⁴Shic et al. (2022) *Molecular Autism*, 13(1), 15.

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