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Social cognition, emotion regulation and social competence in classical galactosemia patients without intellectual disability

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Original Article

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Abstract

Objective: Classical galactosemia (CG) is an inborn error of galactose metabolism. Many CG patients suffer from long-term complications including poor cognitive functioning. There are indications of social dysfunction but limited evidence in the literature. Therefore, this study aims to improve our understanding of social competence in CG by investigating social cognition, neurocognition and emotion regulation. *Methods:* A comprehensive (neuro) psychological test battery, including self and proxy questionnaires, was administered to CG patients without intellectual disability. Social cognition was assessed by facial emotion recognition, Theory of Mind and self-reported empathy. Standardised results were compared to normative data of the general population. *Results:* Data from 23 patients (aged 8–52) were included in the study. On a group level, CG patients reported satisfaction with social roles and no social dysfunction despite the self-report of lower social skills. They showed deficits in all aspects of social cognition on both performance tests (emotion recognition and Theory of Mind) and self-report questionnaires (empathy). Adults had a lower social participation than the general population. Parents reported lower social functioning, less adaptive emotion regulation and communication difficulties in their children. Individual differences in scores were present. *Conclusion:* This study shows that CG patients without intellectual disability are satisfied with their social competence, especially social functioning. Nevertheless, deficits in social cognition are present in a large proportion of CG patients. Due to the large variability in scores and discrepancies between self- and proxy-report, an individually tailored, comprehensive neuropsychological assessment including social cognition is advised in all CG patients. Treatment plans need to be customised to the individual patient.

Significant outcomes

- CG patients are satisfied with their social competence, especially social functioning, but also feel that they possess lower social skills than the general population.
- Deficits are present in all aspects of social cognition (i.e. emotion recognition, Theory of Mind and (self-reported) empathy) in CG.
- Social cognition has the largest impact on social competence in this sample of CG patients.

Limitations

- Data of CG patients were compared to normative data of the general population and not to healthy controls.
- A small sample of CG patients was included ($N = 23$) leading to statistical challenges.
- Social competence in CG patients with severe cognitive complications remains unknown due to the exclusion of patients with mild to severe intellectual disability.

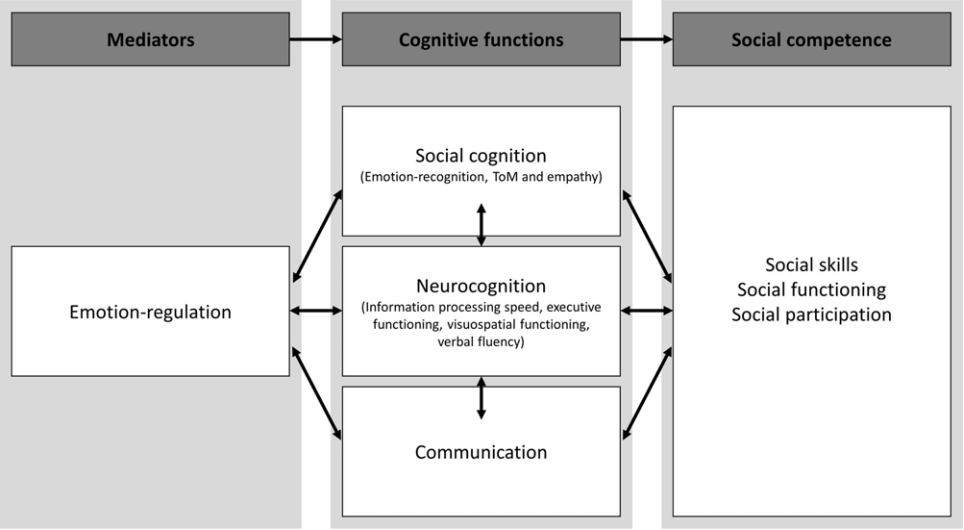

Figure 1. Socio-Cognitive Integration Abilities model, based on Beauchamp and Anderson (2010). Only investigated constructs in the current study are shown.

Introduction

Classical galactosemia (CG) is an autosomal recessive inborn error of metabolism with an incidence of 1:53.000 in the Netherlands (Welling *et al.*, 2017a). Due to a deficiency of galactose-1-phosphate uridyltransferase (*GALT*; EC 2.7.7.12), newborns develop a life-threatening illness after ingestion of breastmilk or galactose-containing infant feeding. The early start of a galactose-restricted diet after newborn or family screening prevents or resolves the critical symptoms but does not prevent the development of long-term complications. Complications vary in severity between patients and include intellectual disability (Welling *et al.*, 2017b), additional neurocognitive deficiency (Hermans *et al.*, 2019; Welsink-Karssies *et al.*, 2020b), speech- and language difficulty, internalising behaviour, movement disorder and primary ovarian insufficiency in female patients (Rubio-Gozalbo *et al.*, 2019; Welsink-Karssies *et al.*, 2020a). The specific pathophysiology of these long-term complications remains unclear (Fridovich-Keil and Berry, 2022; Hermans *et al.*, 2022).

The chronicity of the disease and the long-term complications put CG patients at risk for socio-emotional difficulties (Maurice-Stam *et al.*, 2019). Indeed, the social quality of life of CG patients has been found to be hampered (Bosch *et al.*, 2004; Hoffmann *et al.*, 2012). Patients are known to have difficulty engaging in social activities and/or relationships (Bosch *et al.*, 2009; Gubbels *et al.*, 2011), are more frequently single and are more often unemployed (Hoffmann *et al.*, 2012; Waisbren *et al.*, 2012). This may not be surprising, given the current knowledge of neurocognitive difficulties, speech- and language problems and internalising behaviour in CG. However, the specific factors contributing to the presumed lower level of social competence in CG remain unclear.

Social competence is an important indicator of social skills, social functioning and social participation. It is a sophisticated construct covering numerous skills necessary to navigate social norms and conventions. According to the Socio-Cognitive Integration Abilities Model (SOCIAL model; Beauchamp and Anderson, 2010), social competence is determined by cognitive functions including social cognition (aspects of higher-order cognitive function specifically involved in social situations; Scourfield *et al.*, 1999), neurocognition (information processing speed and executive functions) and communication (cognitive processes involved in verbal- and nonverbal communication; see Fig. 1). The relationship between social competence and the cognitive functions is mediated by individual traits and/or strategies including emotion-regulation strategies (Richards and Gross, 2000; Zeman *et al.*, 2006), external factors including family environment and culture and the development and integrity of the brain. A study evaluating social competence in children with CG in both the school and home setting (Ryan *et al.*, 2013) demonstrated a higher incidence of both lower social skills (as observed by both parents and teachers) and less adaptive social behaviour (as observed by parents) in comparison to the reference population. In contrast, our own group (Welsink-Karssies *et al.*, 2020b) could not establish lower social skills; more specifically, we did not find increased levels of social irresponsiveness on a screening instrument in children or adults. The one study investigating social cognition (namely facial emotion recognition) in CG (Korner *et al.*, 2019) showed that (young) adult patients had more difficulties identifying complex emotional expressions than healthy controls, indicating possible deficits in social cognition.

Social cognition has never been investigated beyond emotion recognition even though social cognition also encompasses other domains such as Theory of Mind and cognitive and affective empathy (Beauchamp and Anderson, 2010; Schurz *et al.*, 2021). Social competence has mainly been investigated by screening measures, which cannot address the full construct. Furthermore, both these constructs have not been investigated simultaneously in the same group. In order to reliably investigate the construct of social competence without the large confounder of severe cognitive impairment, this study focuses on the subgroup of CG patients without intellectual disability.

The main aim of the current study is to assess social competence, and the contributing components of the SOCIAL model of social cognition, neurocognition, communication and emotion regulation, both by performance tests as well as questionnaires (self-report and proxy) in CG patients without intellectual disability. The secondary, exploratory aims are to examine i) the association between social competence and the components of the SOCIAL model, ii) the association between the different subdomains of all constructs and iii) the association between the different subdomains and age and intelligence.

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Material and methods

Patients and recruitment

A single-centre cross-sectional study was performed. All CG patients aged 8 years and older visiting the galactosemia expertise centre of the Amsterdam UMC were assessed for eligibility. Only patients without intellectual disability were eligible due to the usage of questionnaires and tests requiring a certain level of intelligence to maintain the reliability of the measurements. Inclusion criteria were: 1) Patients with a GALT activity<15% of healthy controls, and/or the presence of two null or severe missense variations in the *GALT* gene, 2) Total intelligence quotient (TIQ) of 70 or higher, and/or an independent work- or living situation and 3) No second genetic diagnosis influencing clinical outcome. Consequently, a total of 17 patients had to be excluded due to the intelligence exclusion criterion and 43 patients (16 children and 27 adults) were eligible and were invited to participate by regular mail. Paediatric patients were categorised into two groups: classical phenotypes (two pathogenic *GALT* mutations and absent or barely detectable erythrocyte GALT activity (<3.3%)) and NBS-detected variant phenotype patients (with previously unreported geno- and phenotypes, erythrocyte GALT activity above 3.3%, no clinical symptoms at time of diagnosis and undetectable Gal-1-P levels on dietary treatment).

Procedure

A waiver was given for the data collection by the Medical Ethics Committee of the Amsterdam UMC. Patients and/or parents signed an informed consent. The neuropsychological assessment was performed by a well-trained neuropsychologist in either the hospital or during a home visit. The 1.5-hour assessment consisted of a short conversation regarding social- and cognitive difficulties and social participation followed by the tests and questionnaires. Parents filled out questionnaires about their child during or after the assessment of their child. Medical data including information about the diagnosis, diet and most recent assessment of IQ were obtained from medical files. Socio-demographic data and data of PROMIS self-report measures regarding social functioning and social participation were obtained from previous research records (Hermans *et al.*, 2023).

Measures

The neuropsychological assessment battery was composed following the SOCIAL model (see Fig. 1 and Table 1).

Performance tests: Performance-based measures pertained to emotion recognition in faces, Theory of Mind, information processing speed, executive functioning (i.e. inhibition and cognitive flexibility), visuospatial functioning and verbal fluency (i.e. letter fluency). Other aspects of neurocognition, for example, memory, were not included in the neuropsychological assessment due to the presumed lower attribution to social competence (Beauchamp and Anderson, 2010).

Questionnaires: Patients filled out questionnaires regarding affective and cognitive empathy, emotion-regulation strategies, social skills, social functioning and social participation. Parents of paediatric patients reported about communication, and also about emotion-regulation strategies and social skills of their child. Objective information on social participation of adults (i.e. employment- and marital status and living situation) was derived from recent medical- and research records and the short conversation at the beginning of the assessment. The following PROMIS self- and proxy-report measures were obtained from previous research records and categorised into two categories according to the framework of social health (Hahn *et al.*, 2010): Social functioning (CAT V2.0 Proxy- and self-report – Peer relationships, Short Form V2.0 Companionship 6a, Short Form V2.0 – Emotional Support 8a and Short Form V2.0 – Social isolation 8a) and social participation (CAT V2.0 – Ability to participate in social roles and activities, CAT V2.0 – Satisfaction with social roles and activities).

Tests and questionnaires differed between age groups due to the availability of material and/or normative data (see Supplementary Table 1). All raw scores of performance-based measures and questionnaires were transformed to scaled scores based on normative data of the Dutch general population. The proxy-report of peer relationships only had normative data based on a reference sample of the US general population and a clinical sample. For the Strange Stories Test, no normative data were available for patients under the age of 18. This data will be evaluated descriptively.

Statistical analysis

First, descriptive analyses were performed to describe patient characteristics (i.e. age, gender). Second, all scaled scores were transformed into T-scores ($\mu = 50, \sigma = 10$). For each measure, only the total score or the subscale-total score was used. All measures were evaluated against the reference mean of $T = 50$ by means of two-sided one-sample t-tests. However, the PROMIS self-report measure of peer relationships, ability to participate in social roles and satisfaction with social roles were evaluated against Dutch reference means of respectively $T = 46.9$, $T = 50.6$ and $T = 47.5$ due to differences in the normal distribution between the American and Dutch general population (Terwee *et al.*, 2019; Luijten *et al.*, 2021). According to clinical practice, a T-score equal to or below 30 represents an extremely low score (clinical range) and a T-score between 31 and 36 represents a borderline to extremely low score (subclinical range; Bouma *et al.*, 2012). Outliers were not removed except if a patient consistently reported deviant scores across all domains. Otherwise, it was deemed as part of the range of complications of galactosemia. A p-value of <0.05 was considered a statistically significant difference. No multiple-comparison correction was applied due to the small sample size and consequent power issues. Cohen's d was used as a statistic for effect size. An effect size of $d \geq 0.20$ was considered a small effect, $d \geq 0.50$ was considered a medium effect and $d \geq 0.80$ a large effect (Cohen, 2013). Third, in order to assess the relationships between the different domains in the entire patient group, all measures measuring the same domain were combined without the assignment of any weights. These composite domains can be found in Table 1. Correlation analyses were performed to examine the association between the T-scores of these domains, age and TIQ. Lastly, these composite domains were combined without the assignment of any weights to adhere to the different constructs of the SOCIAL model (i.e. neurocognition, social cognition (distinguishing 'performance-based social cognition' (emotion-recognition and Theory of Mind) and 'self-report social cognition' (self-report measures of empathy)), emotion-regulation and social competence; see Fig. 1 and Table 1). Six univariate regressions were performed with each social construct separately next to the additional parameter age as predictors and social competence as outcome variable. After that, a multiple regression was performed adding the different constructs in a step-wise fashion according to

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Table 1. Overview of the neuropsychological measures

Social construct	Domain*	Measures	Type of measurement	Age range	Norm
Neurocognition	Visual information processing speed	WISC-V Coding	Performance-based	8–15	A
		WAIS-IV Coding	Performance-based	16+	A
		D-KEFS Trail Making Test (1–3)[$]	Performance-based	8–16	A
		Trail Making Test (A)	Performance-based	17+	A/E
	Verbal information	D-KEFS CWIT (1–2)	Performance-based	8–16	A
	processing speed	Stroop Color Word Test (1–2)	Performance-based	17+	A/G/E
	Executive functioning	D-KEFS CWIT (3–4)	Performance-based	8–16	A
	– inhibition	Stroop Color Word Test (3)	Performance-based	17+	A/G/E
	Executive functioning	D-KEFS Trail Making Test (4)	Performance-based	8–16	A
	– cognitive flexibility	Trail Making Test (B)	Performance-based	17+	A/E
	Verbal fluency	NEPSY Word production letter	Performance-based	8–12	A
		Letter fluency	Performance-based	17+	E
	Visuospatial functioning	WISC-V Visual Puzzles	Performance-based	8–15	A
		GIT-2 Spatial Test	Performance-based	16+	A
Social cognition	Emotion-recognition	Emotion Recognition Test	Performance-based	8+	A/E/IQ[@]
	Theory of Mind	WISC-III Picture Arrangement	Performance-based	8–16	A
		Strange Stories Test	Performance-based	8+*	–
		Hinting Task	Performance-based	18+	-~
	Cognitive Empathy	AMES - Cognitive Empathy	Self-report	10–15	G
		EQ - Cognitive Empathy	Self-report	16+	G
	Affective Empathy	AMES - Affective Empathy	Self-report	10–15	G
		EQ – Emotional Empathy	Self-report	16+	G
Communication	Communicative skills	CCC-2-NL – General communication	Proxy-report	8–15	A
		CCC-2-NL – Pragmatics[^]	Proxy-report	8–15	A
Emotion-regulation	Adaptive strategies	FEEL-KJ – Adaptive total	Self-report + Proxy-report	8–17	A
		FEEL-E – Adaptive total	Self-report	18+	–
	Maladaptive strategies	FEEL-KJ – Maladaptive total	Self-report + Proxy-report	8–17	A
		FEEL-E – Maladaptive total	Self-report	18+	–
Social competence	Social skills	VPV – Intrapersonal skills[&]	Self-report + Proxy-report	9–17	–
		VPV – Interpersonal skills	Self-report + Proxy-report	9–17	–
		EQ – social skills	Self-report	16+	G
	Social functioning	PROMIS – Peer relationships	Self-report + Proxy-report	8–17	-~
		Friendship Questionnaire	Self-report	18+	G~
		PROMIS – Companionship	Self-report	18+	-~
		PROMIS – Social isolation	Self-report	18+	-~
		PROMIS – Emotional support	Self-report	18+	-~
	Social participation	PROMIS – Ability to participate in social roles	Self-report	18+	–
		PROMIS – Satisfaction with participation in social roles	Self-report	18+	–

Notes. A = Corrected for age. E = Corrected for level of education. IQ = Corrected for TIQ. G = Corrected for gender. [@]ERT is corrected for age and/or education in adults, and for age and/or IQ in children. *Normative data is only available for patients of 18 years and older. [$]Only digit-sequencing will be incorporated in the domain "visual information processing speed". [^]Pragmatics subscale will not be incorporated in the communicative skills domain. [&]Intrapersonal skills will not be incorporated in the social skills domain. ~ = Non-Dutch normative sample. See for additional information supplementary table 1.

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Table 2. Demographics

	N	All CG patients (*N* = 23)	*N*	Children 8–17	*N*	Adults 18+ (*N* = 11)
Type of visit, %	23		12		11	
Home visit	10	43	6	50	4	36
AMC visit	13	57	6	50	7	64
Gender, %	23		12		11	
Female	14	60	6	50	8	73
Male	9	40	6	50	3	27
Age in years, mean (range)	23	24.1 (8–52)	12	12.6 (8–17)	11	36.6 (26–52)
GALT erythrocyte activity (%), %	23		12		11	
<3.3%	22	96	11	92	11	100
≥3.3%	1	4	1	8	0	0
Diagnosis based on, %	23		12		11	
Clinical symptoms (pre-NBS)	11	48	3	25	8	73
NBS	7	30	7	58	0	0
FS	5	22	2	17	3	27
Total IQ, mean (range)	22	81.8 (69–103)	12	86.1 (70–103)	10	76.6 (69–83)
TIQ < 85	15	68	5	42	10	100
TIQ ≥ 85	7	32	7	58	0	0

N, sample size; CG, Classical galactosemia; NBS, Newborn Screening; FS, Family Screening; TIQ, Total Intelligence Quotient.

the SOCIAL model. The coefficients of the best model, evaluated with significance tests of the squared multiple correlation (R^2), were used to assess the relation between the constructs and social competence.

Results

Twenty-three patients with CG agreed to participate, this is a response rate of 53% of all 43 eligible patients. Participating patients and non-participating patients did not differ except for the formally measured total IQ of adults, which was slightly higher in the non-participating group ($N = 10$; mean IQ of 84.5). The demographics of the patients are listed in Table 2. Ten patients were assessed at home. Their results did not differ from the results of the group that was assessed at the hospital (results not shown). Twelve children (mean age 12.6 years; $SD = 3.15$, Range = 8–17) and eleven adults (mean age 36.6 years; $SD = 8.8$, Range = 18–52) participated. Twenty-two patients had previously received a formal intelligence assessment with a mean IQ of 81.8 ($SD = 8.9$). All patients reported compliance with the galactose-restricted diet. Only one variant phenotype CG patient was included, a female aged nine years old with a GALT activity of 3.6% and a total IQ of 86. Her scores fell within the range of the classical phenotype patient scores, so all analyses were performed including the variant patient.

Performance-based measures

Results of the performance-based measures of neurocognition and social cognition are presented in Table 3.

Neurocognition

Children performed significantly lower than the general population on visual information processing speed, letter fluency and visuospatial functioning. There were no differences in verbal information processing speed, inhibition and cognitive flexibility. Adults performed significantly lower than the general population on visual information processing speed, verbal information processing speed, inhibition, letter fluency and visuospatial functioning. Cognitive flexibility was not different from the general population (see Table 3 for details).

Social cognition

Emotion recognition. The CG patients (both children and adults) performed significantly lower than the general population with significantly lower recognition of the emotions of disgust, fear, happiness and sadness. They equally recognised anger and surprise.

Theory of mind. Children performed significantly lower on the WISC-III subtask Picture arrangement in comparison to the general population. On the Strange Stories Test, 42% of the children (age: 8–14) made five or more mistakes that may be indicative of difficulties in describing the mental state of the characters. Adults performed significantly lower on the Strange Stories Test than the general population. Adults did not differ from the general population on the hinting task in which the implicit message of the character in the stories had to be described.

Self-and proxy-report

Results of the self and proxy questionnaires are presented in Table 4.

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Table 3. Results of the performance-based measures of social cognition and neurocognition

Social construct	Domain Measure	*N*	Age range	Mean T-score (range)	P-value	Effect size (d)	% Borderline – Extremely low[$]	% Extremely low[#]
Neurocognition	**Information processing speed**							
	WISC-V Coding	9	8–15	44.1 (40–53)	0.009**	1.14	0.0%	0.0%
	WAIS-IV Coding	14	16–52	40.3 (30–50)	<0.001***	1.58	14.3%	14.3%
	DKEFS CWIT – Colour naming	10	8–16	48.0 (33–60)	0.577	0.18	20.0%	0.0%
	DKEFS CWIT – Word reading	10	8–16	48.6 (20–60)	0.707	0.12	10.0%	10.0%
	Stroop CWT – Colour naming	13	17–52	39.7 (17–56)	0.008**	0.88	23.1%	23.1%
	Stroop CWT – Word reading	13	17–52	45.9 (30–61)	0.131	0.45	23.1%	7.7%
	DKEFS TMT – Visual scanning	10	8–16	50.7 (40–60)	0.734	0.11	0.0%	0.0%
	DKEFS TMT – Digit sequencing	10	8–16	49.1 (33–60)	0.753	0.10	10.0%	0.0%
	DKEFS TMT – Letter sequencing	9	8–16	43.8 (20–57)	0.132	0.56	11.1%	11.1%
	TMT – Digit sequencing	13	17–52	51.3 (41–64)	0.479	0.20	0.0%	0.0%
	Executive functioning							
	Inhibition							
	DKEFS CWIT – Inhibition	10	8–16	51.0 (33–60)	0.739	0.11	10.0%	0.0%
	DKEFS CWIT – Inhibition/ Switching	10	8–16	51.6 (30–63)	0.606	0.17	10.0%	10.0%
	Stroop CWT – Inhibition	13	17–52	44.8 (27–56)	0.040*	0.64	15.4%	7.7%
	Cognitive flexibility							
	DKEFS TMT – Digit-letter sequencing	9	8–16	45.2 (30–57)	0.180	0.49	22.2%	22.2%
	TMT – Digit-letter sequencing	13	17–52	48.2 (36–58)	0.338	0.28	7.7%	0.0%
	Verbal fluency							
	NEPSY Word production letter	6	8–12	40.7 (34–50)	0.011*	1.60	16.7%	0.0%
	Letter fluency	13	17–52	44.1 (33–64)	0.021*	0.74	7.7%	0.0%
	Visuospatial functioning							
	WISC-V Visual puzzles	9	8–15	40.0 (33–50)	0.002**	1.55	22.2%	0.0%
	GIT-2 Legkaarten	14	16–52	38.4 (28–50)	<0.001***	2.06	50.0%	7.1%
Social cognition	**Emotion recognition**							
	ERT Total score	23	8–52	41.5 (24–58)	<0.001***	0.99	21.7%	13.0%
	ERT Anger	23	8–52	47.2 (30–66)	0.148	0.31	4.3%	4.3%
	ERT Disgust	23	8–52	41.1 (24–58)	<0.001***	1.01	21.7%	17.4%
	ERT Fear	23	8–52	45.6 (34–71)	0.032*	0.48	21.7%	0%
	ERT Happiness	23	8–52	46.3 (30–61)	0.038*	0.46	13.0%	4.3%
	ERT Sadness	23	8–52	45.3 (24–63)	0.034*	0.47	17.4%	17.4%
	ERT Surprise	23	8–52	47.4 (30–71)	0.227	0.26	8.7%	8.7%
	Theory of Mind							
	WISC III Picture Arrangement	10	8–16	40.7 (27–63)	0.027*	0.83	30.0%	30.0%
	Strange Stories (adults) total	11	26–52	30.5 (1–56)	0.004**	1.10	45.5%	45.5%
	Hinting Task	11	26–52	48.4 (34–60)	0.544	0.19	9.1%	0.0%

N = sample size. *d* = Cohen's d. *$p < 0.05$, **$p < 0.01$, ***$p < .001$. T-scores have a mean of 50 with a standard deviation of 10. [$]Percentage of patients scoring in borderline – extremely low/clinical range representing T-values of T36 and lower. [#]Percentage of patients scoring in extremely low/clinical range representing T-values of T30 and lower.

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Table 4. Results of self- and proxy-report of social cognition (empathy), emotion-regulation, communication and social competence

Social construct	Domain measure	*N*	Age range	Mean T-score (range)	P-value	Effect size (d)	% Borderline – extremely low[$]	% Extremely low[#]
Social cognition	**Empathy**							
	AMES Cognitive Empathy	6	10–14	50.5 (35 – 63)	0.914	0.05	16.7%	0.0%
	AMES Affective Empathy	6	10–14	39.7 (35 – 49)	0.006**	1.85	33.3%	0.0%
	EQ Cognitive Empathy	14	16–52	41.1 (25 – 60)	0.009**	0.81	35.7%	28.6%
	EQ Emotional Empathy	14	16–52	43.4 (21 – 58)	0.041*	0.61	28.6%	14.3%
Communication	**Communicative skills**							
	CCC-2-NL Proxy General communication scale[+]	9	8–14	59.9 (39 – 72)	0.027*	0.90	44.4%[+]	11.1%[+]
	CCC-2-NL Pragmatics scale[+]	9	8–14	55.8 (35 – 71)	0.215	0.45	44.4%[+]	11.1%[+]
Emotion- regulation	**Emotion-regulation**							
	FEEL-KJ Proxy Adaptive total	11	8–17	43.2 (23 – 56)	0.028*	0.77	9.1%	9.1%
	FEEL-KJ Proxy Maladaptive total[+]	11	8–17	47.7 (23 – 62)	0.511	0.21	9.1%	9.1%
	FEEL-KJ Proxy External regulation total	11	8–17	51.2 (20 – 66)	0.782	0.09	18.2%	9.1%
	FEEL-KJ Adaptive total	12	8–17	50.7 (35 – 68)	0.817	0.07	8.3%	0.0%
	FEEL-KJ Maladaptive total[+]	12	8–17	44.8 (36 – 57)	0.036*	0.72	0.0%[+]	0.0%[+]
	FEEL-KJ External regulation total	12	8–17	50.8 (43 – 62)	0.627	0.14	0.0%	0.0%
	FEEL-E Adaptive total	11	26–52	45.9 (26 – 69)	0.379	0.28	27.3%	18.2%
	FEEL-E Maladaptive total[+]	11	26–52	48.0 (39 – 60)	0.411	0.26	0.0%[+]	0.0%[+]
Social competence	**Social skills**							
	VPV Proxy Total score	11	9–17	50.4 (40 – 61)	0.864	0.05	0.0%	0.0%
	VPV Proxy Interpersonal skills	11	9–17	48.5 (40 – 64)	0.560	0.18	0.0%	0.0%
	VPV Proxy Intrapersonal skills	11	9–17	52.3 (40 – 64)	0.376	0.28	0.0%	0.0%
	VPV Total score	11	9–17	46.9 (35 – 57)	0.127	0.50	9.1%	0.0%
	VPV Interpersonal skills	11	9–17	44.0 (35 – 51)	0.009**	0.98	18.2%	0.0%
	VPV Intrapersonal skills	11	9–17	51.2 (40 – 61)	0.376	0.16	0.0%	0.0%
	EQ Social skills	14	16–52	40.2 (27 – 54)	<0.001***	1.21	28.6%	14.3%
	Social functioning							
	Friendship Questionnaire	11	26–52	52.0 (34 – 75)	0.629	0.15	9.1%	0.0%
	PROMIS Proxy Peer relationships	8	8–17	44.0 (39 – 50)	0.007**	1.31	0.0%	0.0%
	PROMIS Peer relationships	9	8–17	44.9 (40 – 49)	0.101	0.62	0.0%	0.0%
	PROMIS Companionship	10	26–52	54.0 (35 – 64)	0.168	0.47	10.0%	0.0%
	PROMIS Emotional support	10	26–52	54.5 (32 – 64)	0.213	0.42	10.0%	0.0%
	PROMIS Social isolation[+]	10	26–52	49.8 (34 – 70)	0.948	0.02	10.0%	10.0%
	Social participation							
	PROMIS Participation in social roles	10	26–52	51.2 (35 – 63)	0.813	0.08	10.0%	0.0%
	PROMIS Satisfaction with social roles	10	26–52	49.4 (39 – 56)	0.273	0.37	0.0%	0.0%

N, sample size; *d*, Cohen's *d*. *$p < 0.05$, **$p < 0.01$, ***$p < .001$. T-scores have a mean of 50 with a standard deviation of 10. [$]Percentage of patients scoring in borderline – extremely low/clinical range representing T-values of T36 and lower. [#]Percentage of patients scoring in extremely low/clinical range representing T-values of T30 and lower. [+]Higher scores represent lower levels of functioning. Clinical cut-off values are T63–T69 (borderline) and ≥T70 (extremely low level of functioning).

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Social cognition

Empathy. On the Adolescent Measure of Empathy and Sympathy (AMES), children between the ages of 10 and 15 reported lower levels of affective empathy than the general population. They did not differ in cognitive empathy. Patients of 16 years and older reported both a lower affective and cognitive empathy on the Empathy Quotient.

Communication

Parents of paediatric patients reported significantly more general communication difficulties in their children than in the general population. The pragmatics scale was not significantly different, but a larger percentage of children (44.4% vs. 6.7%) demonstrated (sub)clinical difficulties with pragmatics than in the general population.

Emotion-regulation

Parents reported that their children used significantly less adaptive strategies than children of the general population. They did not overuse maladaptive strategies and/or external regulation. Children themselves reported no difficulties with emotion regulation and reported a lower deployment of maladaptive strategies. Adult patients did not differ from the general population concerning the deployment of adaptive and/or maladaptive emotion-regulation strategies. However, a larger percentage of patients scored in the (sub)clinical range on adaptive emotion-regulation strategies than the general population (27.3% vs. 6.7%).

Social competence

Social skills. Parents reported no differences in interpersonal (i.e. relation skills and affective skills) and intrapersonal (i.e. self-direction and self-awareness) skills. Children, however, were reported to have significantly lower interpersonal skills than the general paediatric population. Intrapersonal skills were evaluated as not different. Patients of 16 years and older also reported significantly lower social skills (i.e. equivalent to interpersonal skills) than the general population. After excluding the three patients below 18, adults still showed significantly lower social skills (results not shown).

Social functioning. Both parents and children reported differences in the quality of peer relationships in comparison to the general population. However, the difference in peer relationships as perceived by the children themselves was not statistically significant. Adult patients did not differ from the general population in the report of caring friendships and/or joy of spending time with others. Descriptive analysis of individual items revealed that most of the adult patients have one or two best friends. Only two patients reported to make plans with friends more than once a month. Moreover, adults reported no differences with the general population in companionship, emotional support and social isolation.

Social participation. Participation was only measured in adults. Adults reported no difference in the ability to participate in social roles and their satisfaction with the participation in social roles, in comparison to the general population. However, more objective measures indicated lower levels of participation. All adult patients worked part-time (mean 22.5 hours/week) in contrast to the Dutch population in the same age range of which 40% worked part-time (mean 35.3 hours/week; Centraal Bureau voor de Statistiek, 2022a). Moreover, 36% of the adult patients lived together with a partner in comparison to 49% of the Dutch population (Centraal Bureau voor de Statistiek, 2022b).

Association with age and intelligence

Exploratory correlation analyses were performed to assess associations between age, TIQ and all outcomes.

Age was related to the Emotional Empathy subscale of the EQ ($r = -0.58$, $p = 0.029$), FEEL-KJ Adaptive strategies self-report ($r = 0.68$, $p = 0.014$), FEEL-KJ External regulation self-report ($r = -0.59$, $p = 0.042$), VPV intrapersonal skills proxy-report ($r = 0.71$, $p = 0.014$), EQ social skills ($r = -0.58$, $p = 0.029$) and PROMIS companionship ($r = -0.65$, $p = 0.040$). Age was not related to measures of social cognition, neurocognition or communication (results not shown).

TIQ was related to one social cognition test: the Strange Stories test in adults ($r = 0.87$, $p = 0.001$). The self-reported deployment of adaptive strategies was related to total IQ in children ($r = 0.64$, $p = 0.025$). Almost all PROMIS-measures of social functioning and social participation in adults were related to TIQ; a higher IQ was associated with higher levels of satisfaction with social roles ($r = 0.82$, $p = 0.007$), more companionship ($r = 0.90$, $p < 0.001$), more emotional support ($r = 0.71$, $p = 0.031$) and less social isolation ($r = -0.71$, $p = 0.031$). TIQ was also not related to any of the neurocognition or communication measures (results not shown).

Association between domains

Zero-order correlations were explored between the different domains in the entire patient group (see Supplementary Table 2) as well as in children and adults separately due to the usage of different measures and a difference in TIQ between children and adults (see Supplementary Table 3 and 4). The different social cognitive domains (i.e. emotion recognition, Theory of Mind, cognitive and affective empathy) were not significantly related to neurocognition. There was no clear pattern of associations between other domains. Since proxy-report was not included in the above-described correlation analyses, the associations between the proxy-report of emotion regulation, communication, social skills and social functioning were investigated separately (see Supplementary Table 5). Again, no clear pattern of associations was found.

Exploratory regression of social constructs

Even though the above-described zero-order correlations provided little evidence for patterns in interrelations between the different constructs based on the SOCIAL model (see Fig. 1), an exploratory hierarchical multiple regression was performed with social competence as outcome measure (see Table 5). Performance-based outcomes of social cognition contributed significantly to social competence ($p = 0.018$), explaining 24.1% of the variance. The other components alone or combinations did not significantly improve the model fit (see Table 5). Therefore, objective social cognition was the best predictor for social competence in this small patient sample.

Discussion

The current study aimed to improve our understanding of social competence in CG by investigating a sample of Dutch paediatric and adult patients without intellectual disability. In our model, social competence covers social skills, social functioning and participation. We also evaluated the other components of the SOCIAL model including emotion regulation and cognitive functions (both neuro- and social cognition and communication).

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Table 5. Results of the hierarchical multiple regression with social competence as outcome

#	Independent variable	*B*	SE	β	p-value	df	*F*	p-value	R^2	ΔR^2
1a	Age	0.081	0.100	0.173	0.430	1,21	0.648	0.430	0.030	
1b						1,21	6.652	0.018*	0.241	0.211
	Social cognition PB	0.438	0.170	0.490	0.017*					
1c						1,18	0.146	0.707	0.008	–
	Social cognition SR	0.070	0.184	0.090	0.707					
1d						1,21	1.582	0.222	0.070	–
	Neurocognition	0.355	0.282	0.264	0.222					
1e	Emotion regulation	0.212	0.164	0.271	0.211	1,21	1.667	0.211	0.074	–
2						3,16	2.000	0.155	0.273	0.032
	Social cognition PB	0.401	0.212	0.443	0.077					
	Social cognition SR	−0.041	0.174	−0.053	0.816					
	Neurocognition	0.294	0.355	0.187	0.420					
3						4,15	1.863	0.169	0.332	0.059
	Social cognition PB	0.345	0.215	0.381	0.130					
	Social cognition SR	−0.073	0.175	−0.093	0.681					
	Neurocognition	0.406	0.364	0.258	0.283					
	Emotion regulation	0.203	0.176	0.260	0.267					

B, unstandardized beta-coefficient; SE, standard error; β, standardized beta-coefficient; df, degrees of freedom; R^2, Squared multiple correlation; ΔR^2, difference in squared multiple correlation.
* $p < 0.05$, ** $p < 0.01$, *** $p < .001$. PB, performance based; SR, self-report.

Our results demonstrate that both paediatric and adult CG patients are satisfied with their social competence. Interestingly, the CG patients do value their social skills to be poorer. Indeed, deficits in social cognition (i.e. emotion recognition, Theory of Mind and (self-reported) empathy) were present. Adult patients participated less in society than the general population. Inter-individual differences were present, with clinical, borderline as well as normal scores across the sample of children and adults with CG.

The primary aim of the current study was to assess each separate construct of the SOCIAL model in CG patients. Confirming previous findings of neurocognitive impairments in CG (Hermans *et al*., 2019; Welsink-Karssies *et al*., 2020b), patients in the current sample showed, on a group level, difficulties on performance-based measures of information processing speed, verbal fluency and visuospatial functioning. Executive functions including cognitive flexibility and inhibition did not differ from the general population. Our study now demonstrated that social cognition is also impaired in CG. An important proportion of the patients (43.5%) performed in the clinical range (≤ T30) on one of the domains of social cognition. Group-level differences were found between CG patients and the general population on performance-based- and self-report measures of social cognition (i.e. Emotion Recognition Test, WISC-III Picture Arrangement, Strange Stories Test, AMES and Empathy Quotient). The finding of emotion-recognition difficulties in both children and adults replicates the report on young adults in the only previous study addressing social cognition in CG (Korner *et al*., 2019). More importantly, the current study revealed deficits in Theory of Mind as well. This indicates that CG patients do experience difficulties both in perceiving socio-emotional cues and in the more complex process of understanding mental states. This fits with the self-report of our sample in which both children and adults report to experience more difficulties with mirroring and understanding the feelings of others (i.e. affective empathy), and adults report to experience more trouble with understanding the beliefs, thoughts and intentions of others (i.e. cognitive empathy) than the general population. With regard to communication, parents of paediatric patients reported more difficulties in general communication. This pattern fits previous reports of language and speech difficulties in CG (e.g. Potter *et al*., 2008; Hoffmann *et al*., 2011).

Based on self-report, paediatric and adult patients did not differ on a group level in their deployment of adaptive and maladaptive emotion-regulation strategies for fear, sadness and anger from the general population. A proportion of the adult patients in the current sample (27.3%) did report a clinically low deployment of adaptive strategies in contrast to none of the paediatric patients. Parents of our sample had a different perception and evaluated their children as less equipped with adaptive emotion-regulation strategies.

CG patients perceived their social competence as adequate with regard to social functioning and participation, but not with regard to their social skills. On a group level, both children and adults evaluated their social skills as lower than the general population. Especially in adults, almost 30% reported to be in the (sub)-clinical range. Despite the reported lower social skills, both paediatric and adult patients felt as a group that they did not differ from the general population in social functioning and participation in contrast to previous self-reports of social difficulties in CG (Bosch *et al*., 2004; Bosch *et al*., 2009; Gubbels *et al*., 2011; Hoffmann *et al*., 2012). Based on the Friendship Questionnaire, the social networks of the adult patients in the current sample seemed to be restricted. However, they evaluated the quality of their friendships as well as the level of proximity to-, and emotional support of others no different than the general population. Adult patients participated

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less in society compared to the general Dutch population based on working hours/week and the percentage of patients who were living together with a partner. However, again they felt like they were sufficiently capable and were satisfied with their participation in social roles. Based on these findings, it is clear that patients with CG acknowledge their lower social skills, but are satisfied with their current social network and level of social participation. It is possible that CG patients do need to put in more energy and effort for the same level of social functioning than people without CG. Our results are in line with the findings in young adults with other causes of mild to borderline intellectual abilities. These young adults also had smaller social networks than healthy controls, but 73% were still satisfied with their social network (van Asselt-Goverts *et al.*, 2015a; van Asselt-Goverts *et al.*, 2015b). Moreover, (Dutch) society has changed in the last decade making it more of a standard practice to work part-time (Centraal Bureau voor de Statistiek, 2021).

In contrast to the perception of the paediatric patients, and in contrast to earlier reports of parents and teachers (Ryan *et al.*, 2013), parents in our sample did not report lower social skills in their children but they did perceive their children's level of social functioning within peer relationships as lower and less. Together with the discrepancy between self- and proxy report for emotion regulation, these findings highlight the importance of addressing the needs and worries of not only CG patients but also their parents.

The secondary aims of the study were to explore the associations between the different domains and age and total intelligence. Intelligence was not consistently related to the different domains of cognition including social cognition. This finding is somewhat puzzling but might be attributable to the usage of the full-scale intelligence quotient obscuring differences in subdomains (Lezak *et al.*, 2012). The dissociation between intelligence and social cognition is in line with findings in other patient populations including autism spectrum disorder in which intelligence can be relatively spared despite deficits in social cognition (Abdi and Sharma, 2004). This implies that the lower levels of intelligence in this relatively 'high-functioning' subset of CG patients cannot solely explain the lower levels of social cognition, communication and emotion regulation. A critical note to this finding is that the total IQ between children and adults had a mean difference in IQ score of 9.5, possibly leading to differences in the pattern of correlations in children and adults. However, the small sample size limited the in-depth evaluation of subgroup differences. An exploratory hierarchical multiple regression further investigated in the entire patient group the impact of age, social cognition (both performance-based and self-report), neurocognition and emotion regulation on social competence. In the current sample of CG patients, performance-based social cognition predicted social competence the most.

According to the level of concern of the patient and their parents, customised treatment might be indicated. Together with the individual (neuro)psychological profile, a treatment plan can be determined focussing on training or compensating for underlying (social) cognitive defects (Roelofs *et al.*, 2017), or strengthening social communicative skills and/or enhancing self-esteem and emotion-regulation (e.g. Scholten *et al.*, 2013).

Limitations

One of the main limitations of the current study is the lack of matched controls. We compensated for this by using normative data from the general population, which was of high quality for the majority of the used tests and questionnaires. However, especially for the domain of Theory of Mind, the tests suffered from small samples of the general population. This has been a problem throughout the social cognitive literature (Henry *et al.*, 2016; Van den Berg *et al.*, 2018). Additionally, the average IQ of the current sample was lower than the average IQ of the samples of the general population. If possible, education-corrected normative data were used. Due to the small dataset leading to power issues, the current study should be seen as the first exploratory description of social competence in CG. However, with a response rate of more than 50% in one of only two galactosemia expertise centres in the Netherlands, the current study sample represents a significant percentage of the total Dutch CG population. Unfortunately, only one patient with the variant phenotype (detected through NBS only since 2007) participated making it impossible to assess this specific phenotype group. By excluding patients with mild to severe intellectual disability, social competence remains unknown for this 'lower-functioning' group of CG patients. However, social difficulties are common in patients with intellectual disabilities and are difficult to study separately (Gilmore and Cuskelly, 2014). The total IQ of the adult patients declining participation was slightly higher than in the participating group, which might have led to bias. However, the range of IQ in the participating group was large and represents the entire cohort without intellectual disability. Finally, the SOCIAL model encompasses more mediators than emotion regulation, including external factors and brain development (Beauchamp and Anderson, 2010). However, the statistical power of the study limited the number of mediators, making it impossible to investigate all proposed mechanisms of the SOCIAL model influencing social competence. Since our findings show difficulties in social cognition and social competence, it is of interest to explore the influence of the other proposed mediators in future, larger studies. With a larger dataset, subgroup analyses of patients based on level of social competence and/or social cognition might also lead to additional insights.

Strengths

This study is the first to investigate social competence in CG in a CG-homogenous sample, given their clinical outcome, of both paediatric and adult patients without intellectual disability. By excluding patients with mild to severe intellectual disability, the results regarding social competence and all its constructs were more reliable in this 'higher-functioning' group of CG patients who are able to adequately provide self-report. The broad assessment of social competence together with multiple domains of social cognition, neurocognition and emotion-regulation together with proxy-report of communication in children, provides an extensive impression of the abilities of CG patients in social situations. By using both performance-based measures and proxy- and self-report questionnaires, differences between observable deficits and experiences of patients and parents could be determined.

Conclusion

The current study provides insights into social competence and its related constructs in patients with CG without intellectual disability. As a group, CG patients are satisfied with their social competence, especially social functioning, but also feel that they possess lower social skills than the general population. Indeed, underlying impairments were found in all aspects of social

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cognition (i.e. emotion recognition, Theory of Mind and self-reported empathy) with a large proportion of CG patients performing in the clinical range. Moreover, social participation was in fact lower in adult patients, and parents reported lower social functioning, poorer communication and more emotion-regulation problems in their children than in the general population. Social competence could not be solely explained by neurocognitive difficulties and/or intelligence and was best predicted by performance-based measures of social cognition in this sample of CG patients. Due to the large variability in scores and discrepancies between self- and proxy-report, an individually tailored, comprehensive neuropsychological assessment including performance-based measures and proxy- and self-report regarding social cognition and social competence is advised in all CG patients. Based on the individual (neuro)psychological profile and the level of concern of the patient and the parents, a personalised treatment plan needs to be determined.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/neu.2023.61.

Authors' contribution. MEH administered the neuropsychological assessment, contributed to the study design, the data collection, the data analysis and interpretation, drafted the initial manuscript and critically revised the manuscript. GJG and KJO supervised the neuropsychological assessment and contributed to the study design, the data analysis and interpretation, drafted the initial manuscript and critically revised the manuscript. CEMH, JGL, MCHJ and EO contributed to the data collection and critically reviewed the manuscript. VLVM administered the neuropsychological assessment and critically reviewed the manuscript. AMB contributed to the study design, the data collection, the data analysis and interpretation, drafted the initial manuscript and critically revised the manuscript. All authors read and approved the final manuscript.

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Competing interests. MEH, GJG, MCHJ, JGL, VLCM, EO, KJO and AMB declare that they have no conflict of interest. CEMH declares that she is involved in premarketing studies of Sanofi and Idorsia. JGL declares to participate in contract studies with Clinuvel, Alnylam and Ultragenyx, these companies are not involved in treatment or otherwise for galactosemia.

Ethical standards. The local medical ethics committee gave a waiver for the data collection (reference number METC W21_409 # 21.456). All included patients, their parents or representatives gave informed consent for the use of their data for research purposes. 'The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008'.

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