

Appendix 1 to Berthelot N, Paccalet T, Gilbert E, et al. Childhood abuse and neglect may induce deficits in cognitive precursors of psychosis in high-risk children. *J Psychiatry Neurosci* 2015.

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Supplementary Methods

Kindred ascertainment: the Eastern Quebec Kindred Study (EQKS)

The kindred ascertainment was described in detail in previous reports.¹⁻⁶ Briefly, we targeted all the multigenerational families densely affected by schizophrenia or bipolar disorder in the eastern Quebec (Canada) catchment area. Family inclusion criteria were (1) having at least 1 first-degree relative affected by the same disorder (schizophrenia or bipolar disorder) as the proband and (2) having at least 4 affected individuals sharing the same disorder. We gathered 48 kindreds with schizophrenia or bipolar disorder over 25 years comprising a total of 1500 adult members, 405 of whom had a DSM-IV diagnosis of schizophrenia or bipolar disorder. There was an average of 26 members per kindred with an average of 6 members affected by schizophrenia or bipolar disorder. The mean age at onset was 25.4 ± 8.5 years for schizophrenia and 28.8 ± 10.3 years for bipolar disorder.²

With the assistance of the regional psychiatric clinical departments, we progressively enrolled all the multiaffected multigenerational families with specific entry criteria in the catchment district. This recruitment was facilitated by the Quebec universal health care system providing efficient screening of patients and relatives and by official and systematic church and parish genealogical records.⁷ Screening in the catchment area reached a point where almost all the new disease incidences occurred in individuals who had a strong family history descended from the 48 EQKS kindreds under scrutiny.

Childhood adverse life events chart (CALEC)

Items of the CALEC were placed on a life chart ranging from birth to age 25 years. Our group has already reported findings using a life chart method modified from Post and colleagues.⁸ Information for the lifetime presence and the timing of adverse events came out of direct interviews with the young offspring, with the parents and their relatives and from the review of all lifetime medical records of the parents and offspring. Each event was rated blind, year by year from birth, by filling in the life chart.

Abusive and neglectful stressors were comparable to those reported in meta-analytic work on childhood adversities⁹ and to the scales of established instruments, such as the Childhood Trauma Questionnaire¹⁰ or the Child Experience of Care and Abuse Questionnaire.¹¹ These stressors were physical abuse, sexual abuse, parental neglect, parental emotional abuse, and exposure to domestic violence. Complete description of these items can be found below, and detailed frequencies are provided in Table S1.

Physical abuse included both physical abuse by a parent and physical abuse by a peer. Physical abuse by a parent was coded when there was evidence of (i) aggression objectified by a third party, (ii) aggression leaving marks on the body, or (iii) disciplinary behaviour clearly inappropriate or out of proportion (ex. repeatedly slapping the face, hitting with the fist, hitting with a solid object, kicking, burning). Physical abuse by a peer was coded when there was evidence of unprovoked aggression leaving marks or requiring the intervention of an authority figure, such as a police officer.

Sexual abuse included both intrafamilial and extrafamilial sexual abuse. Definite sexual abuse consisted of (i) forced sexual contacts underneath the clothes, or (ii) sexual abuse involving penetration. Other sexual abuse consisted of (i) forced sexual contacts above the clothes, (ii) the child being surprised by exhibitionism, or (iii) inappropriately and nonaccidentally exposing the child to sexuality (pornography, parental sexuality).

Parental neglect included both physical and emotional neglect. Physical neglect was coded when there was objectified evidence of the child (i) lacking food, (ii) wearing clothes in very poor condition, or (iii) being left alone at an early age for a significant period of time. Emotional neglect was coded when there was evidence that the parents (i) did not consider needs for affection and reassurance; (ii) did not show signs of interest in the child's activities, school performance and feelings; (iii) administered only basic care; or (iiii) repeatedly refused or failed to bring the child to required medical treatments.

Emotional abuse included both repeated insults toward the child and clearly inappropriate punishment of the child. Insults and threats were coded when one of the parents constantly (i) diminished the child, (ii) humiliated the child, (iii) made the child feel undesired, or (iiii) deliberately exposed the child to failure. For example, the parent might have frequently threatened the child with sending him away from home, repeatedly calling the child diminishing names in public, or asking the child to perform tasks clearly too demanding for his/her age. Clearly

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inappropriate punishment of the child was coded when one of the parents punished the child in mean, painful and inconsiderate ways, such as in (i) not talking to the child for many days, (ii) locking the child in a room or outside of the house for a few hours, or (iii) hurting/killing a child's pet for disciplinary purposes.

Exposure to domestic violence was coded when the child was the passive witness of (i) intimate partner violence, (ii) parents deliberately breaking objects, (iii) homicide, or (iiii) severe sibling violence.

Table S1: Correspondence of the items used in the childhood adverse life events chart (CALEC) with items of known instruments on childhood trauma

Category	CALEC*	Other instruments		
		CTQ	TESI	CECA.Q
Traumatic events (abuse and neglect)†	1) Physical abuse by a parent	x	x	x
	2) Physical abuse by a peer		x	x
	3) Definite sexual abuse	x	x	x
	4) Other sexual abuse	x	x	x
	5) Parental physical neglect	x	x	x
	6) Parental emotional neglect	x	x	x
	7) Parental emotional abuse	x	x	x
	8) Bizarre or clearly inappropriate punishment of the child	x	x	
	9) Exposure to domestic violence	x	x	
Other stressful events	10) Inadequate parental supervision or frequent open conflicts between parents	x		
	11) Report to child protective services or safety placement of the child	x	x	
	12) Peer rejection			
	13) Parent suicide attempt		x	
	14) Psychiatric hospitalization or psychiatric episode of parent		x	
	15) Drug or alcohol abuse by parent	x		
	16) Parent in jail		x	
	17) Death of a parent		x	x
	18) Chronic physical illness of a parent			
	19) Death of a sibling		x	
	20) Death of a close friend		x	
	21) Death of a family member			
	22) Parental separation or divorce	x		
	23) Significant decrease of contacts with one of the parents		x	
	24) Parent frequently away from home for long periods	x		
	25) Natural disaster		x	
	26) Serious car accident		x	
	27) Fire or robbery at home		x	
	28) Parent hospitalized for a physical problem		x	
	29) Chronic or serious illness of a sibling		x	
	30) Serious or chronic illness/hospitalization		x	

CECA.Q = Childhood Experience of Care and Abuse Questionnaire; CTQ = Childhood Trauma Questionnaire; TESI = Traumatic Event Screening Inventory.

*The CALEC captures 30 adverse life events that may affect the offspring's life: traumatic events corresponding to abuse and neglect (items 1–9) and other stressful events (items 10–30). Categories of abuse and neglect were comparable to those reported in meta-analytic work on childhood adversities^{9,12} and in established instruments.^{10,11}

†The presence of 1 item among items 1–9 defined a child as exposed to traumatic events (abuse and neglect). A recent meta-analysis confirmed separate statistical associations between these types of trauma and psychosis.⁹ Other studies used similar presence/absence coding of trauma.^{13–16}

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Neuropsychological assessments

IQ was measured with a full standard intelligence scale (Wechsler Intelligence Scale for Children-III [WISC-III]/Wechsler Adult Intelligence Scale-III [WAIS-III]).^{17,18} The global IQ of high-risk offspring was 97.6. The domain of visual episodic memory was assessed with the Rey Complex Figure Test,¹⁹ immediate and delayed recall. Participants had to copy a figure and then recall it after 3 minutes (immediate recall) and 30 minutes (delayed recall). The domain of verbal episodic memory was assessed with the California Verbal Learning Test,²⁰ total and delayed recall in which participants had to learn series of words presented verbally over 5 trials and to recall them immediately after each presentation (total recall) or after a 20-minute delay (delayed recall). The domain of working memory was assessed with the digit span (WISC-III or WAIS-III subtest), in which participants had to recall serially sequences of digits, and the Corsi,^{17,18} in which the participants had to recall series of blocks. The domain of executive functions/initiation was assessed with the Verbal Fluency Test,²¹ in which participants had to produce a maximum number of words in a 1-minute interval. The first condition consisted of producing as many words as possible from the same semantic category (i.e., “animals”). In the second condition, participants were asked to produce words from a phonological cue (i.e., words beginning with the letter “p”). The raw scores were converted to z-scores using the mean performance of young controls ($n = 170$) balanced for age and sex. To compose the cognitive domains, we then calculated the average z-score of the 2 subtests.

Table S2: Frequency of abuse and neglect, and of other stressful events, in the 66 offspring of bipolar and schizophrenia parents

Category	Specific type of adversity	Items	Frequency, no (%) $n = 66$	
Traumatic events (abuse and neglect)*	Physical abuse ($n = 13, 20\%$)	1) Physical abuse by a parent	6 (9%)	
		2) Physical abuse by a peer	8 (12%)	
		3) Definite sexual abuse	3 (5%)	
	Sexual abuse ($n = 7, 11\%$)	4) Other sexual abuse	5 (8%)	
		5) Parental physical neglect	7 (11%)	
	Parental Neglect ($n = 14, 21\%$)	6) Parental emotional neglect	7 (11%)	
		7) Parental emotional abuse	6 (9%)	
	Emotional abuse ($n = 10, 15\%$)	8) Bizarre or clearly inappropriate punishment of the child	6 (9%)	
		9) Exposure to domestic violence	17 (26%)	
Other stressful events	Uncaring relationship	10) Inadequate parental supervision or frequent open conflicts between parents	19 (29%)	
		11) Report to child protective services or safety placement of the child	16 (24%)	
		12) Peer rejection	9 (14%)	
		Psychiatric disorder in parents	13) Parent suicide attempt	8 (12%)
			14) Psychiatric hospitalization or psychiatric episode of parent	62 (94%)
			15) Drug or alcohol abuse by parent	12 (18%)
		Diminished accessibility of attachment figures	16) Parent in jail	9 (14%)
			17) Death of a parent	4 (6%)
			18) Chronic physical illness of a parent	6 (9%)
			19) Death of a sibling	1 (2%)
			20) Death of a close friend	13 (20%)
			21) Death of a family member	44 (67%)
	22) Parental separation or divorce		38 (58%)	
	23) Significant decrease of contacts with one of the parents		15 (23%)	
	24) Parent frequently away from home for long periods		4 (6%)	
	Environmental and personal stressors	25) Natural disaster	2 (3%)	
		26) Serious car accident	8 (12%)	
		27) Fire or robbery at home	1 (2%)	
		28) Parent hospitalized for a physical problem	14 (21%)	
		29) Chronic or serious illness of a sibling	5 (8%)	
		30) Serious or chronic illness / hospitalization	12 (18%)	

*The presence of 1 item among items 1–9 defined a child as exposed to traumatic events (abuse and neglect). A recent meta-analysis confirmed separate statistical associations between these types of trauma and psychosis.⁹ Other studies used similar presence/absence coding of trauma.^{13–16}

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Supplementary Results

Table S3: Sociodemographic and clinical characteristics of high-risk offspring exposed and not exposed to trauma

Characteristic	Group, mean ± SE or no. (%)		Statistical test*	p value
	Nonexposed, n = 36	Exposed, n = 30		
Socioeconomic status†	44.63 ± 2.90	35.39 ± 3.37	$F_{45,2} = 4.32$	0.043
Age	17.30 ± 0.75	17.70 ± 0.85	$F_{46,8} = 0.13$	0.73
Male sex	20 (56)	12 (40)	$\chi^2_1 = 1.59$	0.21
Substance abuse‡	5 (14)	6 (20)	$\chi^2_1 = 0.31$	0.58
Nonpsychotic DSM-IV diagnoses§	17 (47)	18 (60)	$\chi^2_1 = 1.07$	0.30

SE = standard error.

*To account for possible correlation among participants within the same sibship, a multilevel model was carried out using the MIXED procedure of SAS version 9.1.3 (SAS Institute Inc.). Sibships nested in the group were used as the second level and modelled according to a random effect. Degrees of freedom were obtained using the Kenward–Roger method.²²

†Assessed using the Blishen index according to the highest socioeconomic status of the 2 parents. This index is based on education and income and on a Canadian census of 514 occupational categories according to the Canadian Classification and Dictionary of Occupations.²³

‡Lifetime substance abuse or dependence was coded using all available medical records, family informant interviews and clinical semistructured interviews with the parents or the participants.

§Nonpsychotic DSM-IV diagnoses were evaluated using all available medical records, family informant interviews and semistructured interviews (Kiddie-Schedule for Affective Disorders and Schizophrenia) with the parents of children younger than 18 years or the Structured Clinical Interview for DSM disorders with participants aged 18 years or older.

Table S4: Association between childhood trauma and impairments in visual episodic memory and executive functions of initiation

Domain	Cognitive impairment†	Group, frequency (standardized residual)*			p value	OR
		Nonexposed, n = 36	Exposed, n = 30	χ^2		
Visual episodic memory	Not impaired	26 (3.2)	10 (-3.2)	9.98	0.002	5.20
	Impaired	10 (-3.2)	20 (3.2)			
Executive functions of initiation‡	Not impaired	30 (2.7)	15 (-2.7)	7.53	0.006	4.67
	Impaired	6 (-2.7)	14 (2.7)			

OR = odds ratio.

*Offspring exposed to trauma have significantly higher rates of cognitive impairments (as indexed by percentile 16) than nonexposed offspring.

†A cognitive deficit is defined by a performance below percentile 16, a cut-off often used in clinical neuropsychology.^{24,25}

‡Missing data on executive functions for 1 offspring.

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Table S5: Trauma and sociodemographic characteristics of high-risk offspring with a parent with schizophrenia or bipolar disorder

Characteristic	Group, mean ± SE or no. (%)		Statistical test*	p value
	Schizophrenia, n = 23	Bipolar disorder, n = 43		
Socioeconomic status†	33.84 ± 3.87	44.38 ± 2.86	$F_{41,2} = 4.80$	0.034
Age	18.23 ± 0.96	16.97 ± 0.70	$F_{41,5} = 1.13$	0.29
Any trauma‡§	13 (57)	17 (40)	$\chi^2_1 = 1.74$	0.19
Physical abuse	4 (17)	9 (21)	$\chi^2_1 = 0.12$	0.73
Sexual abuse	3 (13)	4 (9)	$\chi^2_1 = 0.22$	0.64
Parental neglect	10 (44)	4 (9)	$\chi^2_1 = 10.47$	0.001
Emotional abuse	5 (22)	5 (12)	$\chi^2_1 = 1.19$	0.28
Domestic violence	10 (44)	7 (16)	$\chi^2_1 = 5.80$	0.021
Male sex	8 (35)	24 (56)	$\chi^2_1 = 2.65$	0.10

SE = standard error.

*To account for possible correlation among participants within the same sibship, a multilevel model was carried out using the MIXED procedure of SAS version 9.1.3 (SAS Institute Inc.). Sibships nested in the group were used as the second level and modelled according to a random effect. Degrees of freedom were obtained using the Kenward–Roger method.²²

†Assessed using the Blishen index according to the highest socioeconomic status of the 2 parents. This index is based on education and income and on a Canadian census of 514 occupational categories according to the Canadian Classification and Dictionary of Occupations.²³

‡Exposure to trauma was defined as the presence of at least 1 experience of physical abuse, sexual abuse, parental neglect, emotional abuse or domestic violence.

§Most trauma (67%) occurred before age 7 years.

Table S6: ANCOVAs comparing the cognitive functioning of offspring exposed to childhood trauma with parents with schizophrenia or bipolar disorder

Domain	Group, cognitive mean scores ± SE		Group, adjusted means ± SE*		Statistical test†	p value
	Schizophrenia, n = 13	Bipolar disorder, n = 17	Schizophrenia, n = 13	Bipolar disorder, n = 17		
IQ‡	93.4 ± 8.92	93.0 ± 13.00	-1.180 ± 0.303	-0.936 ± 0.246	$F_{26,0} = 0.36$	0.55
Visual episodic memory§	16.81 ± 14.00	19.79 ± 28.21	-0.706 ± 0.355	-0.700 ± 0.277	$F_{18,1} = 0.005$	0.98
Executive functions (initiation)§	24.09 ± 18.01	18.09 ± 12.15	-0.467 ± 0.197	-0.523 ± 0.151	$F_{20,1} = 0.05$	0.83

ANCOVA = analysis of covariance; SE = standard error.

*Adjusted means are in z-scores (adjusted for age and sex).

†To account for possible correlation among participants within the same sibship, a multilevel model was carried out using the MIXED procedure of SAS version 9.1.3 (SAS Institute Inc.). Sibships nested in the group were used as the second level and modelled according to a random effect. Degrees of freedom were obtained using the Kenward–Roger method.²²

‡The IQ mean score was calculated using the full-scale IQ.

§The average scores for visual episodic memory and executive functions were calculated using percentiles.

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Tables S7 and S8 show that when controlling for age, sex and the other cognitive domain associated with trauma (i.e., controlling for visual episodic memory when testing executive functions of initiation and controlling for executive functions of initiation when testing visual episodic memory, respectively), the effect of trauma remained the principal predictor of cognitive performance. Importantly, this result suggests that both functions are affected by trauma independently of each other. Trauma would thus exert its impacts on the brain through 2 independent pathways.

Table S7: Regression analysis examining the influence of trauma, age, sex and executive functions of initiation on visual episodic memory

Factor	B (95% CI)	SE B	β	<i>p</i> value
Trauma exposure	-0.48 (-0.93 to -0.04)	0.23	-0.27	0.034
Age	0.08 (0.02 to 0.14)	0.03	0.35	0.011
Sex	0.17 (-0.23 to 0.56)	0.20	0.09	0.40
Executive functions of initiation	0.20 (-0.12 to 0.53)	0.16	0.18	0.22

CI = confidence interval; SE = standard error.

Table S8: Regression analysis examining the influence of trauma, age, gender and visual episodic memory on executive functions of initiation

	B (95% CI)	SE B	β	<i>p</i> value
Trauma exposure	-0.64 [-.96, -0.32]	0.16	-0.39	< 0.001
Age	0.10 [.06, 0.14]	0.02	0.51	< 0.001
Gender	-0.33 [-.62, -0.03]	0.15	-0.20	0.030
Visual episodic memory	0.12 [-.62, -0.03]	0.10	0.14	0.22

CI = confidence interval; SE = standard error.

Table S9: ANCOVAs comparing the cognitive functioning of female offspring exposed and nonexposed to abuse or neglect

Domain	Group, adjusted means \pm SE*		Statistical test	<i>p</i> value	Effect size†
	Nonexposed, <i>n</i> = 16	Exposed, <i>n</i> = 18			
IQ	-0.220 \pm 0.231	-0.918 \pm 0.218	$F_{1,31} = 4.82$	0.036	0.76
Visual episodic memory	-0.139 \pm 0.193	-0.852 \pm 0.182	$F_{1,31} = 7.22$	0.011	0.93
Executive functions of initiation	0.241 \pm 0.137	-0.349 \pm 0.129	$F_{1,31} = 9.80$	0.004	1.08

ANCOVA = analysis of covariance; LSMeans = difference of adjusted means; SE = standard error.

*The offsprings' raw scores on each neuropsychological test were converted to z-scores based on the cognitive performance of 170 young healthy controls. Means were adjusted for age.

†Effect sizes were calculated using LSMeans between offspring exposed and nonexposed to trauma standardized by a pooled standard deviation. The pooled standard deviation was obtained by dividing the SE of the difference of LSMeans by the square root of

$$\frac{1}{nHR_{exposed}} + \frac{1}{nHR_{nonexposed}}$$

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Table S10: ANCOVAs comparing the cognitive functioning of male offspring exposed and nonexposed to abuse or neglect

Domain	Group, adjusted means ± SE*		Statistical test	p value	Effect size†
	Nonexposed, n = 20	Exposed, n = 12			
IQ	-0.347 ± 0.297	-1.161 ± 0.384	$F_{1,29} = 2.80$	0.11	0.61
Visual episodic memory	0.069 ± 0.142	-0.773 ± 0.184	$F_{1,29} = 13.01$	0.001	0.74
Executive functions of initiation	0.241 ± 0.137	-0.349 ± 0.129	$F_{1,29} = 9.80$	0.004	1.31

ANCOVA = analysis of covariance; LSMeans = difference of adjusted means; SE = standard error.

*The offsprings' raw scores on each neuropsychological test were converted to z-scores based on the cognitive performance of 170 young healthy controls. Means were adjusted for age.

†Effect sizes were calculated using LSMeans between offspring exposed and nonexposed to trauma standardized by a pooled standard deviation. The pooled standard deviation was obtained by dividing the SE of the difference of LSMeans by the square root of

$$\frac{1}{nHR_{Exposed}} + \frac{1}{nHR_{nonexposed}}$$

Table S11 shows that exposure to trauma will lead to a higher combination rate of deficits in visual episodic memory and executive functions of initiation. Table S12 extends this result by showing that offspring exposed to trauma present a significantly higher combination rate of deficits in 4 cognitive domains recognized as core impairments of schizophrenia and bipolar disorder (visual episodic memory, verbal episodic memory, executive functions of initiation, working memory). Thus, years before disease onset, the data may suggest that offspring exposed to trauma will more frequently have cognitive profiles resembling those of adult patients.

Table S11: Aggregation of cognitive deficits* in visual episodic memory and executive functions according to trauma exposure

Trauma exposure	Group, no. (%)		
	No cognitive deficit, n = 28	1 cognitive deficit, n = 22	2 cognitive deficits, n = 14
Nonexposed, n = 36	22 (61)	12 (33)	2 (6)
Exposed, n = 28†	6 (21)	10 (36)	12 (43)

*Defined by a performance below percentile 16, a cut-off often used in clinical neuropsychology.^{24,25} Cognitive domains included visual episodic memory and executive functions of initiation. The distributions differed significantly ($\chi^2_2 = 15.71$, $p < 0.001$, $n = 64$).

†Two offspring had missing data for 1 cognitive domain.

Table S12: Aggregation of cognitive deficits* in visual episodic memory, verbal episodic memory, executive functions of initiation, and working memory according to trauma exposure

Trauma exposure	Group, no. (%)		
	No cognitive deficit, n = 25	1 cognitive deficit, n = 22	2 cognitive deficits, n = 17
Nonexposed, n = 36	20 (56)	13 (36)	3 (8)
Exposed, n = 28†	5 (18)	9 (32)	14 (50)

*Defined by a performance below percentile 16, a cut-off often used in clinical neuropsychology.^{24,25} Cognitive domains included visual episodic memory and executive functions of initiation. The distributions differed significantly ($\chi^2_2 = 6.10$, $p < 0.001$, $n = 64$).

†Two offspring had missing data for 1 cognitive domain.

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Table S13: Comparison of offspring not exposed to trauma, offspring exposed to trauma with ≤ 1 cognitive deficit, and offspring exposed to trauma with a combination of cognitive deficits on the GAF*

Measure	Group, adjusted mean† ± SE			Post hoc analyses, <i>p</i> value‡ (95% CI)		
	Exposed with a combination of cognitive deficits, <i>n</i> = 11	Exposed with ≤ 1 cognitive deficit, <i>n</i> = 14	Nonexposed, <i>n</i> = 33	Nonexposed v. exposed with ≤ 1 cognitive deficit	Nonexposed v. exposed with a combination of cognitive deficits	Exposed with ≤ 1 cognitive deficit v. exposed with a combination of cognitive deficits
GAF§	57.6 ± 4.31	65.0 ± 3.84	72.0 ± 2.50	0.09 (−1.32 to 17,17)	0.003 (5.53 to 25.41)	0.20 (−4.08 to 18.99)

ANCOVA = analysis of covariance; CI = confidence interval; GAF = Global Assessment of Functioning scale; LSD = least significant difference; SE = standard error.

*We compared the 3 groups of offspring (nonexposed to trauma, exposed to trauma with ≤ 1 cognitive deficit; exposed to trauma with a combination of cognitive deficits) on the GAF by means of an ANCOVA. The main effect was significant ($F_{5,56} = 5.91, p < 0.001$). Post hoc analyses showed that only the group of offspring with a combination of cognitive deficits differed from nonexposed offspring on the GAF.

†Adjusted for age and sex.

‡The *p* values were derived from post hoc analyses using the LSD procedure based on the Student *t* test.

§Scores could not be assessed for 8 participants.

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