It is illegal to post this copyrighted PDF on any website.

Relationships Between Self-Injurious Behaviors, Pain Reactivity, and β-Endorphin in Children and Adolescents With Autism

Sylvie Tordjman, MD, PhD[a,b,*]; George M. Anderson, PhD[c]; Annaëlle Charrier, MD[a]; Cécile Oriol, MD[a]; Solenn Kermarrec, MD[a,b]; Roberto Canitano, MD, PhD[d]; Michel Botbol, MD[e]; Nathalie Coulon, MD, PhD[b]; Corinne Antoine, PhD[f]; Sylvie Brailly-Tabard, MD, PhD[g]; David Cohen, MD, PhD[h]; Hazar Haidar, PhD[g]; Séverine Trabado, MD, PhD[g]; Michèle Carlier, PhD[i]; Guillaume Bronsard, MD, PhD[j]; and Laurent Mottron, MD, PhD[k,l]

ABSTRACT

Objective: Autism and certain associated behaviors including self-injurious behaviors (SIB) and atypical pain reactivity have been hypothesized to result from excessive opioid activity. The objective of this study was to examine the relationships between SIB, pain reactivity, and β-endorphin levels in autism.

Methods: Study participants were recruited between 2007 and 2012 from day care centers and included 74 children and adolescents diagnosed with autism (according to *DSM-IV-TR*, *ICD-10*, and CFTMEA) and intellectual disability. Behavioral pain reactivity and SIB were assessed in 3 observational situations (parents at home, 2 caregivers at day care center, a nurse and child psychiatrist during blood drawing) using validated quantitative and qualitative scales. Plasma β-endorphin concentrations were measured in 57 participants using 2 different immunoassay methods.

Results: A high proportion of individuals with autism displayed SIB (50.0% and 70.3% according to parental and caregiver observation, respectively). The most frequent types of SIB were head banging and hand biting. An absence or decrease of overall behavioral pain reactivity was observed in 68.6% and 34.2% of individuals with autism according to parental and caregiver observation, respectively. Those individuals with hyporeactivity to daily life accidental painful stimuli displayed higher rates of self-biting ($P < .01$, parental evaluation). No significant correlations were observed between β-endorphin level and SIB or pain reactivity assessed in any of the 3 observational situations.

Conclusions: The absence of any observed relationships between β-endorphin level and SIB or pain reactivity and the conflicting results of prior opioid studies in autism tend to undermine support for the opioid theory of autism. New perspectives are discussed regarding the relationships found in this study between SIB and hyporeactivity to pain.

J Clin Psychiatry 2018;79(2):16m10889

To cite: Tordjman S, Anderson GM, Charrier A, et al. Relationships between self-injurious behaviors, pain reactivity, and β-endorphin in children and adolescents with autism. *J Clin Psychiatry.* 2018;79(2):16m10089.

To share: https://doi.org/10.4088/JCP.16m10889

© Copyright 2018 Physicians Postgraduate Press, Inc.

[a]Hospital-University Department of Child and Adolescent Psychiatry, CHGR and University of Rennes 1, Rennes, France

[b]Laboratory of Psychology of Perception, CNRS UMR 8158, Paris, France

[c]Child Study Center, Yale University School of Medicine, New Haven, Connecticut

[d]Division of Child and Adolescent Neuropsychiatry, University Hospital of Siena, Siena, Italy

[e]Hospital-University Department of Child and Adolescent Psychiatry, UBO, Brest, France

[f]University Paris 8, Saint Denis, France

[g]INSERM U 693, University Paris-South, School of Medicine Paris-South; AP-HP, CHU Bicêtre, Department of Molecular Genetics, Pharmacogenetics and Hormonology, Kremlin-Bicêtre, France

[h]Department of Child and Adolescent Psychiatry, AP-HP, GH Pitié-Salpétrière, CNRS FRE 2987, University Pierre and Marie Curie, Paris, France

[i]Aix Marseille University, CNRS, LPC, Marseille, France.

[j]Laboratory of Public Health EA3279, School of Medicine of La Timone, Marseille, France

[k]Center of Excellence for Pervasive Developmental Disorders of the University of Montreal (CETEDUM), Rivières-des-Prairies Hospital, Montreal, Quebec, Canada

[l]Research Center of CIUSSS of the North of Montreal and Department of Psychiatry, University of Montreal, Montreal, Quebec, Canada

**Corresponding author:* Pr Sylvie Tordjman, MD, PhD, PHUPEA (Pôle Hospitalo-Universitaire de Psychiatrie de l'Enfant et de l'Adolescent), CHGR, Université de Rennes 1, 154 rue de Châtillon, Rennes 35000, France (s.tordjman@yahoo.fr).

Intriguing questions exist concerning the role of opioid peptides in the self-injurious behaviors (SIB) often seen in autism. Some authors[1,2] have suggested that excessive brain opioid activity could contribute to or even determine the pathogenesis of autism. This hypothesis has been based on symptom profiles observed in autism, the effects of opiate antagonists, and reported alterations in β-endorphin (BE) and related compounds in autism. The main points in support of endorphin theories of autistic behaviors and SIB are summarized as follows, along with counter-arguments:

1. There are apparent behavioral similarities (social withdrawal, reduced expression of emotion and pain reactivity) between autistic behaviors and opiate addiction or behavioral states following injections of opioid agents in animals.[3–5] Additionally, children with autism often show stereotypies and SIB that have been suggested to be mediated and maintained by abnormally high BE levels.[6] From this perspective, some authors[7] have suggested that SIB could be viewed as an addictive behavior.
2. Therapeutic effects of opiate antagonists naltrexone and naloxone (nonspecific opioid antagonists), when administered to individuals with autism, were reported for SIB and autism-related behaviors.[8–10] However, a similar number of studies[11–13] observed no beneficial effects of opiate antagonists in core symptoms of autism. Furthermore, Roy et al[14] undertook a systematic review on the effects of opioid antagonists in core symptoms of children with autism and concluded that naltrexone may improve hyperactivity and restlessness in children with autism but that there was no sufficient evidence for a significant effect on core features of autism in the majority of the participants. Willemsen-Swinkels et al[12] found even that naltrexone actually increased autistic

You are prohibited from making this PDF publicly available.

For reprints or permissions, contact permissions@psychiatrist.com. ♦ © 2018 Copyright Physicians Postgraduate Press, Inc.

It is illegal to post this copyrighted PDF on any website.

Clinical Points

- Because of methodological problems (sample sizes, behavioral assessments, or biochemical measures), there are discrepant results regarding relationships between self-injurious behaviors (SIB), β-endorphin levels, and pain reactivity in autism.
- The absence of any observed relationships between β-endorphin levels and SIB or pain reactivity in this study does not support the opioid theory of autism and the use of opiate antagonist therapies in autism spectrum disorder.

stereotypies, and other authors[15] reported that acute naltrexone treatment led to increased SIB. Focusing on SIB, several authors have conducted literature reviews on the therapeutic effects of naltrexone, and most reported no significant effects[16,17] or significant reduction of SIB frequency particularly in intellectually disabled adults.[18,19] Concerning the discrepant results of naltrexone effectiveness for SIB, it is noteworthy that most of the studies[16,18] were uncontrolled studies and/or were limited by small sample sizes. Furthermore, opioid peptides, such as BE, interact with numerous opioid receptor types,[20] and different biological bases for various subtypes of SIB in autism may exist.[21,22] Thus, Herman et al[21] found a significant reduction of head banging following naltrexone administration, whereas self-biting was not decreased. Th finding suggests that different types of SIB may be mediated by different biological mechanisms and, according to Willemsen-Swinkels et al,[23] merits further study.

3. As seen in Table 1, levels of plasma BE are reported by several authors to be abnormally high in autism. However, results are not totally congruent, and discrepancies with regard to SIB are of special relevance. It appears important to examine SIB as a separate and quantifiable variable and to take into consideration the severity of SIB and the level of cognitive functioning. The apparently contradictory data concerning plasma BE levels in autism could be partly explained by methodological problems (ie, specificity of immunoassays, small sample sizes, and cognitive-behavioral heterogeneity of autism). Also, similar inconsistent results have been reported in central opioid studies in autism (Table 1). Thus, cerebrospinal fluid (CSF) BE levels measured in individuals with autism were reported to be increased, decreased, or similar to controls. Furthermore, Gillberg et al[24] observed a trend toward a correlation between CSF endorphin fraction II and self-destructiveness or decreased pain sensitivity, whereas Nagamitsu et al[25] reported no significant correlations between CSF BE levels and SIB or pain insensitivity. As shown in Table 1, the available data, presented in chronological order, are quite mixed in terms of providing support for the hypothesis that alterations in opioid biochemistry play a role in autism-related behaviors. More specifically, the studies show discrepant results regarding the relationships between BE and SIB due to methodological differences in sample characteristics (sample sizes and cognitive-behavioral phenotype), biochemical measures (different types of fluid and opioid, but also different immunoassay methods), or behavioral assessments (types of SIB studied, assessment instruments, observational situations, assessment duration).

We have conducted the present study in an attempt to clarify the potential role of BE in SIB and to examine the relationships between SIB and pain reactivity in autism. Plasma BE levels were measured—for the first time using 2 different BE immunoassays—in a large group of 74 individuals with autism to examine potential biochemical method effects, and behavior was carefully and thoroughly assessed using validated quantitative and qualitative scales in different observational situations so that behavioral and biochemical interrelationships could be fully examined.

METHOD

Participants

Children and adolescents with autism (n = 74) were recruited in 2007 from day care centers and participated in a larger study until 2012. Based on direct clinical observation by 2 independent child psychiatrists, a diagnosis of autism was made according to *DSM-IV-TR*,[46] *ICD-10*,[47] and CFTMEA[47] criteria and was confirmed by the Autism Diagnostic Interview-Revised (ADI-R).[48] The ADI-R is an extensive semistructured parental interview and was conducted by a trained psychiatrist certified in the scale's administration. On the basis of the ADI-R algorithm, individuals with autism displayed severe behaviors in the main domains of autism (mean ± SD score for reciprocal social interaction was 22.94 ± 5.71 with a cutoff of 10; for nonverbal communication, was 10.01 ± 1.88 with a cutoff of 7; for repetitive behaviors and stereotyped patterns, was 8.99 ± 2.5 with a cutoff of 3; and for abnormalities of development evident at or before age 36 months, was 4.49 ± 0.66 with a cutoff of 1).

All individuals were determined to be physically healthy based on the examination by a pediatrician. All individuals with autism were intellectually disabled as determined with the age-appropriate Wechsler intelligence scales and the Kaufman Assessment Battery for Children (K-ABC).[49] The demographic, clinical, and cognitive characteristics are presented in Table 2. The protocol was approved by the ethics committee of Bicêtre Hospital, and written informed consent was obtained from all parents.

Behavioral Assessments

Behavioral assessments were performed using the Self-Injurious Behavior Scale (SIBS) and the Pre-Linguistic

You are prohibited from making this PDF publicly available.

For reprints or permissions, contact permissions@psychiatrist.com. ♦ © 2018 Copyright Physicians Postgraduate Press, Inc.

It is illegal to post this copyrighted PDF on any website.

Table 1. Studies of Opioid Levels in Individuals With Autism and/or Self-Injurious Behaviors

Study	Fluid	Study Group (N)	Opioid	Results
Gillberg et al (1985)[24]	CSF	Autism (N = 20)	Endorphin fraction II (mainly Met-enkephalin)	Increased in SIB and low pain sensitivity
Ross et al (1987)[26]	CSF	Autism (N = 9)	BE	Increased compared to the TDC group
Gillberg et al (1990)[27]	CSF	Autism children (N = 31)	BE	Decreased compared to the control group
Nagamitsu (1993),[28] Nagamitsu et al (1997)[25]	CSF	Autism (N = 19)	BE	Similar to the TDC group No correlation with SIB or pain insensitivity
Brambilla et al (1997)[29]	PBMC	Autism (N = 12)	BE	Increased compared to the TDC group
Cazzullo et al (1999)[30]	PBMC	Autism (N = 11)	C-terminal BE	Increased compared to the TDC group
Coid et al (1983)[31]	Plasma	Borderline SIB (N = 10)	Met-enkephalin–like immunoactivity	Increased in SIB
Weizman et al (1984)[32]	Plasma	Autism (N = 10)	Humeral endorphin	Decreased compared to the TDC group
Zelnik et al (1986)[33]	Plasma	Males with SIB (N = 3)	BE	Decreased compared to the TDC group
Herman et al (1988)[34]	Plasma	Autism (N = 5)	BE	Similar to the TDC group
Weizman et al (1988)[35]	Plasma	Autism (N = 22)	BE	Decreased compared to the TDC or schizophrenic groups
Sandman et al (1990)[36]	Plasma	Intellectually disabled (ID) individuals with SIB and/or stereotyped behavior (N = 40)	BE	Decreased compared to the TDC group Increased compared to ID individuals without SIB or stereotyped behavior
Herman (1990)[37]	Plasma	SIB (N = 7)	BE	Decreased compared to the TDC group
Bouvard et al (1992)[38]	Plasma	Autism (N = 4)	BE	Increased compared to the TDC group
Ernst et al (1993)[39]	Plasma	Autism (N = 5)	BE	Similar to the TDC group No correlation with SIB
Leboyer et al (1994,[40] 1999[41])	Plasma	Autism (N = 67 and N = 62)	N-terminal BE	Decreased compared to the TDC group or girls with Rett syndrome No correlation with SIB
			C-terminal BE	Increased compared to the TDC group or girls with Rett syndrome No correlation with SIB
Bouvard et al (1995)[42]	Plasma	Autism (N = 10)	C-terminal BE	Increased compared to control normative values
Willemsen-Swinkels et al (1996)[23]	Plasma	ID individuals with severe SIB including 4 individuals with autism (N = 13)	BE	Decreased compared to autism + ID group without severe SIB
Tordjman et al (1997)[43]	Plasma	Autism (N = 48)	Both N-terminal and C-terminal BE	Increased compared to the TDC group No correlation with SIB
Sandman et al (2002)[44]	Plasma	Chronic SIB (N = 45)	Both N-terminal and C-terminal BE	Dissociation between BE (elevated morning levels of BE) and ACTH in patients with the highest probabilities of patterns of SIB
Kemp et al (2008)[10]	Plasma	Severe developmental disabilities with SIB (N = 25)	Both N-terminal and C-terminal BE	Significant correlations between recurrent temporal patterns of SIB and basal levels of BE
Tordjman et al (2009)[45]	Plasma	Autism (N = 57)	C-terminal BE	Increased compared to the TDC group Significant association with autism severity

Abbreviations: ACTH = adrenocorticotropic hormone, BE = β-endorphin, CSF = cerebrospinal fluid, ID = intellectually disabled, PBMC = peripheral blood mononuclear cells, SIB = self-injurious behaviors, TDC = typically developing control.

Behavioral Pain Reactivity Scale (PL-BPRS).[45,51,52] The SIBS assesses 13 different types of current and lifetime SIB and allows the same instrument to be applied across settings, including at home (video recording of SIB using analytic methods with time series is usually done in care centers during a limited time but not at home and/or during a 1-month period). This scale has been previously found to have good discriminative capacity, reliability (interrater reliability was excellent with an interjudge agreement of 91% between 2 independent raters in day care center), and validity (internal and external validity) for assessment of SIB in autism.[51,52] The PL-BPRS assesses behavioral pain reactivity based on observable reactions to noxious stimuli.[45,51] The SIBS and PL-BPRS (including types of behaviors, and quantitative as well as qualitative ratings) are described in Table 3.

SIB and pain reactivity were assessed in 3 different observational situations, defined as follows:

1. The day care center, where 2 caregivers independently rated SIB and pain reactivity on a daily basis every time that these behaviors were observed in day care activities during the month preceding the blood drawing.
2. At home, where parents rated behavior during the same month as caregivers. In this situation, there were enough daily life situations involving pain to

You are prohibited from making this PDF publicly available.

For reprints or permissions, contact permissions@psychiatrist.com. ♦ © 2018 Copyright Physicians Postgraduate Press, Inc.

It is illegal to post this copyrighted PDF on any website.

Table 2. Demographic, Clinical, and Cognitive Characteristics of the Sample[a]

Characteristics	Individuals With Autism (N = 74)
Descriptive variables	
Male/female, n (%)	49 (66.2)/25 (33.8)
Age, y	11.6 ± 4.5
Pubertal status,[b] n (%)	
Prepubertal	32 (43.2)
Pubertal	16 (21.6)
Postpubertal	26 (35.1)
Medication status, n (%)	
Unmedicated	48 (64.9)
Anticonvulsants (idiopathic epilepsy)	14 (18.9)
Antipsychotics	15 (20.3)
Autistic behavioral domains and autism diagnosis: ADI-R[c]	
Abnormalities of development evident at or before 36 mo (cutoff = 1)	4.49 ± 0.66
Reciprocal social interaction (cutoff = 10)	22.94 ± 5.71
Nonverbal communication (cutoff = 7)	10.01 ± 1.88
Repetitive behaviors and stereotyped patterns (cutoff = 3)	8.99 ± 2.5
Cognitive functioning: Wechsler intelligence scales[d]	
Full-scale IQ (minimum–maximum)	42.2 ± 3.2 (40–58)

[a]Values shown as mean ± SD unless otherwise noted.
[b]Pubertal status was assessed by a pediatrician using the Tanner scale[50]: prepubertal = Tanner stage 1; pubertal = Tanner stages 2, 3 and 4; postpubertal = Tanner stage 5.
[c]According to the algorithm of the ADI-R[48] (parental interview), the diagnostic criteria for autistic disorder are fulfilled when the total scores of each domain reach the cutoff.
[d]Age-appropriate Wechsler intelligence scales[49]: WPPSI-R for 22 children aged between 2 and 7 years, WISC-IV for 42 children and adolescents aged between 6 and 16 years, and WAIS-R for 10 individuals older than 16 years.
Abbreviations: ADI-R = Autism Diagnostic Interview-Revised, K-ABC = Kaufman Assessment Battery for Children, WAIS-R = Wechsler Adult Intelligence Scale-Revised, WISC-IV = Wechsler Intelligence Scale for Children-Fourth Edition, WPPSI-R = Wechsler Preschool and Primary Scale of Intelligence-Revised.

distinguish reactions to a variety of types of noxious and painful stimuli such as being burned, having internal pain (tooth pain, ear infection, headache, etc), and frequent daily life accidental painful stimuli (cutting, pinching, banging, etc). It is noteworthy that daily life accidental painful stimuli were the most frequent and objectionable noxious stimuli currently observed by the parents, given that internal pain related to painful illness is difficult to identify in nonverbal children with autism.

3. During the blood drawing, when a direct clinical observation was conducted by a nurse and a child psychiatrist not working with the caregiver team. The observational situation of the blood drawing followed a standardized procedure, described in the next paragraph.

Blood Drawing Procedures and Biochemical Analyses

The blood drawing was proposed for 63 children and adolescents with autism based on previous blood drawing experiences reported by the parents and was finally performed in 57 participants (25 prepubertal, 8 pubertal, 24 postpubertal). Attrition was due to the inherent difficulties of venipuncture in low-functioning children with autism. The blood drawing occurred between 8:00 and 9:00 AM in the department of pediatrics at the nearest general hospital rather than at the day care center to avoid an association of the pain with the therapeutic milieu. It followed a standardized procedure to minimize and control the possible stressful conditions. Specifically, parents were present during the blood drawing, and no white coats were worn in the presence of the patients. Additionally, the children stayed in a play room for 15 minutes before the blood drawing, which was performed by the same nurse particularly experienced with handicapped children. Plasma BE concentrations were measured using 2 different immunoassay methods: an immunoradiometric sandwich assay (IRMA) procedure and a radioimmunoassay (RIA) procedure (see Table 3 and eAppendix 1).

Statistical Analysis

The Kolmogorov-Smirnov test indicated that BE levels were not normally distributed; thus, all statistical analyses were performed using log-transformed BE values. Untransformed means and SEMs for BE are given in the Results section to allow comparisons to previous studies. Group and subgroup comparisons of plasma BE levels were performed using analysis of variance and 2-tailed *t* test. The comparison between parental and caregiver evaluations for the presence of SIB was performed using χ^2 test. Correlations were determined by Spearman or Pearson correlation analyses. Relationships between SIB and pain reactivity were analyzed using the Wilcoxon test. Bonferroni correction was used to control for type I errors.

RESULTS

SIB in the 3 Observational Situations

High percentages of individuals with autism displayed SIB, either at the day care center (caregiver evaluation: 52/74, 70.3%) or at home (parental evaluation: 37/74, 50.0%), especially head banging and hand biting (Table 4).

During the blood drawing situation, 5 (8%) of 63 children with autism showed SIB (self-biting, head/body banging) occurring immediately after the venipuncture, suggesting a possible causal relationship between the blood drawing event and the observed SIB. No SIB were observed in typically developing children and adolescents (n = 115) during the blood drawing performed in our previous study.[45] Similar SIB following painful stimuli in individuals with autism were also described by parents and caregivers.

A comparison of the 1-month parental and caregiver observational situations in individuals with autism using the χ^2 test showed no significant relationship between the parental and caregiver evaluations for the presence of SIB (all different types of SIB combined). Additionally, an absence of significant correlations between these 2 observational situations was found for the quantitative scores (Spearman correlations) of 5 types of SIB: self-injury by repeated stereotypies, pulling off one's skin, self-punching, inserting objects into the body, and swallowing objects.

You are prohibited from making this PDF publicly available.

For reprints or permissions, contact permissions@psychiatrist.com. ♦ © 2018 Copyright Physicians Postgraduate Press, Inc.

It is illegal to post this copyrighted PDF on any website.

Table 3. Behavioral and Biochemical Assessments

Assessments	Detailed Information
Behavioral Scales	
Self-Injurious Behavior Scale	
Types of SIB	Banging self; biting self; punching self; pinching self; self-injury by repeated stereotypies (eg, rubbing); cutting self or clawing self until bleeding; burning self; inserting objects into body or into bodily orifices; swallowing objects; ripping off one's skin, picking scabs (scratching self, scraping self), or pulling one's hair; holding self tight (eg tightly binding the body with belt, rope, or straps); putting self into dangerous situations; tearing one's clothes; and others
Quantitative ratings (scored from 1 to 7 for each rating)	Frequency, severity, duration
Qualitative ratings	Circumstances in which SIB occur, concurrent behaviors, locations where SIB occur, body localizations of SIB, tools (objects/body parts) used to provoke SIB
PL-BPRS	
Types of behavioral pain reactivity	Paradoxical pain reactivity, absence of pain reactivity, hyporeactivity to pain, typical/normal pain reactivity, and hyperreactivity to pain (each type/class is precisely defined by Tordjman et al[45])
Types of accidental painful stimulus	Being burned, painful illness (tooth or stomach pain, ear infection, headache, etc) and other diverse accidental painful stimuli (cutting, pinching, banging, etc)
Immunoassay Methods	
IRMA kit[a]	
High affinity and specificity	Both N-terminal and C-terminal BE
Limit of detection	4 pmol/L
Reproducibility	
Intraassay coefficient of variation	4.1%
Interassay coefficient of variation	9%
RIA procedure[53,54]	
High affinity and specificity	C-terminal BE
Limit of detection	5 pmol/L
Reproducibility	
Intraassay coefficient of variation	5%
Interassay coefficient of variation	6%

[a]Nichols Institute, Allégro BE Immunoassay, San Juan Capistrano, California.
Abbreviations: BE = β-endorphin, IRMA=immunoradiometric sandwich assay, PL-BPRS = Pre-Linguistic Behavioral Pain Reactivity Scale, RIA = radioimmunoassay, SIB = self-injurious behaviors.

Table 4. Caregiver and Parental Evaluations of Different Types of Self-Injurious Behavior in Children and Adolescents With Autism (N = 74)[a]

Type of Self-Injurious Behavior (SIB)[b]	Caregiver Evaluation	Parental Evaluation
Banging head or body[c]	30 (40.5)	22 (29.7)
Biting self[c]	16 (21.6)	16 (21.6)
Self-injury by repeated stereotypies (eg, rubbing)	14 (18.9)	4 (5.4)
Ripping off one's skin, picking scabs (scratching self, scraping self), pulling one's hair	8 (10.8)	5 (6.8)
Punching self	8 (10.8)	3 (4.1)
Putting self into dangerous situations (eg, falling, dashing in front of cars)	8 (10.8)	2 (2.7)
Holding self tight (eg, tightly binding the body with belt, rope, or straps)	7 (9.5)	1 (1.4)
Pinching self	8 (10.8)	1 (1.4)
Inserting objects into body or into bodily orifices	7 (9.5)	1 (1.4)
Swallowing objects	6 (8.1)	4 (5.4)
Cutting self or clawing self until bleeding	4 (5.4)	4 (5.4)
Tearing one's clothes	4 (5.4)	0 (0)
Burning self	0 (0)	2 (2.7)

[a]Data shown as n (%) of individuals displaying each type of SIB.
[b]The same individual can present with different types of SIB. Most individuals displayed only 1 type of SIB (caregiver evaluation: n = 17; parental evaluation: n = 20) or 2 types of SIB (caregiver evaluation: n = 18; parental evaluation: n = 13), with fewer showing 3 (caregiver evaluation: n = 8; parental evaluation: n = 2) or more (caregiver evaluation: n = 9; parental evaluation: n = 2) types of SIB. Most frequently, the combined SIB involved at least head banging associated with self-biting (caregiver evaluation: n = 8; parental evaluation: n = 8).
[c]The most frequent types of SIB were banging head (caregiver evaluation: 18/74; parental evaluation: 15/74) and biting hands (caregiver evaluation: 16/74; parental evaluation: 14/74).

Behavioral Pain Reactivity in the 3 Observational Situations

The distributions of the different types of behavioral pain reactivity seen in the 3 observational situations are summarized in Table 5 based on our previous study.[45] A large proportion of individuals with autism displayed an absence or decrease of pain reactivity according to the parental, caregiver, and blood drawing assessments (68.6%, 34.2%, and 55.6%, respectively).

Relationships Between SIB and Pain Reactivity

The parental evaluation showed a significant relationship between self-biting and hyporeactivity to daily life accidental painful stimuli (eg, cutting, pinching, banging) with the exception of burning (Wilcoxon $Z = 2.85$, $P < .01$; this result was still significant after Bonferroni correction [$P < .05$]). Also, the parental evaluation showed a relationship between self-biting and hyporeactivity to painful illness (eg, ear/

You are prohibited from making this PDF publicly available.

For reprints or permissions, contact permissions@psychiatrist.com. ♦ © 2018 Copyright Physicians Postgraduate Press, Inc.

It is illegal to post this copyrighted PDF on any website.

Table 5. Frequency of Behavioral Pain Reactivity in Children and Adolescents With Autism in the 3 Different Observational Situations (Parental, Caregiver, Blood Drawing)[a]

Observational Situation	Paradoxical	Absent	Hyporeactivity	Normal	Hyperreactivity
Home setting/parental evaluation in individuals with autism (n = 73)					
Evaluation of overall pain reactivity	1 (1.4)	2 (2.8)	48 (65.8)	20 (27.4)	2 (2.8)
Evaluation of pain reactivity to different types of noxious stimulus[b]					
Burning self	3 (4.1)	0 (0)	11 (15)	57 (78.1)	2 (2.7)
Painful illness (eg, tooth pain, ear infection)	0 (0)	2 (2.8)	34 (47.2)	33 (4.8)	3 (4.2)
Other pain (eg, accidentally cutting self, banging self)	1 (1.4)	1 (1.4)	46 (64.8)	19 (26.8)	4 (5.6)
Day care/caregiver evaluation in individuals with autism (n = 73)					
Evaluation of overall pain reactivity	2 (2.7)	3 (4.1)	22 (30.1)	43 (58.9)	3 (4.1)
Nurse/psychiatrist during venipuncture in individuals with autism (n = 63)					
Evaluation of pain reactivity to the venipuncture	4 (6.3)	26 (41.3)	9 (14.3)	14 (22.2)	10 (15.9)

[a]Data are frequency of individuals (% of group) for each type/class of pain reactivity (each type/class is precisely defined by Tordjman et al[45]).
[b]Parental evaluation shows descriptively in autism a gradient of pain reactivity according to noxious stimuli: based on parental observation, reaction to burning self appears to be more normal and less reduced than reaction to internal pain, which appears itself more normal and less reduced than reaction to other painful stimuli.

tooth infection) (Wilcoxon $Z = 1.98$, $P < .05$; this result was not significant after Bonferroni correction). In addition, the caregiver evaluation showed a relationship between past SIB (early SIB from birth to 3 years old) and current decreased behavioral pain reactivity (Wilcoxon $Z = 1.98$, $P < .05$; this result was not significant after Bonferroni correction). There was no significant relationship between pain reactivity observed during the blood drawing and either parent-rated or caregiver-rated SIB.

Effects of Descriptive Variables (IQ, Age, Sex, and Medication Status) on Plasma BE Levels, SIB, or Pain Reactivity

No significant relationships were found between log-transformed BE values and IQ or medication status (antipsychotics or anticonvulsants). A general linear model procedure performed with a sex factor, an age factor, and a puberty factor (prepubertal, pubertal, postpubertal), with BE (log-transformed values) as the dependent variable, showed no significant effect of puberty, age, or sex. Interestingly, these results were found regardless of the method of measure of BE levels (untransformed mean ± SEM BE) using either the RIA method (9.61 ± 1.05 pmol/L, n = 57) or the IRMA method (9.18 ± 0.63 pmol/L, n = 57). There were also no significant effects of IQ, age, sex, or pubertal status on SIB or pain reactivity regardless of the observational situation (parental, caregiver, or blood drawing).

Relationships Between Plasma BE Levels and SIB or Pain Reactivity

No significant correlations were found in autism between plasma BE concentrations (determined with either the RIA or IRMA method) and present or lifetime SIB assessed in the 3 observational situations (caregiver, parental, blood drawing). The absence of relationships between plasma BE and SIB was observed in the present study even when different types and aspects of SIB were considered using quantitative scores of frequency, severity, or duration. Additionally, no association was observed between plasma BE and pain reactivity.

DISCUSSION

Behavioral pain reactivity and SIB were assessed in 3 observational situations (home, day care center, and during blood drawing) using quantitative and qualitative scales in a large group of intellectually disabled children and adolescents with autism. The main finding of the study was that SIB, especially head banging and self-biting, were observed at a high frequency in this population and were not associated with BE levels but with hyporeactivity to pain.

The observed absence of association between plasma BE and SIB replicates the results of our previous study[43] conducted on 48 American individuals with autism. Indeed, when the current and lifetime SIB variables were dichotomized according to their presence or absence, or according to a high or low score, based on several different clinical assessments (Autism Behavior Checklist, Autism Diagnostic Observation Schedule, Vineland Adaptive Behavior Scales, Ornitz Developmental Inventory), no significant association was found with plasma BE data in either the autistic or intellectually disabled group.[43] Our findings are also consistent with the results of studies by Leboyer et al[40,41] conducted on a large sample of individuals with autism (BE levels were not correlated with SIB), but contradict certain studies (see Table 1). Furthermore, they are in partial agreement with the report by Willemsen-Swinkels et al[23] given that, in their report, individuals with mild and occasional SIB had plasma BE levels comparable to those of individuals without SIB, but BE levels of the 13 individuals with severe SIB were significantly lower than those seen for the individuals without severe SIB. We feel confident in our finding of no association between plasma BE and SIB given the large number of subjects studied, the use for the first time of 2 different BE immunoassay methods in autism, the wide range of SIB assessed, the quantitative ratings used, and the existence of multiple observational situations involving different locations and raters. Thus, our data do not support the hypothesis that certain types of SIB could be mediated by disturbances in the endogenous opioid.

You are prohibited from making this PDF publicly available.

For reprints or permissions, contact permissions@psychiatrist.com. ♦ © 2018 Copyright Physicians Postgraduate Press, Inc.

It is illegal to post this copyrighted PDF on any website.

The observed association between hyporeactivity to pain and certain SIB such as self-biting, one of the most frequent types of autistic SIB, is suggestive of several mechanisms for the production of SIB:

First, the individual with autism might bite himself or herself to feel painful sensations that he or she otherwise has difficulty perceiving. It is noteworthy that hand biting and head banging, the 2 most frequent types of SIB observed in this study but also in other studies on autism,[21,23,52,55] involve one's hand and head, which are the most important areas of the brain-body representation in the sensory homunculus (these 2 body parts are the most sensitive to stimuli). Our results underline the importance of distinguishing different types of SIB, which questions the potential role of characteristic autistic SIB such as hand biting or head banging. Certain SIB might fill a need to perceive bodily sensations even if the sensation involves pain. For example, Temple Grandin,[56] a woman with autism and high academic achievement, constructed a corset and a squeeze machine that exerted very strong pressure on her body, which she considered slightly painful. The painful sensations arising from SIB would allow individuals with autism to increase their bodily sensations and to enhance the development of body representation.[56,57] As discussed by Forgeot d'Arc et al,[58] the role and factors underlying the mechanisms of SIB remain to be better ascertained and understood, and SIB may have positive effects for individuals with autism.

Second, the reduced behavioral pain reactivity might reflect the autistic withdrawal that corresponds to a social communication withdrawal and creates a lack of environmental stimulation. In this context, SIB can be considered as self-stimulation behaviors (SIB provide sensory stimulation[59]) compensating for the lack of environmental stimuli. Inversely, SIB can help individuals with autism to withdraw from their environment by being engaged in and focused on bodily sensations. In both cases, the preferential hand and head localizations of SIB in autism strengthen the hypothesis that SIB might fulfill a sensory stimulation function (self-stimulation) in autism spectrum disorder.

Third, lasting and severe SIB could provoke chronic pain leading to hyporeactivity to acute pain. Our results showing a significant relationship between frequency, severity, and duration of SIB from birth to 3 years old and current decreased pain reactivity suggest that the early existence of repetitive, severe, and persistent SIB modifies later pain reactivity. However, research suggests that chronic stimulation of nociceptors facilitates pain responsiveness in animals.[60]

Finally, this association between self-biting and hyporeactivity to pain might be explained by a third variable, which is stress. It is noteworthy that anxiety symptoms were associated with the presence of SIB in individuals with learning disability.[61,62] Thus, SIB could enable individuals to release stress and might reflect stress coping mechanisms following painful stimuli. Our descriptive results of SIB occurring immediately after known painful stimuli in the 3 observational situations (home, day care center, and blood drawing) support this hypothesis. Due to verbal and nonverbal communication impairments, intellectually disabled individuals with autism may perceive painful sensations following noxious stimuli but not express typical behaviors of pain. The review by Moore[63] and our previous study[45] support this hypothesis by showing that self-/parent/clinical reports indicate pain hyporeactivity in autism whereas medical/experimental procedures suggest normal/hypersensitive pain responses. Intellectually disabled individuals would discharge the physical and psychological stress provoked by painful stimuli through SIB, resulting in an association between apparent behavioral hyporeactivity to pain and SIB. A related mechanism would be that stress-induced SIB produce a noxious stimulus inhibiting the response to other noxious stimuli by Diffuse Noxious Inhibitory Controls[64] with a hypnotic effect leading to hyporeactivity to acute pain.[65]

Also, the results highlight the key role of the situation and the observers in evaluations of SIB. The different results between the parental and caregiver observational situations underline the relational aspect subtending the expression of SIB. This relational aspect manifests itself (*a*) in the modulation of behaviors as a function of the situation and the people who are around and (*b*) in the observer who can perceive, interpret, and thus score differently SIB. SIB appear to have a social-communicative[66] and contextual dimension between a person who expresses himself or herself through a behavior related to a situation and another person who interprets and reacts to this behavior.

Some limitations of the study should be acknowledged. A first issue is the extent to which plasma BE, although used by some to support the opioid theory, reflects central opioid functioning given that the measure is peripherally derived and related to stress responses.[67,68] Future studies on the relationships between SIB and BE might measure CSF BE in order to reflect better central opioid function. Furthermore, future studies would benefit from neurophysiologic studies in autism assessing simultaneously pain sensitivity thresholds and behavioral pain reactivity. Finally, the narrow Wechsler IQ range (40–58) observed in the present study limits the ability to examine the relation of IQ to the behavioral and BE measures. It also limits the potential generalizability of the findings to a non–intellectually disabled population. However, even if some studies showed an association between SIB and the severity of intellectual disability,[61,69,70] it is noteworthy that a recent study[71] on autistic SIB suggests that cognitive factors alone do not adequately explain common measures of SIB and highlights the need for further research to better understand factors contributing to SIB.

In conclusion, the absence of relationships between BE and any type of SIB or behavioral pain reactivity assessed in the present study, taken together with the absence of clear benefits of opiate antagonist therapies and the inconsistent results of studies measuring opioid levels in autism (including central opioid levels), does not support the opioid theory of autism and the use of opiate antagonists in autism

You are prohibited from making this PDF publicly available.

For reprints or permissions, contact permissions@psychiatrist.com. ♦ © 2018 Copyright Physicians Postgraduate Press, Inc.

It is illegal to post this copyrighted PDF on any website.

spectrum disorder. Furthermore, opiate antagonist therapies can have important adverse effects, including hepatic toxicity. However, our findings depend on the methodology applied to assess behaviors and concern therefore only the types of SIB assessed in this study. Also, our data do not dismiss a potential role of the opioid system in the pathophysiology of autism with regard to other endogenous opioids possibly involved (such as enkephalins[24,31] and dynorphins[72]), genetic risk factors regulating the opioid system,[1,73] or altered central opioid functioning. The definitive assessment of possible central opioid alterations in autism will require additional CSF studies, neuroendocrine challenge studies, brain imaging, or postmortem analyses. Finally, future studies are also required to better ascertain the relationships found in this study between SIB and hyporeactivity to pain and to understand their underlying mechanisms.

Submitted: April 22, 2016; accepted August 8, 2017.

Published online: March 13, 2018.

Potential conflicts of interest: The authors report no conflict of interest (ie, no financial conflict or other relationship relevant to the subject of this article).

Funding/support: This research was supported by the Institut National de la Santé et de la Recherche Médicale (contrat Equipe de Recherche Clinique Associée à l'INSERM, Director of the Contract: Pr Tordjman).

Role of the sponsor: The funders of the study had no role in the design or conduct of the study or in the collection, management, analysis, or interpretation of the data; they were not involved in the preparation, writing, or revision of the manuscript or in the decision to submit the paper for publication.

Supplementary material: See accompanying pages.

REFERENCES

1. Čupić B, Hranilovic D, Jernej B, et al. Association study of genes regulating opioid system in autism. *Psychiatry Res*. 2012;198(1):169–170.
2. Panksepp J. A neurochemical theory of autism. *Trends Neurosci*. 1979;2:174–177.
3. Tordjman S, Carlier M, Cohen D, et al. The role of endorphins, enkephalins and dynorphins in aggression. *Behav Genet*. 2003;33(5):529–536.
4. Chamberlain RS, Herman BH. A novel biochemical model linking dysfunctions in brain melatonin, proopiomelanocortin peptides, and serotonin in autism. *Biol Psychiatry*. 1990;28(9):773–793.
5. Tordjman S, Drapier D, Bonnot O, et al. Animal models relevant to schizophrenia and autism: validity and limitations. *Behav Genet*. 2007;37(1):61–78.
6. Neuhaus E, Beauchaine TP, Bernier R. Neurobiological correlates of social functioning in autism. *Clin Psychol Rev*. 2010;30(6):733–748.
7. Nixon MK, Cloutier PF, Aggarwal S. Affect regulation and addictive aspects of repetitive self-injury in hospitalized adolescents. *J Am Acad Child Adolesc Psychiatry*. 2002;41(11):1333–1341.
8. Richardson JS, Zaleski WA. Naloxone and self-mutilation. *Biol Psychiatry*. 1983;18(1):99–101.
9. Symons FJ, Tapp J, Wulfsberg A, et al. Sequential analysis of the effects of naltrexone on the environmental mediation of self-injurious behavior. *Exp Clin Psychopharmacol*. 2001;9(3):269–276.
10. Kemp AS, Fillmore PT, Lenjavi MR, et al. Temporal patterns of self-injurious behavior correlate with stress hormone levels in the developmentally disabled. *Psychiatry Res*. 2008;157(1–3):181–189.
11. Campbell M, Anderson LT, Small AM, et al. Naltrexone in autistic children: a double-blind and placebo-controlled study. *Psychopharmacol Bull*. 1990;26(1):130–135.
12. Willemsen-Swinkels SHN, Buitelaar JK, Nijhof GJ, et al. Failure of naltrexone hydrochloride to reduce self-injurious and autistic behavior in mentally retarded adults: double-blind placebo-controlled studies. *Arch Gen Psychiatry*. 1995;52(9):766–773.
13. Bodfish JW. Treating the core features of autism: are we there yet? *Ment Retard Dev Disabil Res Rev*. 2004;10(4):318–326.
14. Roy A, Roy M, Deb S, et al. Are opioid antagonists effective in attenuating the core symptoms of autism spectrum conditions in children: a systematic review. *J Intellect Disabil Res*. 2015;59(4):293–306.
15. Benjamin S, Seek A, Tresise L, et al. Case study: paradoxical response to naltrexone treatment of self-injurious behavior. *J Am Acad Child Adolesc Psychiatry*. 1995;34(2):238–242.
16. McDougle CJ. Pyschopharmacology. In: Cohen DJ, Volkmar FR, eds. *Handbook of Autism and Pervasive Developmental Disorders* 2nd ed. New York: John Wiley & Sons, Inc.; 1997:707–729.
17. Rana F, Gormez A, Varghese S. Pharmacological interventions for self-injurious behaviour in adults with intellectual disabilities. *Cochrane Database Syst Rev*. 2013;(4):CD009084.
18. Symons FJ, Thompson A, Rodriguez MC. Self-injurious behavior and the efficacy of naltrexone treatment: a quantitative synthesis. *Ment Retard Dev Disabil Res Rev*. 2004;10(3):193–200.
19. Roy A, Roy M, Deb S, et al. Are opioid antagonists effective in reducing self-injury in adults with intellectual disability? a systematic review. *J Intellect Disabil Res*. 2015b;59(1):55–67.
20. Mansour A, Hoversten MT, Taylor LP, et al. The cloned mu, delta and kappa receptors and their endogenous ligands: evidence for two opioid peptide recognition cores. *Brain Res*. 1995;700(1–2):89–98.
21. Herman BH, Hammock MK, Egan J, et al. Role for opioid peptides in self-injurious behavior: dissociation from autonomic nervous system functioning. *Dev Pharmacol Ther*. 1989;12(2):81–89.
22. Buitelaar JK. Self-injurious behaviour in retarded children: clinical phenomena and biological mechanisms. *Acta Paedopsychiatr*. 1993;56(2):105–111.
23. Willemsen-Swinkels SH, Buitelaar JK, Weijnen FG, et al. Plasma beta-endorphin concentrations in people with learning disability and self-injurious and/or autistic behaviour. *Br J Psychiatry*. 1996;168(1):105–109.
24. Gillberg C, Terenius L, Lönnerholm G. Endorphin activity in childhood psychosis: spinal fluid levels in 24 cases. *Arch Gen Psychiatry*. 1985;42(8):780–783.
25. Nagamitsu S, Matsuishi T, Kisa T, et al. CSF beta-endorphin levels in patients with infantile autism. *J Autism Dev Disord*. 1997;27(2):155–163.
26. Ross DL, Klykylo WM, Hitzemann R. Reduction of elevated CSF beta-endorphin by fenfluramine in infantile autism. *Pediatr Neurol*. 1987;3(2):83–86.
27. Gillberg C, Terenius L, Hagberg B, et al. CSF beta-endorphins in childhood neuropsychiatric disorders. *Brain Dev*. 1990;12(1):88–92.
28. Nagamitsu S. CSF beta-endorphin levels in pediatric neurologic disorders. *Kurume Med J*. 1993;40(4):233–241.
29. Brambilla F, Guareschi-Cazzullo A, Tacchini C, et al. Beta-endorphin and cholecystokinin 8 concentrations in peripheral blood mononuclear cells of autistic children. *Neuropsychobiology*. 1997;35(1):1–4.
30. Cazzullo AG, Musetti MC, Musetti L, et al. Beta-endorphin levels in peripheral blood mononuclear cells and long-term naltrexone treatment in autistic children. *Eur Neuropsychopharmacol*. 1999;9(4):361–366.
31. Coid J, Allolio B, Rees LH. Raised plasma metenkephalin in patients who habitually mutilate themselves. *Lancet*. 1983;2(8349):545–546.
32. Weizman R, Weizman A, Tyano S, et al. Humoral-endorphin blood levels in autistic, schizophrenic and healthy subjects. *Psychopharmacology (Berl)*. 1984;82(4):368–370.
33. Zelnik N, Herman BH, Hammock MK, et al. Role of opioid peptides in self-injurious behavior. *Soc Neurosci Abstract*. 1986;12:41.
34. Herman BH, Arthur-Smith A, Hammock MK, et al. Ontogeny of beta-endorphin and cortisol in the plasma of children and adolescents. *J Clin Endocrinol Metab*. 1988;67(1):186–190.
35. Weizman R, Gil-Ad I, Dick J, et al. Low plasma immunoreactive beta-endorphin levels in autism. *J Am Acad Child Adolesc Psychiatry*. 1988;27(4):430–433.
36. Sandman CA, Barron JL, Chicz-DeMet A, et al. Plasma B-endorphin levels in patients with self-injurious behavior and stereotypy. *Am J Ment Retard*. 1990;95(1):84–92.
37. Herman BH. A possible role of proopiomelanocortin peptides in self-injurious behavior. *Prog Neuropsychopharmacol Biol Psychiatry*. 1990;(suppl 14):S109–S139.
38. Leboyer M, Bouvard MP, Launay JM, et al. Brief report: a double-blind study of naltrexone in infantile autism. *J Autism Dev Disord*. 1992;22(2):309–319.
39. Ernst M, Devi L, Silva RR, et al. Plasma β-endorphin levels, naltrexone, and haloperidol in autistic children. *Psychopharmacol Bull*. 1993;29(2):221–227.
40. Leboyer M, Bouvard MP, Recasens C, et al. Difference between plasma N- and C-terminally directed beta-endorphin immunoreactivity in infantile autism. *Am J Psychiatry*. 1994;151(12):1797–1801.
41. Leboyer M, Philippe A, Bouvard M, et al. Whole blood serotonin and plasma

You are prohibited from making this PDF publicly available.

For reprints or permissions, contact permissions@psychiatrist.com. ♦ © 2018 Copyright Physicians Postgraduate Press, Inc.

It is illegal to post this copyrighted PDF on any website.

beta-endorphin in autistic probands and their first-degree relatives. *Biol Psychiatry*. 1999;45(2):158–163.
42. Bouvard MP, Leboyer M, Launay JM, et al. Low-dose naltrexone effects on plasma chemistries and clinical symptoms in autism: a double-blind, placebo-controlled study. *Psychiatry Res*. 1995;58(3):191–201.
43. Tordjman S, Anderson GM, McBride PA, et al. Plasma beta-endorphin, adrenocorticotropin hormone, and cortisol in autism. *J Child Psychol Psychiatry*. 1997;38(6):705–715.
44. Sandman CA, Touchette P, Marion S, et al. Disregulation of proopiomelanocortin and contagious maladaptive behavior. *Regul Pept*. 2002;108(2-3):179–185.
45. Tordjman S, Anderson GM, Botbol M, et al. Pain reactivity and plasma beta-endorphin in children and adolescents with autistic disorder. *PLoS One*. 2009;4(8):e5289.
46. American Psychiatric Association. *Diagnostic and Statistical Manual for Mental Disorders*. Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000.
47. Misès R, Quemada N. *CIM-10. Classification française des troubles mentaux de l'enfant et de l'adolescent (3e ed.).* Classification internationale des troubles mentaux et du comportement (chapitre V de la CIM 10-OMS): version officielle du chapitre V de l'International Statistical Classification of Diseases and Related Health Problems, ICD-10, 1992, OMS Genève), Vanves, CTNERHI, diffusion PUF. 1993.
48. Lord C, Rutter M, Le Couteur A. Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord*. 1994;24(5):659–685.
49. Tanner JH. *Growth of Adolescents*. Oxford, UK: Blackwell Scientific Publications; 1962.
50. Anastasi A. *Psychological Testing*. 6th ed. New York, NY: Macmillan Publishing Co Inc.; 1988.
51. Tordjman S, Antoine C, Cohen DJ, et al. Study of the relationships between self-injurious behavior and pain reactivity in infantile autism [in French]. *Encephale*. 1999;25(2):122–134.
52. Tordjman S, Cohen DJ, Haag G. *Manual for the Self-Irious Behavior Scale*. Paris, France: Editions du Centre de Psychologie Appliquée (ECPA);2008.
53. Colas-Linhart N, Perdrisot R, Petiet A, et al. A beta-endorphin radioimmunoassay-specificity studies. *Journal de Biophysique et de Biomecanique*. 1986;10(3):131–134.
54. Rigaud D, Verges B, Colas-Linhart N, et al. Hormonal and psychological factors linked to the increased thermic effect of food in malnourished fasting anorexia nervosa. *J Clin Endocrinol Metab*. 2007;92(5):1623–1629.
55. Canitano R. Self injurious behavior in autism: clinical aspects and treatment with risperidone. *J Neural Transm (Vienna)*. 2006;113(3):425–431.
56. Grandin T. Calming effects of deep touch pressure in patients with autistic disorder, college students, and animals. *J Child Adolesc Psychopharmacol*. 1992;2(1):63–72.
57. Bullinger A. *Le développement sensori-moteur de l'enfant et ses avatars: L'espace de la pesanteur, le bébé prématuré et l'enfant avec TED*. Volume 2. Toulouse, France: Editions Eres; 1995.
58. Forgeot d'Arc B, Dawson M, Soulières I, et al. Self-injury in autism is largely unexplained: now what? *J Autism Dev Disord*. 2012;42(11):2513–2514.
59. Edelson SM. Implications of sensory stimulation in self-destructive behavior. *Am J Ment Defic*. 1984;89(2):140–145.
60. Gutstein HB, Trujillo KA, Akil H. Does chronic nociceptive stimulation alter the development of morphine tolerance? *Brain Res*. 1995;680(1–2):173–179.
61. Minshawi NF, Hurwitz S, Fodstad JC, et al. The association between self-injurious behaviors and autism spectrum disorders. *Psychol Res Behav Manag*. 2014;7:125–136.
62. Moss S, Emerson E, Kiernan C, et al. Psychiatric symptoms in adults with learning disability and challenging behaviour. *Br J Psychiatry*. 2000;177:452–456.
63. Moore DJ. Acute pain experience in individuals with autism spectrum disorders: a review. *Autism*. 2015;19(4):387–399.
64. Le Bars D, Villanueva L. Electrophysiological evidence for the activation of descending inhibitory controls by nociceptive afferent pathways. *Prog Brain Res*. 1988;77(1):275–299.
65. Dumesnil F. *Autisme, psychoses précoces et automutilations*. Montreal, Quebec, Canada: Presses Universitaires de Montréal; 1989:59–90.
66. Schroeder SR, Oster-Granite ML, Thompson T, eds. *Self-Injurious Behavior: Gene-Brain-Behavior Relationships*. Washington, DC: American Psychological Association; 2002.
67. Angelogianni P, Gianoulakis C. Ontogeny of the beta-endorphin response to stress in the rat: role of the pituitary and the hypothalamus. *Neuroendocrinology*. 1989;50(4):372–381.
68. Gerra G, Volpi R, Delsignore R, et al. ACTH and beta-endorphin responses to physical exercise in adolescent women tested for anxiety and frustration. *Psychiatry Res*. 1992;41(2):179–186.
69. Murphy O, Healy O, Leader G. Risk factors for challenging behaviors among 157 children with autism spectrum disorder in Ireland. *Res Autism Spectr Disord*. 2009;3(2):474–482.
70. Oliver C, Richards C. Practitioner review: self-injurious behaviour in children with developmental delay. *J Child Psychol Psychiatry*. 2015;56(10):1042–1054.
71. Dempsey J, Dempsey AG, Guffey D, et al. Brief report: further examination of self-injurious behaviors in children and adolescents with autism spectrum disorders. *J Autism Dev Disord*. 2016;46(5):1872–1879.
72. Fluegge K. Environmental factors in the development of autism spectrum disorders: a reply to Sealey et al, (2016). *Environ Int*. 2016;97:256–257.
73. Becker JA, Clesse D, Spiegelhalter C, et al. Autistic-like syndrome in mu opioid receptor null mice is relieved by facilitated mGluR4 activity. *Neuropsychopharmacology*. 2014;39(9):2049–2060.

Supplementary material follows this article.

You are prohibited from making this PDF publicly available.

For reprints or permissions, contact permissions@psychiatrist.com. ♦ © 2018 Copyright Physicians Postgraduate Press, Inc.

THE JOURNAL OF CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: Relationships Between Self-Injurious Behaviors, Pain Reactivity and β-Endorphin in Children and Adolescents With Autism

Author(s): Sylvie Tordjman, MD, PhD[a,b,*]; George M. Anderson, PhD[c]; Annaëlle Charrier, MD[a]; Cécile Oriol, MD[a]; Solenn Kermarrec, MD[a,b]; Roberto Canitano, MD, PhD[d]; Michel Botbol, MD[e]; Nathalie Coulon, MD, PhD[b]; Corinne Antoine, PhD[f]; Sylvie Brailly-Tabard, MD, PhD[g]; David Cohen, MD, PhD[h]; Hazar Haidar, PhD[g]; Séverine Trabado, MD, PhD[g]; Guillaume Bronsard, MD, PhD[i]; and Laurent Mottron, MD, PhD[j,k]

DOI Number: https://doi.org/10.4088/JCP.16m10889

List of Supplementary Material for the article

1. **eAppendix 1** Immunoassay Methods

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

© Copyright 2018 Physicians Postgraduate Press, Inc.

It is illegal to post this copyrighted PDF on any website. ♦ © 2018 Copyright Physicians Postgraduate Press, Inc.

eAppendix 1. Immunoassay Methods

Blood was obtained from the antecubital foci and collected in EDTA-containing tubes, between 8 and 9 am. After centrifugation (4 °C, 15 min, 1000 g), the plasma was acidified to pH 4.0, and frozen at - 80 °C until assayed. Levels of intact β-endorphin (1-31) were measured using immunoradiometric "sandwich" assay (IRMA) kits purchased from Nichols Institute (Allégro β-Endorphin Immunoassay, San Juan Capistrano, CA). The sample containing BE is incubated simultaneously with antibody immobilized on a plastic bead and ^{125}I-labeled antibody. These two antibodies have high affinity and specificity for both N-terminal and C-terminal defined amino acid regions of the β-endorphin (1-31) molecule. The β-endorphin present in the sample is bound by both the immobilized and labeled antibodies to form a "sandwich" complex. The Allégro β-Endorphin Immunoassay has a calculated detection limit of 4 pmoles/litre and is reproducible (the intra- and inter-assay coefficients of variations are 4.1% and 9 % respectively). In addition, plasma BE concentrations were also determined using a radioimmunoassay (RIA) procedure previously described.[53,54] Gel filtration on Sephadex G75 was used to isolate a BE-containing fraction. After lyophilization, the fraction was assayed using rabbit anti-serum directed against the C-terminal portion of human BE. The assay is sensitive (limit of detection = 5 pmoles/litre) and reproducible (the intra- and inter-assay coefficients of variations are 5 and 6 % respectively).

It is illegal to post this copyrighted PDF on any website. ♦ © 2018 Copyright Physicians Postgraduate Press, Inc.